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Betimi i Hipokratit

Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur. Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfehet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.

Kolegët e mi do t'i konsideroj si vëllezër të mi.

Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë apsolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.

The Oath of Hippocrates

Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.

My colleagues will be my brothers.

I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor

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VALUES OF ACTIVATED PARTIAL THROMBOPLASTIN TIME IN PATIENTS HOSPITALIZED FOR SUSPICION OF ACUTE ISCHEMIC STROKE – RESULTS FROM RETROSPECTIVE SINGLE CENTER STUDY

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ABSTRACT

Introduction – Although the diagnosis of acute ischemic stroke (AIS) remains one of the most prevalent causes of mortality and morbidity, so far there are no routine laboratory parameters that can confirm the diagnosis in the acute setting. The actual study revisits the value of activated partial thromboplastin time (aPTT) with the aim to investigate if there are differences in levels of aPTT measured in first 12 hours in patients experiencing stroke and in patients were stroke was latter excluded.

Methods – We conduct retrospective analysis of data from all hospitalized patients in single centrein the time-frame from 01-01-2017 to 12-12-2018. Patients with confirmed AIS on discharge were intended as cases, while patients with ruled-out stroke were intended as controls. Measurement of the value for aPTT was done as part of routine hemostasis investigation at hospitalization. Case validation was done by serial clinical examinations, CT-imaging of the head and follow-up in settings of hospital care.

Results –Data was available from 620 patients, where 493 patients were with confirmed stroke and 127 patients were with excluded acute ischemic stroke. The mean age in the stroke/control groups was 67.26 years (SD = 6.36) and 63.94 years (SD = 8.42)respectivelly. The overall mean value for aPTT from whole sample was 27.41 seconds (SD = 2.52), with mean value for the stroke/control group of 27.11 sec (SD = 2.24) and 28.40 sec (SD = 2.20). Comparison of the both groups for the mean value of aPTT yielded statistically significant difference ($p < 0.001$).

Conclusion – The timely investigation of aPTTcould provide additional information in the setting of hyper-acute monitoring of brain stroke. The value of the parameter lies in its accessibility, price and short time to obtain result. Literature so far provides mixed findings, while the authors suggest few scenarios where this parameter could be properly tested.

INTRODUCTION

Acute ischemic brain stroke (AIS) represents one of the sources for worldwide mortality and morbidity. According to a global burden of disease study, there were 11.6 million people in 2017 experiencing AIS worldwide, with age-standardized stroke rate on the rise in middle-income countries in comparison with 1990(1). The occurrence of AIS is mainly prevalent in older age groups and it is mainly associated with traditional cardiovascular risk factors, such as tobacco use, arterial hypertension, metabolic syndrome and the presence of atrial fibrillation(2). The actual approach to treatment is dependent on promptness of presentation and underlying etiology. The mainstay of treatment for patients with acute occlusion in the medial cerebral artery with thrombolytic in the first 4.5 hours produced success in patients affected with AIS, but

studies also report that ~10% of the patients admitted for thrombolytic treatment for stroke and turned out to be stroke-mimic, do not show increased frequency of unwanted side effects when comparing to patients with AIS that received thrombolytic therapy(3). This finding points out that in real time work-up for stroke, where time is limited, there is substantial portion of patients that are falsely diagnosed with stroke on admission. Furthermore, recent analysis in the setting of hyper-acute treatment for stroke points out that in-hospital delay for treatment is partially affected by physician assessment, which is aided with imaging of the brain(4). The occurrence of ischemic stroke actually remains a diagnosis of exclusion in the hyper-acute work-up, when magnetic resonance imaging is unavailable or deemed time-consumptive. As laboratory markers that might suggest the occurrence of stroke, few have been investigated, but none has been demonstrated to reliably point out to the diagnosis of acute ischemic stroke.

Reports on the value of activated partial thromboplastin time (aPTT) in cases with thromboembolism are not without conflicting findings. aPTT represents a stable marker for the intrinsic pathway of coagulation and it is dependent on the concentrations of coagulation factors I, II, V, VIII, X, XI and XII. Furthermore, aPTT represents standard marker of efficacy of therapy with heparin, where prolongation of the time is the expected finding. Our revisit to this parameter was motivated by few studies that report altered values for aPTT in patients experiencing stroke(5–8). Namely, the prolongation of the aPTT is associated with bleeding in patients using drug that alter blood clothing(9), use of heparin(10), consumption of the fore-mentioned factors of coagulation (or their deficit) or presence of antiphosphilipid bodies. On the other hand, short time for aPTT has been associated with thromboembolic events, which are the culprit behind substantial portion of acute ischemic stroke. For instance, in a recent prospective study, short aPTT was associated with worse neurological outcome of stroke(8). Another study reveals that shortened aPTT was associated with F1+2 levels (prothrombin fragments that are proxy for generation of thrombin) (6). The association is not full-proof, as previously it has been found out that patients experiencing AIS after carotid stenting have on average same values for aPTT as patients that did not experience stroke(11). In other study, the finding of shortened aPTT in patients experiencing acute myocardial infarction (AMI) was associated with rise in 3-methoxy-4-hydroxyphenylglycol, a metabolite of norepinephrine production, entertaining the link between autonomic adrenergic activity during suffering of ischemia (12). These findings can be corroborated with later study that reports shortening of aPTT in healthy subjects after inhalation of b2-adrenoreceptor agonists(13). Other study performed on patients suffering from AMI, found out somewhat shorter aPTT time on average in the portion of patients that complicated with acute ischemic stroke, although this was not statistically tested (14). Another study performed on young patients that suffered from stroke reveals that patients with antiphospholipid antibodies (as presumed etiological factor) have characteristically finding of aPTT prolongation(15,16). On the other hand, older study measured different markers of hemostasis in patients admitted for stroke (17), but the study did reveal that aPTT dynamics in the first days after stroke is not correlated with neurological worsening. Latest, in the wake of the SARS-COV-2 pandemic, many studies point out the deranged hemostatic function in patients with viral pneumonia due to SARS-COV-2, with noted shortening of the APTT in patients with severe clinical picture (18).

The evaluation of this factor could be problematic, since AIS can occur from wide array of possible etiologies. Given the actual findings, the aim of our study is to retrospectively compare the values of aPTT between patients with findings for anacute ischemic stroke and hospitalized patients where acute ischemic stroke was ruled out by the end of their hospital stay. The null hypothesis that there is no difference in aPTT times in the first hours between patients hospitalized for acute ischemic stroke and patients hospitalized for other neurological conditions or where acute ischemic stroke is ruled out.

METHODS

Study design and population

The actual study is retrospective analysis of hospital record data from single center. For the aims of the study, we analyzedhospital record data from the University Clinic of Neurology – Skopje from patients hospitalized for suspicion of acute ischemic stroke in the period of from 01-01-2017 to 31-12-2018. Per hospital protocol, all patients that are hospitalized for suspicion of stroke undergo native computed tomography of the brain, electrocardiography and laboratory work-up with complete blood count, metabolic panel and markers of hemostasis in the first 12 hours of admission.The patient

records were checked for confirmation of diagnosis of stroke, defined as diagnosis of acuteischemic stroke on discharge (ICD I63.3, I63.9). The patient samplewas divided in two groups, patients with confirmed AIS and patientshospitalized for other diagnosis on admission and discharge where measurements of aPTT were made. The differentiation between transient ischemic attack and stroke mimics on the basis of the provided data was deemed unreliable, since the follow-up of the patients is not necessarily conducted our institution, and it represents an essential step in the diagnosis of stroke-related conditions without findings on computed tomography of the brain.

Blood sampling was done by drawing venous blood into tubes with sodium citrate, which was centrifuged (1500 g, 10 min), with determining the values for aPTTwith the SIEMENS BFT II Analyzer. The reference values for this parameter were previously determined on a healthy sample, resulting in reference range of 22 to 32 seconds. The case ascertainment for acute ischemic stroke is done by neurological follow up in conjunction with repeated CT scan of the head per hospital protocol. The cases where AIS was ruled out were cases where the diagnosis on discharge is changed to other diagnosis/finding. Patients that were with diagnosis for acute ischemic stroke (I63.n) on discharge, with confirmatory finding on CT on the head were included as cases. As this study is retrospective in design, and doesn't require additional sampling of blood (as these analyses are in the hospital protocol), informed consent was not required.

Statistical analyses

Statistical evaluation was conducted using IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). All gathered data was described in terms of appropriate descriptors (mean, median, proportion, standard deviation) on age, gender and mean time in seconds for aPTT of the participants. Differences between groups were checked by testing for presence of significant difference in age and gender between the two groups. Next, data was analyzed for significant values for aPTT, defined as values that deviate for 2.5 SD from the group mean; all outliers are planned to be reported and removed from final comparison. The null hypothesis assuming no difference for the value of aPTT between the two groups is tested by using the independent samples t-test. As acceptable type I error rate in this study is considered a = 0.05.

Results

The search of the hospital record system for the specified period yielded 954 hospitalized unique patients with initially investigated for stroke with CT scan and available measurements on hemostasis. 675 patients were with confirmed ischemic stroke at discharge while 279 patients were without CT finding for new stroke. From 675 patients in the stroke group, there were 493 (75%) patients with sufficient records, without finding for previous heparin use and with stroke onset in the first 12 hours to be included in the study, while 127 (45.5%) patients were included in the second group.

The analysis included 620 patients, with mean age of 66.58 years (SD = 6.95). Overall, 286 (46.1%) patients were male, and 493 (79.5%) patients were with confirmed stroke, while 127 (20.5%) patients belonged to the control group. The descriptive statistics of the sample is represented in table 1. As follows, the group of patients with confirmed stroke was somewhat older (67.26 years vs 63.94 years), although both groups had similar proportion of male and female patients.

Table 1. Descriptive statistics of the sample

	All patients	Patients with confirmed stroke	Patients without new stroke
Number of patients count, %)	620	493 (79.5%)	127 (20.5%)
Age (average, SD)	66.58, 6.95	67.26, 6.36	63.94, 8.42
Gender (male, %)	286 (46.1%)	227 (46%)	59 (46.4%)
aPTT in seconds (mean, SD)	27.41, 2.52	27.08, 2.24	28.69, 3.08

The mean value for aPTT in our sample was 27.41 seconds, with 95%CI of 22.48 – 32.34 seconds, which roughly corresponded to the reference range for aPTT given by our laboratory. The mean value for aPTT in the stroke group was 27.08 seconds, while in the other group was 28.69 seconds. More descriptive values are present in table 2. As outliers, we defined values that deviate 2.5 standard deviations from the overall mean statistic for aPTT (21.11 ; 33.71 seconds). Our sample contained 7 patients with values that were out of this range; namely two patients measurement of below 21.11 seconds and 5 patients had measurements above 33.71 seconds. The patients with these values were excluded from further analysis. Upon removal, the mean values (SD) for aPTT for the stroke and the other group were 27.11 (SD = 22.02) and 27.91 (SD = 2.67) respectively. The comparison between the two groups via the independent t-test yielded t-statistics of 5.5 (df = 611)

and statistically significantp-value of 5.3608-8.

Table 2. Patients with extreme values for aPTT

n = 620	All patients	Patients with confirmed stroke	Patients without new stroke
aPTT< 22 sec (below ref. range)	7	6	1
aPTT> 32 sec (above ref. range)	17	4	13
Patients with values for aPTT outside lab. reference range	24	10	14
Outliers (<21.11 sec)	2	2	0
Outliers (>32.48 sec)	5	0	5
Total number of outliers	7	2	5

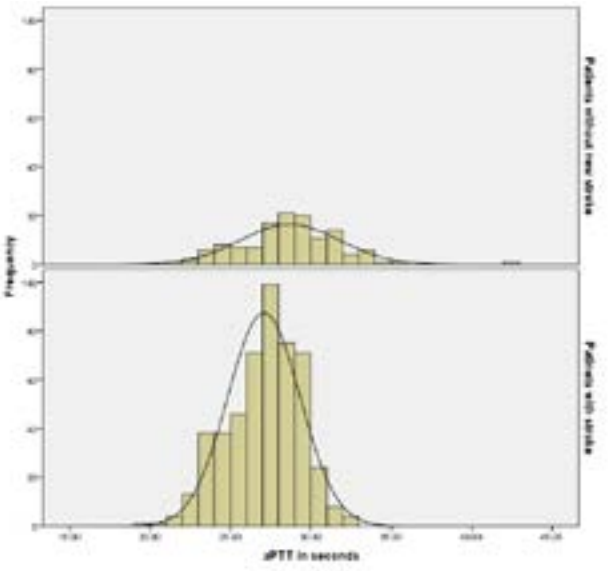

Figure 1. Distribution of aPTT values for the patients with ruled out stroke (histogram above) and patients with confirmed stroke (histogram below).

DISCUSSION

The results of the present study are in line with the previous studies that measured shorter aPTT for patients experiencing stroke. Our first hand impression is that the majority of patients that are admitted for suspected stroke are screened with hemostasis tests for overt hemostasis abnormalities. Although this counts for the majority of the patients that experience AIS, 25 % of all found cases were not included because of late presentation at hospital, previous use of heparin or agents that affect blood hemostasis or measurement for hemostasis later.

The results of the present study point out shorter times for aPTT measured in the first twelve hours in patients with confirmed stroke and patients with excluded acute ischemic stroke. This is in line with the seminal study on this topic from McKenna (7), the prospective study thromboembolic events (6), the statistically insignificant but same-directed finding from (5) and the findings from Lin (8). The last study correlates the severity of presentation of stroke with shorter aPTT, while previous made coexistent correlation with bad glycemic control and hypertensive diseases. Shorter aPTT times were also found in incident stroke patients that underwent percutaneous coronary intervention (19). Prospective serial measurements in the first hours of stroke for aPTT were found to be initially stable around any worsening (17). Of note is that patients included in these studies had coincident worse glycemic control (19), more prevalent arterial hypertension and smoking (8). An prospective observational study measured statistically insignificant difference between incident stroke patients and controls (5), with direction consistent with the abovementioned findings. Still, previous findings put different look on this parameter in patients with anti-phospholipid syndrome, where it was that they have on average prolonged aPTT and propensity for embolic events (15). This finding has been understood as result of the influence of anti-bodies which can disable certain coagulation factors and lead to prolongation of aptt in these patients(16). Furthermore, our study revealed substantial number of outliers below ref. range in the stroke group in comparison with the other, which were rendered not suitable for testing due to the small number of members in two cells for analysis via chi-square test for independence.

In light with previous findings, the value of aPTT was not associated with incident strokes after carotid artery stenting procedures in a prospective study where MRI was employed (11), but it differs in methodology by collecting the samples longer than <24 hours before the intervention and < 24 + n hours before the occurrence of new ischemic lesion on MRI, in both symptomatic and asymptomatic patients. The issue of time of measurement of this parameter is multilayered. In health patients, it has been confirmed as stable during the circadian cycle (20). It is persistently prolonged in patients with anti-phospholipid syndrome (15), it is prolonged for 1-2 days after withdrawal of heparin use. Other study reported that aPTT values were stable +-3 days around the neurological worsening in patients suffering from stroke(17) with reported rise of the value for AT-III 2 days before the occurrence of the worsening. An animal study with stroke induction and subsequent thrombolysis (21) reports that the value of aPTT remained stable after both

steps in the time frame of 5 hours via use of homologous fibrin rich blood clots. The association of beta-agonistic release and shortening of aPTT has been confirmed with the use of short-acting β2-agonists (13) and significant rise of prothrombin activation fragments one hour after administration. It seems that aPTT is quickly responsive to certain adrenergic stimuli and heparin use, its baseline value reflects the activity of the factors of coagulation (I, II, V, VIII, X, XI and XII) and it should be taken into account in certain scenarios of stroke depending on the etiology.

Although the conducted comparison yielded statistically significant result, the study has few sources of bias. First, the present study is retrospective study. Second, the present study assumes an analogue to "intention-to-treat analysis", which means that there is no other confirmation that blood samples were withdrawn before administering therapy with heparin products that could influence the results, besides the hospital protocol. The hospital conduct maintains that these measurements should be mandatory before admission of therapy, especially in the context of thrombolysis. The next sources of bias come from missing data due to unavailability of aPTT measurement result (or erroneous readings) and the validation of cases done on basis of clinical observation and CT of the brain, both of which can suffer from low agreement and lower sensitivity when compared with advanced MR techniques. Among the advantages of the study is its big sample size and consistency of findings with previous studies, such as the direction of association between age and values for aPTT and differences between male and female patients for values of aPTT.

The authors of the study find the present association with conjunction of previous findings an option that could be tested further. First, shortened aPTT and its association with thromboembolic stroke has plausible biological explanation. The association of aPTT with worsening of stroke could be owned to a general adrenergic response in patients experiencing moderate or worse stroke. The value of this parameter can be investigated in subgroup analysis according to stroke etiology, for instance groups with undetermined cause of stroke, patients with small vessel disease or in patients already burdened with risk factors such as poorly regulated diabetes mellitus and worsening arterial disease. Due to above-stated reasons, we could not make comparisons between patients with stroke and patients experiencing transient ischemic attack, which could further evaluate this association. Another possible role could be its value as predictor of neurological worsening and success/failure of therapy in the hyper acute stroke. The worth of this parameter lies in its availability in routine settings and low price, short time for measurement and responsive dynamics to factors that can influence it.

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Original scientific paper

ЗГОЛЕМЕНИ КОНЦЕНТРАЦИИ НА TNF-α ВО АМНИОНСКА ТЕЧНОСТ КАКО ЗНАК ЗА РИЗИК ЗА ПРЕДВРЕМЕНО ПОРОДУВАЊЕ

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АПСТРАКТ

Резиме: Во денешно време голем предизвик во акушерството претставува предвременото породување и пронаоѓање на начин односно метода за намалување на ризикот за негово настанување. Тоа е секое породување кое настанува помеѓу 24 и 37 гестациска недела. Во нашата земја предвременото породување има преваленца од 12 %. Моменталните дијагностички процедури достапни за одредување на ризик на овој мошне значаен проблем во нашата држава се доста оскудни. Одредување на концентрацијата на одредени биомаркери и нивната концентрација во амнионската течност има мошне големо значајње во предвидување и дијагностика на овој проблем а со тоа и навремено постапување. Цитокините се од исклучително значење во бременоста а се произведуваат од страна на постелката во амнионската течност а постои можност тие да се зголемат доколку постои некој тригер на интраамнионска инфламација или инфекција кој би влијаел и допринел за нивно зголемување.

Цел на студијата: е да се докаже влијанието на TNF-α и неговата концентрација во амнионската течност при постоењето на интраутерина инфламација или инфекција.

Материјал и методи: Во оваа проспективна, лонгитудинална студија беа вклучени 74 пациентки кај кои беше извршена медицински индицирана амниоцентеза во раното второ тримесечје. Оваа студија се изведуваше на Клиниката за гинекологија и акушерство и на Институтот за имунологија и хумана генетика, Скопје, Р.Северна Македонија. При влез во студијата и потпишување согласност за учество во неа се вршеше ултразвучен преглед, по што следуваше амниоцентезата при што се земаа дополителни 5 мл амнионска течност во која пак потоа се одредуваа концентрациите на, TNF-α. Сите пациентки се следеа до датумот на нивното породување .

Резултати: Сите 74 пациентки беа во периодот од 18 г.н. до 23 г.н. Кај 12 од вкупно 74 пациентки беше нотирано предвремено породување, за разлика од останатите 62 се породија во текон на нивниот термин. Пациентките предвреме породени имаа сигнификантно различни концентрации на TNF-α во амнионската течност (p=0.0013). Во групата породени пред 37-ма г.н. беа измерени значајно повисоки TNF-α вредности. Овој инфламаторен маркер во амнионската течност имаше просечна вредност од 12.04 ± 26.6 pg/ml кај пациентките предвреме породени, а 4.04 ± 2.1 pg/ml кај пациентките породени во термин; средните концентрации на TNF-α во двете групи пациентки изнесуваа 6.67 и 3.96 pg/ml консеквентно.

Заклучок: TNF-α биомаркерот мерен во амнионската течност во вториот триместар се покажаа како одлични предиктори на ризик за предвремено породување кај трудници.

Клучни зборови: биомаркери, TNF- α, предвремено породување, амнионска течност, амниоцентеза.

РЕЗИМЕ

Предвременото породување представува еден од најголемите предизвици во денешницата, и сеуште е проблем кој не е во целост доистражен и докажан механизмот и причината за негово настанување (1). Тоа претставува секое породување помеѓу 24 и 37 гестациска недела кој ги афектира 11 % од бременостите во целиот свет (2). Предвременото породување е асоцирано со неонатален морбидитет и морталитет. Достапните алатки за дијагностицирање на ризикот за предвремено породување се од голема важност како за пациентката така и за плодот. Амнионската течност претставува стерилна средина кај нормална бременост. Таа е комплексна телесна течност која има многу значајна улога во секоја бременост (3). Мерење на концентрацијата на одредени биомаркери во амнионската течност кај трудници во последно време е од голем интерес како потенцијален извор за дијагностика и терапија на оваа проблематика. Се смета дека цитокините играат важна улога во воспоставувањето и одржувањето на бременоста. Развиен полуалоген фетус е потенцијална цел за имунолошкиот систем на мајката каде постои антиинфламаторна пристрасност на цитокинот кај фетоматерналната површина (2,4). Цитокините спречуваат отфрлање од потенцијален воспалителен одговор. Се лачат од страна на постелката во амнионската течност. Се зголемуваат доколку постои одредена интраутерина инфламација (5). Предвременото породување е силно поврзано со инфламација и инфекција и затоа големо внимание е посочено на детерминирање на алтернативни биомаркери кои можат да го идентификуваат раниот инфламациски процес кој се јавува кај асимптоматски пациентки (2,6). Зголемени вредности на овие биомаркери во крвта и во амнионската течност се детектирани во второто тримесечје кај асимптоматски пациентки кој ќе развијат инфламаторен синдром, а постои зголемен ризик за да се породат предвремено. Во последните неколку години се поголеми се доказите за способноста на овие биомаркери во амнионската течност за предвидување на предвремено породување (7, 8). Еден од позначајните биомаркери е TNF-α, а негова примарна улога е во регулирање на имуните клетки. TNF-α како ендоген пироген е во состојба да предизвика треска, апоптотична смрт на клетки, кахексија, воспаление и да ја инхибира тумор генезата и репликацијата на вирусот како и да одговори на сепса преку клетки што произведуваат IL1- и IL6 (8,9,10). Нерегулираното производството на овој фактор е вмешан во најразлични човечки заболувања (9). Во бременоста TNF-α е провоспалителен Th1-цитокин кој игра голема улога во воспалителниот механизам кој ја регулира имплантацијата, плацентацијата и на крајот учествува во исходот од бременоста (8). TNF-α се излачува не само со вродени имунолошки клетки, но исто така, и од плацентата. Точно рамнотежа помеѓу Th1 цитокини, главно TNF-α, Th17 и Th2 цитокини, особено IL-10 е од суштинско значење за да се постигне добар акушерски исход. Од друга страна, неколку акушерски нарушувања особено повторливи загуби на бременост, рани и тешки преeклампсии и синдром на рекурентен неуспех на имплантација може да се должи на зголемување на цитокините зависни од Th1 особено TNF-α (11).

ЦЕЛ НА СТУДИЈАТА

Е да се докаже влијанието на TNF-α и неговата концентрација во амнионската течност при постоењето на интраутерина инфламација или инфекција.

МАТЕРИЈАЛ И МЕТОДИ

Во оваа проспективна, лонгитудинална студија беа вклучени 74 пациентки кај кои беше извршена медицински индицирана амниоцентеза во раното второ тримесечје. Оваа студија се изведуваше на Клиниката за гинекологија и акушерство и на Институтот за имунологија и хумана генетика, Скопје, Р.Северна Македонија. При влез во студијата сите пациентки потпишаа писмена согласност за учество во неа. Пред започување на студијата истата беше одобрена од медико- етичката комисија при Медицинскиот факултет во Скопје. Сите пациентки беа регрутирани во амбулантата за амниоцентези на Универзитетската клиника за гинекологија и акушерство, Скопје, Р.С. Македонија. Кај сите пациентки беше направен ултразвучен преглед и рутинска биометрија на плодот, за детерминирање на гестациската старост. Сите пациентки беа со единечна бременост, без знаци за предвремено породување. Кај сите пациентки амниоцентезата беше индицирана од медицински причини како што се : мајчина возраст над 35 год, висок ризик на комбиниран серумски тест, позитивен неинвазивен пренатален тест, детекција на суспекти аномалии при ултразучен преглед. Потоа сите пациентки беа хоспитализирани на одделот за високоризична бременост. По земање

на детална анамнеза, кај пациентките беше вршена амниоцентезата по сите протоколи при што се земаа дополителни 5 мл амнионска течност во која пак потоа се одредуваа концентрациите на TNF-α. Сите пациентки се следеа до датумот на нивното породување. Примерокот од амнионска течност се транспортираше, во лабораторијата на Институтот за имунологија и хумана генетика при Медицинскиот факултет во Скопје каде што по прием се центрифугираше со вртежи од 1500 g. во рок од 10 мин., а потоа се замрзнуваа на температура од – 20 °C се до нивна обработка. Резултатите се читаа според референтните вредности на самиот производител.

СТАТИСТИЧКА ОБРАБОТКА

Податоците од студијата беа обработени во статистичката програма SPSS за Windows 23.0. Нумеричка, т.е. квантитативните параметри беа прикажано со просечно, стандардно отстапување. Квалитативни, односно атрибутивни параметри се прикажани со дистрибуција на фреквенции. За споредување на жени кои се породиле предвремено и кои родиле во термин беше користен Mann-Whitney тестот. За статистички значајна сигнификанта беше земена вредноста од $p < 0.05$.

РЕЗУЛТАТИ

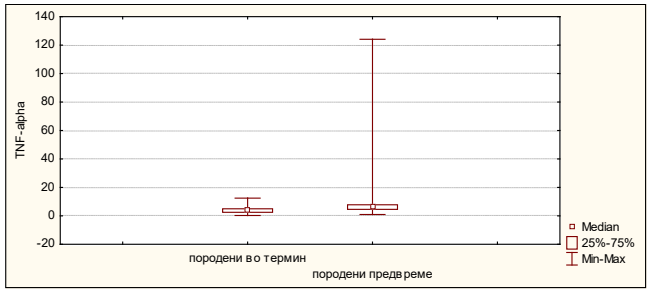
Сите 74 пациентки беа во периодот од 18 г.н. до 23 г.н. Кај 12 од вкупно 74 пациентки беше нотирано предвремено породување, за разлика од останатите 62 кои се породија во текон на нивниот термин. Пациентките предвреме и терминski породени имаа сигнификантно различни концентрации на TNF-α во амнионската течност (p=0.0013). Во групата породени пред 37-ма г.н. беа измерени значајно повисоки TNF-α вредности.

Табела 1 Вредност на TNF-α во амнионска течност кај пациентки породени предвреме и во термин

завршено раѓање	Descriptive Statistics (TNF -α pg/ml)			p-level
	n	mean ± SD	median (IQR)	
во термин	62	4.04 ± 2.1	3.96 (2.49 – 4.94)	Z=-3.22
предвреме	12	12.04 ± 26.6	6.67 (4.55 – 7.76)	p=0.0013 sig

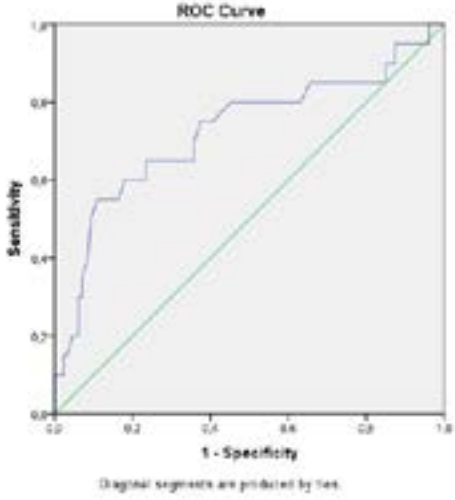
Z (Mann-Whitney test)

Овој инфламаторен маркер во амнионската течност имаше просечна вредност од 12.04 ± 26.6 pg/ml кај пациентките предвреме породени, а 4.04 ± 2.1 pg/ml кај пациентките породени во термин; средните концентрации на TNF-α во двете групи пациентки изнесуваа 6.67 и 3.96 pg/ml консеквентно (табела 1, слика 1).



Слика 1 Графички приказ на средни вредности на TNFα во амнионска течност - пациентки породени предвреме и во термин

Резултатите од ROC анализата за предикција на предвремено породување со TNF-α вредностите, покажаа дека големината на површината под ROC кривата има вредност од 0.724 (95% CI 0.585-0.864) со сензитивност од 65% и специфичност од 70.5% (слика 2, табела 2). Ова сугерира на заклучок дека TNF-α во амнионската течност има добра дискриминаторска способност во одделување на бремените жени со предвремено и терминско породување.



Слика 2. ROC крива за предикција на предвремено породување со TNF-α

Табела 2. Вредности на ROC кривата за TNF- α

Area	Std. Errora	Asymptotic Sig.b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.724	0.071	0.001	0.585	0.864

ДИСКУСИЈА

Идентификацијата на специфичен имунолошки медијатор и нивната концентрација во амнионската течност има привлечено мошне големо внимание како потенцијален извор за дијагностика и терапија на оваа проблематика. Ова поле сеуште останува недоистражено бидејќи постојат многу различности во испитувањата во разни студии (12). Составот на амнионската течност се менува за време на бременоста, што и е докажано во многубројни студии (13). Соодветно на тоа, АТ го менува милјето за време на бременоста и е под влијание на различни фактори, како што се: гестациската недела, утеринатa перфузија и многу други. Особено во втората половина на бременоста составот на АТ се чини дека се менува (14,15). Факторите кои влијаат врз вредноста на цитокините биле испитувани во минатото и се опишани бројни варијабли, како што се: етничка припадност, заболувања на фетусот, мали за гестациска возраст и индекс на телесна маса (16). TNF-α е воспалителен цитокин што се произведува во амнионската течност и кој игра улога во иницирање на предвременото породување. Неговата концентрација во амнионската течност, исто така, значително се зголемува за време на породувањето (17, 18). Присуството на интраутерина инфекција, исто така, го поттикнува производство на TNF-α во амнионската течност и затоа TNF-α е поврзана во патологијата на инфекција поврзана со предвременото породување (19). TNF-α го регулира делувањето на рецепторите на IL-1 во амнионските клетки. Исто така, докажано е дека го стимулира производството на IL-6 и IL-8. TNF-α е вклучен во транскриптивно активирање на простагландин синтаза која доведува до зголемено производство на PGE2 во амнионската течност за време на предвременото породување каде постои инфекција. Дејствата на TNF-α се посредуваат преку мембрански рецептори 1 (TNFR1) и 2 (TNFR2). Активирање на TNFR1 го активира производството на MMP (матрикс метало протеази) додека TNFR2 иницира проинфламаторен имунолошки одговор. Студиите покажале сигнификантна поврзаност во концентрациите на TNF-α (и IL-6) со ПРОМ (предвремено прскање на околу плодовите обвивки) и постоење на хориоамнионит (20,21). Во студијата каде што се мерени концентрациите на TNF-α во амнионската течност за време на медицински индицирана амниоцентеза во второто тримесечје, покажале сигнификантно зголемени вредности на овој цитокин кај тие пациентки кои потоа се породиле предвремено односно пред 37 г.н. споредувано со тие кои се породиле во термин. Истата оваа студија заклучила дека концентрациите на TNF-α (и/или IL-6) во амнионската течност во второто тримесечје може да ги идентификува трудниците кои се на ризик за настанување на хориоамнионит кој би можел да доведе до предвремено породување (22). Во нашата студија резултатите беа сосема слични на тие добиени во другите студии. Пациентките предвремено и термински породени имаа сигнификантно различни концентрации на TNF – α во амнионската течност (p=0.0013). Во групата породени пред 37-ма гестациска недела беа измерени значајно повисоки TNF–α вредности. Овие резултати јасно ја покажуваат важноста на овој маркер во одредувањето и проценувањето на ризикот за настанување на предвремено породување. Резултатите од ROC анализата за предикција на предвремено породување со TNF вредностите, сугерира на заклучок дека TNF во амнионската течност има добра дискриминаторска способност во одделување на трудниците со предвремено и терминско породување.

Заклучок: Биомаркерите мерени во амнинската теност поточно TNF–α вредностите во вториот триместар се покажаа како одлични предиктори на ризик за предвремено породување кај трудници, односно TNF во амнионската течност има добра дискриминаторска способност во одделување на трудниците со предвремено и терминско породување.

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Original scientific paper

ФЕТАЛЕН НЕОНАТАЛЕН И ПЕРИНАТАЛЕН МОРТАЛИТЕТ И НИВНОТО ДВИЖЕЊЕ НА КЛИНИКАТА ЗА ГИНЕКОЛОГИЈА И АКУШЕРСТВО ВО СКОПЈЕ

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АБСТРАКТ

Вовед: Феталната, неонаталната и перинатална смртност (морталитет), кај новородените е огледало на здравствениот систем и здравствените политики на една земја. Развиените и прогресивни земји имаат ниски стапки на фетален, неонатален и перинатален морталитет. Најголеми стапки на морталитет кај новородените во светски рамки, се забележани во неразвиените земји и во земјите во развој, од каде потекнува и најголемиот процент на смртноста кај новородените. Организираната перинатална грижа за трудниците, соодветната здравствена заштита и нега во текот на породувањето и по породувањето за мајките и новородените, водат до минимални стапки на смртност кај новородените. Перинаталниот период ги опфаќа новородените породени по 22 г.с. од бременоста и со породилна тежина поголема од 500 гр., на илјада новородени. Бројот на мртвородените и починатите живородени во првите седум дена по породувањето, ја даваат перинаталната смртност. Феталната смртност е бројот на мртвородени новородени во истиот период, а неонаталната смртност ја опфаќа смртноста на живородените во првите четири недели по породувањето на илјада живородени.

Цел на трудот: Целта на трудот е да се прикаже стапката на феталниот, неонаталниот и перинаталниот морталитет кај новородените, родени на У ГАК-Скопје и трендовите на негово движење во периодот од 2011-2017 година. У ГАК- Скопје е најголемиот и релевантен перинатален и неонатален центар во државата, каде се третираат комплицираните бремености и новороденчиња со компликации на Одделот за интензивна неонатална нега, поради недоносеност, незрелост, инфекции, аномалии и др.причини, кои може да доведат до зголемена смртност кај новородените.

Материјал и методи: Оваа анализа е ретроспективна, пресечна анализа во која се обработува смртноста кај новороденчињата: феталната, неонаталната и перинаталната смртност на новородените породени на У ГАК-Скопје, во период од 7 години (од 2011-2017 година), во однос на вкупниот број на раѓања во тој период. Податоците се собрани од Дата базата на У ГАК- Скопје и Неонаталната интензивна нега и историите на болести на породените жени и новородените во овој период. Феталниот, неонаталниот и перинаталниот морталитет и неговото движење во текот на овие 7 години, е обработен за секоја година посебно и вкупно за целиот период од овие 7 години. Обработена е бројката на починати новородени и тоа поделени во три категории:

- Фетален морталитет- мртвородени во вкупната бројка на родени, на 1000 новородени;

- Неонатален морталитет- починати живородени од 0-28 дена по породување, на 1000 живородени;

- Перинатален морталитет- вкупната бројка на мртвородени и живородени починати во раниот неонатален период до седмиот ден по породувањето, на 1000 новородени.

Резултати : Во овој период од 7 години имало 37381 новороденче родени на У ГАК- Скопје, од кои 36706 живородени новороденчиња. Останатите 675 новородени се родени како мртвородени. Стапката на фетален морталитет или мртвородените новородени во овој период, изнесува средно 18,06 ‰ или 675 мртвородени во

период од седум години, од вкупната бројка на родени новороденчиња. Од вкупната бројка на живородени, починале 912 новороденчиња во неонаталниот период по породувањето, од 0-28 ден по породување. Вкупниот неонатален морталитет на У ГАК-Скопје, во овој 7 годишен период изнесува средно 24,85‰, или 24,8 починати новороденчиња во неонаталниот период по породувањето (0-28 ден), на илјада живородени бебиња.Од добиените резултати се гледа дека бројката на рано неонатално починати новороденчиња, од 0-7 ден по породувањето е поголема и изнесува 19,25 ‰, а во касниот неонатален период од 8-28 дена по породување, стапката изнесува 5,56 ‰. Перинаталната смртност или перинаталниот морталитет, кои ги опфаќа мртвородените и починатите живородени новородени до 7 дена по породување, изнесува средно 37 ‰ или 1383 починати новородени во вкупната бројка на родени, во овој седум годишен период. Феталниот, неонаталниот и перинаталниот морталитет на У ГАК- Скопје, во овој временски интервал е поголем одколку во Европските земји и сите три параметри имаат тенденција на пораст за овој седум годишен период.

Заклучок: Стапката на феталниот, неонаталниот и перинаталниот морталитет на У ГАК-Скопје и во Македонија е доста висока, повисока отколку во земјите во нашето опкружување, Балканските земји и Европските земји. Потребно е превземање на ургентни мерки за негово намалување.

Водечки зборови: фетален морталитет, неонатален морталитет, перинатален морталитет, У ГАК- Скопје.

ВОВЕД

Развојот и опстанокот на секое општество зависи од природниот прираст и бројот на здрави породувања, што е слика на секој организиран здравствен систем и економски развиена држава. Организираната грижа за мајките и децата, како посебно ранливи категории од населението, се наога мегу најголемите приоритети на социјалната и здравствена политика на многу држави во современиот свет (1). Оваа грижа е поткрепена и со многу мегународни конвенции и документи, како што се Конвенцијата за правата на детето (ООН,1989) (2) и Милениумските развојни цели (3) , чиј потписник е и Македонија, како земја членка на ООН. Перинаталниот период го опфака периодот на фетален раст и развој, од навршена 22 г.с. од бременоста до навршени 6 дена по породувањето. Перинаталниот морталитет е морталитетот или смртност,кој ги опфака сите мртвородени и живородени кои починале по породувањето од 0-7 дена, со родилна тежина поголема од 500 гр.или родени по навршена 22 г.с. од бременоста, на 1000 новородени (4) (5). Неонаталниот морталитет ќи опфаќа починатите живородени новородени, кои починале во првите четири недели од животот (4). Неонаталниот период, е период со најголема опасност по преживувањето во човековиот живот и смртноста е најголема во овој период од животот, од 0-28 ден по породувањето. Бројот на мртвородени во периодот над 22 г.с. од бременоста и со родилна тежина повеќе од 500 гр. на 1000 новородени, се дефинира како фетален морталитет. Збирот на фетално починати и рано неонатално починати го дава перинаталниот морталитет. Доенечкиот морталитет е морталитетот кај доенчињата во првата година од животот. Морталитетот под пет години е морталитет кај децата до навршена петта година од животот (4) (5). Сите тие имаат свои специфики и значење во вкупниот морталитет кај децата. Мајчиниот морталитет го претставува морталитетот на трудниците, кој е резултат на копликациите во бременоста и во текот на породувањето и се пресметува како смртност кај мајките на 100.000 жени во тековната година. Перинаталниот морталитет е смртност која ги опфака сите мртвородени и живородени кои починале по породувањето од 0-7 дена, со родилна тежина поголема од 500 гр.или родени по навршена 22 г.с. од бременоста, на 1000 новородени (6). Секоја година во светот умираат околу 6 милиони новородени, во перинаталниот период од животот најмногу во неразвиените земји и земјите во развој. Од нив околу 3 милиони се раѓаат како мртвородени, од кои една третина умираат од компликации во текот на породувањето (6). Неонатално починати од вкупната бројка на живородени, односно починати новородени во првите 4 недели по породувањето, во светски рамки секоја година има околу 4 милиони бебиња, од кои 3 милиони умираат во раниот неонатален период од 0-7 дена по породувањето. 98 % од смртноста кај новородените се случува во неразвиените земји и земјите во развој (6),(8). Неонаталнниот морталитет, е процентот на неонатална (новороденечка) смртност на живородените, во неонаталниот период од 0-28 дена по породувањето, или породени после 22 г.с. од бременоста и со породилна тежина поголема од 500 гр., на илјада живородени (5) (6). Неонаталниот морталитет се дели на рана неонатална смртност,

која го опфаќа периодот од 0-7 дена по породувањето (168 h.),независно од големината на бременоста и касна неонатална смртност која ја опфака смртноста на живите новородени од 8-28 ден по породувањето (7). Смртноста по 28 ден од породувањето спага во т.н. постнатална или доенечка смртност (8). Во светски рамки, раната неонатална смртност е поголема и поради тоа е многу важно преживувањето на новороденото во првите 7 дена од породувањето (7). Преку 130 милиони бебиња се рагаат во светот секоја година (5), а 4,4 милиони умирале во првите 4 недели од животот, или 32 неонатално починати на 1000 живородени во 1990 година (6),(7) . Неонаталната смртност има тренд на опагање во следните 20 години, во светски рамки. Во 2010 година бројот на неонатално починати изнесува 3 милиони или 23 на 1000 живородени глобално (7) . Во 2013 година неонаталната смртност во светот е 2,8 милиони или 18,4 на 1000 живородени неонатуси (8),(9). Во светски рамки неонаталниот морталитет учествува со 40% во тоталниот морталитет кај децата до 5 години, што зборува за неговото значење и голем удел во вкупната смртност кај децата. Неонаталниот морталитет е највисок во Суб-Сахарска Африка каде изнесува 34 на 1000 живородени во 2011 година, а слична е и бројката во некои земји од југоисточна Азија (10),(11),(12). Во овие региони на светот исто така е највисок и феталниот и перинаталниот морталитет. Низок фетален, перинатален и неонатален морталитет имаат развиените Европски земји и земјите на Северна Америка (5) . Во периодот од 2011-2017 година бројките на феталниот, перинаталниот и неонаталниот морталитет на У ГАК- Скопје и воопшто во Македонија покажуваат тренд на пораст, за разлика од трендовите за нивно намалување во светски рамки (13). За таа цел од посебно значење е обезбедување на ефикасна антенатална заштита, превенирање на патологијата во бременоста, технолошко подобрување во перинаталната заштита и неонаталната нега и терапија, како и подобрување на социјалните услови и здравственото просветување на идните мајки (14). Поголемата грижа за бремените жени за време на бременоста и во текот на породувањето,како и напреднатата грижа за новородените, секако води до намалена фетална, перинатална и неонатална смртност (15),(16). Целта на студијата е да се покаже движењето на феталниот, перинаталниот и неонаталниот морталитет на У ГАК-Скопје, во период од седум години од 2011- 2017 година, како најголем перинатален и неонатален центар во државата, каде се третираат ризични и комплицирани бремености, породувања и се спроведува грижа за новородените со компликации од целата држава.

МАТЕРИЈАЛИ И МЕТОДОЛОГИЈА

Анализата за феталниот, неонаталниот и перинаталниот морталитет на У ГАК-Скопје во период од 7 години, од 2011-2017 година, е пресечна ретроспективна анализа, за која податоците се обезбедени од Дата базата на УГАК- Скопје и од историите на породените мајки и новородените кои се третирани на Одделот за Интензивна неонатална нега. Целта е да се прикаже застапеноста и развојната тенденција (тренд) на мртвородените новородени, перинаталниот морталитет и неонаталната смртност кај новородените во периодот 2011 – 2017 година. Обработени се новородените, мртвородени и живородени на УГАК- Скопје, или породени после 22 г.с. од бременоста и со породилна тежина поголема од 500 гр., на илјада новородени. Пресметана е стапката на феталниот, раниот и касен неонатален морталитет, како и перинаталниот морталитет и нивното движење во период од седум години, поединечно за секоја година посебно и збирно за сите години заедно.

Инклузиони критериуми беа:

-фетално, неонатално и перинатално починати новородени на УГАК- Скопје, со родилна тежина над 500 гр. и навршена 22 г.с. од бременоста при породувањето;

Ексклузиони критериуми:

-новородени родени вон У ГАК-Скопје и во домашни услови;

-новородени постнеонатално починати после 28 дена од породување;

Резултатите се табеларно и графички прикажани.

РЕЗУЛТАТИ

Во периодот од 2011- 2017 година на У ГАК- Скопје, родени се вкупно 37381 новороденче. Од нив 36706 се живородени новороденчиња а останатите 675 новороденчиња се породени како мртвородени. Вкупната стапката на феталниот морталитет или мртвородени за овие 7 години изнесува 18,06 ‰ или 675 мртвородени новороденчиња, од вкупната

бројка на новородени. Најниска стапка на фетален морталитет е забележан во 2012 година од 12,62 ‰ или 63 мртвородени новороденчиња. Највисока стапка на фетален морталитет има во 2016 година од 20,86 ‰ или 116 мртвородени, од вкупната бројка на новородени, породени на У ГАК- Скопје (Табела 1).

Табела 1. Вкупно новородени и мртвородени / У ГАК – Скопје / 2011 – 2017 година

Година	2011	2012	2013	2014	2015	2016	2017	Вкупно
Вкупно новородени	4984	4993	5714	5737	5740	5561	4652	37381
Фетално починати	99	63	101	105	96	116	95	675
Фетален морталитет	19,86‰	12,62‰	17,67‰	18,30‰	16,72‰	20,86‰	20,4‰	18,06‰

Трендот на феталниот морталитет во овие седум години на У ГАК- Скопје, покажува тенденција на пораст и зголемување на бројот на мртвородени новородени (Графикон 1).

Графикон 1. Тренд на фетален морталитет на У ГАК- Скопје од 2011 – 2017 г.

Во периодот од 2011-2017 година на Универзитетската клиника за гинекологија и акушерство- Скопје, биле регистрирани вкупно 36706 живородени новороденчиња. Во истиот период од седум години, на одделот за Интензивна нега на новородените на У ГАК-Скопје починале 912 новородени во неонаталниот период од 0-28 дена по породувањето, што ја дава бројката од 24,85‰, или 24,8 починати новородени на илјада живородени бебиња. Најниска стапка на смртност на новороденчиња што починале во неонаталниот период (0-28 дена), е регистрирана во 2015 година од 17,2 ‰, додека највисока стапка на смртност на новороденчиња кои починале во неонаталниот период од (0-28 дена), е регистрирана во 2017 година од 34 ‰, или 34 починати новородени во неонаталниот период од 0-28 дена по породувањето (Табела 2).

Табела 2. Неонатален морталитет / УГАК – Скопје / 2011 – 2017 година

Година	2011	2012	2013	2014	2015	2016	2017	Вкупно
Вкупно живородени	4885	4930	5613	5632	5644	5445	4557	36706
Починати до 7 дена	90 18,42‰	71 14,4‰	94 16,75‰	105 18,64‰	75 13,29‰	143 26,26‰	130 28,53‰	708 19,29‰
Починати 8-28 дена	25 5,12‰	38 7,7‰	29 5,17‰	30 5,33‰	22 3,9‰	35 6,43‰	25 5,49‰	204 5,56‰
Неонатален морталитет	115 23,54‰	109 22,11‰	123 21,91‰	135 24‰	97 17,2‰	178 32,7‰	155 34‰	912 24,85‰

Најголема е смртноста кај новородените до седмиот ден по породувањето, или во раниот неонатален период, која сочинува 3/4 од вкупниот неонатален морталитет. Таа изнесува 19,29 ‰ или 708 починати новороденчиња во текот на овие седум години од 2011-2017 година. Касната стапка на неонатален морталитет од 8-28 ден по породувањето, изнесува 5,56 ‰, или 204 починати новороденчиња во касниот неонатален период по породувањето. Трендот или движењето на стапката на неонатланиот морталитет од 0-28 ден по породувањето на У ГАК- Скопје, во овој период од седум години 2011- 2017 година, покажува тенденција на пораст, која е прикажана во Табела 2 и во Графикон 2.

Графикон 2. Тренд на стапка на неонатален морталитет 0-28 ден/У ГАК- Скопје/2011 – 2017

Перинаталната смртност во перинаталниот период, кој го опфаќа морталитетот или смртноста на сите мртвородени фетуси и починатите живородени новороденчиња до 7 от ден по породувањето, во овој период од седум години изнесува 37 ‰, или 1383 починати новородени во перинаталниот период на У ГАК- Скопје. Најниска стапка на перинатална смртност од 26,8 ‰ или 134 новороденчиња, е забележана во 2012 година. Највисока стапка на перинатална смртност од 48,4 ‰ или 225 починати новородени од вкупната

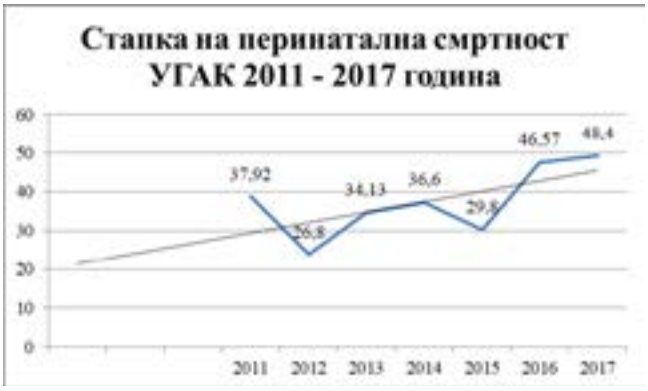
бројка на новородени, е забележана во 2017 година (Табела 3).

Табела 2. Перинатален морталитет / УГАК – Скопје / 2011 – 2017 година

Година	2011	2012	2013	2014	2015	2016	2017	Вкупно
Вкупно новородени	4984	4993	5714	5737	5740	5561	4652	37381
Фетален морталитет	99	63	101	105	96	116	95	675
Ран ННМ 0-7 дена	90	71	94	105	75	143	130	708
Перинатален морталитет	189 37,92‰	134 26,8‰	195 34,13‰	210 36,6‰	171 29,8‰	259 46,57‰	225 48,4‰	1383 37 ‰

Трендот или движењето на стапката на перинаталниот морталитет во овие седум години од 2011- 2017 година, покажува тенденција на пораст, исто како и феталниот и неонаталниот морталитет на У ГАК- Скопје (Графикон 3).

Графикон 3. Тренд на стапката на перинатален морталитет /У ГАК- Скопје/2011 – 2017



ДИСКУСИЈА

Стапките на хоспиталниот фетален, неонатален и перинатален морталитет на У ГАК- Скопје во период од седум години од 2011-2017 г., изнесуваат 18,06 ‰, 24,85 ‰ и 37 ‰ последователно. Тие се високи, повисоки одколку во земјите од опкружувањето, Балканските земји и во Европските земји. Во студии од соседството се изнесуваат многу пониски стапки на фетален морталитет 4- 5 ‰, неонатален 3-5 ‰ и перинатален 5-10 ‰ (17-20). Исто така трендовите на движење на феталниот, неонаталниот и перинаталниот морталитет во Европа и светот, покажуваат тенденција на намалување во периодот од 2011-2017 година, додека на У ГАК- Скопје трендот на феталниот, неонаталниот и перинаталниот морталитет покажуваат тенденција на пораст во овие седум години, од 2011-2017 година (17-20).

Заклучок

Стапката на феталниот, неонаталниот и перинаталниот морталитет на У ГАК-Скопје и во Македонија е доста висока, повисока отколку во земјите во нашето опкружување, Балканските земји и Европските земји. За негово намалување и доближување до земјите кои имаат ниска стапка на морталитет кај новородените, потребно е унапредување на грижата за бремените жени, зголемување на квалитетот на антенаталната заштита, подобрување на условите за живот и стандард на населението, ефикасна и соодветна грижа за новородените во перинаталните центри, згрижување на новородените и здравствено воспитување и просветување на населението. Поради тоа пожелно е да се одредат некои предиктори и состојби, кои се важни и може да влијаат на стапката на морталитетот кај новородените и неговото намалување, како што би можеле да бидат: причини од страна на мајката; причини од страна на новороденото; репродуктивни; социоекономски и системски причини кои потекнуваат од антенаталната и перинатална здравствена заштита. Сите овие причини заедно или одделно, ја покачуваат стапката на морталитет кај новородените.

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Original scientific paper

РЕДУКЦИЈА НА КАРДИЈАЛНИ НАСТАНИ ПРИ ПЕРКУТАНИ ИНТЕРВЕНЦИИ НА ДОЛГИ ЛЕЗИИ СО УПОТРЕБА НА ИВУЗ

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АБСТРАКТ

Вовед: Повеќе клинички студии покажаа дека Перкутаните Коронарни Интервенции (ПКИ) водени со Интраваскуларен Ултразвук (ИВУЗ) водат кон подобрување на краткорочните и долгорочните исходи во однос на ангиографски водените ПКИ.

Цели: Да се покаже зависноста на клиничките исходи од употреба на ИВУЗ при третман на долги лезии, споредено со ангиографски-водените интервенции,.

Материјал и методи: 60 пациенти со ангиографски докажана долга коронарна лезија (>20 mm), со дијаметар стеноза над 70% и со клиничка експресија, ќе бидат поделени во две групи: група со ангиографско-водено стентирање (n=30), и група со ИВУЗ-водено стентирање (n=30). И во двете групи ќе се употребуваат стентови обложени со зотаролимус (ZES). Кај пациентите со ангиографски-водено стентирање процедурален успех ќе биде дефиниран како <30% дијаметар стеноза споредена со дисталниот референтен лумен и отсуство на ангиографски евидентна дисекција. Кај ИВУЗ-воденатa група ќе се пристапи кон стент оптимизација според AVID критериумите. Примарни иследувани исходи ќе бидат мајорните несакани срцеви збиднувања (Major Adverse Cardiac Events - MACE): смрт, миокарден инфаркт и исхемија-водена реваскуларизација на целната лезија (TLR). Клиничкото следење на пациентите ќе содржи: интервју, физикален преглед, електрокардиографија (ЕКГ) на 30 дена, 6 месеци и 12 месеци по интервенцијата. Анализата на податоците изведена е во статистички програми Statistica 7.1 for Windows и SPSS Statistics 23.0

Резултати: Следење на пациентите од двете групи беше комплетирано на еден, шест и дванаесет месеци кај сите 60 пациенти (по 30 од двете групи). Посебно беа следени поединчени и збирни мајорни несакани кардијални настани (MACE). На контрола по еден и шест месеци примарните иследувани исходи (MACE) не покажаа значани статистички разлики повмеѓу двете групи. Резултатите по 12 месеци од интервенцијата во групата на ангиографски водено стентирање 3(10,00%) пациенти имале акутна стент тромбоза, 1(3,30%) пациент имал смртен исход, кај 2(6,70%) пациенти изведена е рестеноза, а 2(6,70%) пациенти имале акутен миокарден инфаркт, додека во групата на ИВУЗ-водено стентирање, само кај 1(3,30%) пациент регистриран е смртен исход. Статистички значајна разлика добивме и во резултатите од збирни мајорни несакани кардијални настани каде во групата на ангиографски водено стентирање се евидентирани 8(26,70%) пациенти кои имале збирни мајорни несакани срцеви збиднувања (MACE), додека во групата на ИВУЗ-водено стентирање само 1(3,30%) пациент со евидентирани збирни мајорни несакани срцеви збиднувања (MACE).

Заклучок: Од добиените резултати употребата на ИВУЗ во оптимизација на резултати при стентирање на долги лезии доведе до намалување на долгорочните мајорни несакани кардијални настани (MACE), споредбено со ангиографски-воденото стентирање. Репрезентативниот примерок кој беше иследуван е мал. За да се извлечат дефинитивни заклучоци по однос на претпоставените цели потребен е поголем репрезентативен примерок.

Клучни зборови: ИВУЗ, долги лезии, оптимизација

ВОВЕД

ИВУЗ претставува 3-димензионален модалитет за прикажување на слика кој обезбедува комплетна евалуација на ѕидот на коронарниот крвен сад. Оваа техника беше создадена за да ги надмине ограничувањата на ангиографската луминографија. ИВУЗ е посебно корисен во евалуација на лезии лоцирани на остиум, бифуркации и тортуозни сегменти, каде со ангиографија добиваме често преклопување на крвните садови, скратување и недостаток на оптимална слика, како и во случај на аневризматски проширувања, интралуминални дефекти во полнење, тромби, ексцентрични плаки итн. Оваа техника одигра клучна улога во полето на перкутаните коронарни интервенции, прикажувајќи ни ги недостатоците од аплицирањето на стентовите, што следствено водеше кон подобрување на техниките на стентирање. За истакнување е оптимизацијата на аплицирањето на стентови обложени со лек која ни ја овозможува ИВУЗ. Недоволната експанзија на стентовите обложени со лек, граничната рестеноза, резидуалните дисекции, пролапсот на плаките, фрактурата на стентот, инкомплетната апозиција на стентот и аневризмите поврзани со стентовите обложени со лек можат да се проценат со ИВУЗ. Употребата на ИВУЗ за справување со несаканите исходи кои потекнуваат од пропусти при аплицирањето на овие стентови, особено инстент рестенозата и DES тромбозата, драматично ги намали перипроцедуралните компликации.

Особено значајна примена ИВУЗ наоѓа во евалуација и третман на долги лезии. Во зависност од должината, лезиите можат да се поделат на три групи (1):

Кратки, фокални лезии: под 10 мм

Средни, тубуларни лезии: 10-20 мм

Долги, дифузни лезии: над 20 мм

Во ерата на перкутани коронарни интервенции, долгите (дифузни) лезии претставуваат поголем предизвик од фокалните поради повисокиот степен на несакани исходи (ин-стент рестенози и ин-стент тромбози). Неколку фактори го зголемуваат процедуралниот и пост-процедуралниот ризик кај долгите лезии:

При употреба на долги метални стентови (BMS), едноставно поголемата количина на метална конструкција на стентот доведува до поголем ризик од ин-стент рестеноза. Овој проблем е надминат со стентовите обложени со лек (DES) и биоресорптивните васкуларни скафолди (BVS).

Кај долгите лезии има поголема веројатност од решавање со преклопувачки (overlapping) стентови.

Има поголема веројатност при интервенцијата да се превиди некој сегмент од лезијата.

Поголема можност за погрешно поставување (maldeployment) на стентот.

Долгите лезии индицираат поголем атеросклеротски товар на организмот и повеќе несакани срцеви збиднувања.

Сепак, во поново време, со појавата на новите генерации на DES, како и употребата на ИВУЗ, резултатот од перкутаните коронарни интервенции на долгите лезии значително се подобри, за што сведочат бројни студии и мета-анализи кои покажуваат значително намалување на мајорните несакани срцеви збиднувања (Major Adverse Cardiac Events: MACE).(2,3) ИВУЗ може да се користи преинтервентно за проценка на должината на лезијата, како и во идентификација на проксимален и дистален референтен сегмент како зона на поставување (landing зона) за стентот. Сепак, неговата најзначајна улога е во постинтервентната употреба, при оптимизација на стентирањето.

Употреба на ИВУЗ оптимизација при стентирањето овозможува:

Проценка на покриеност на лезијата - присутен резидуален плак, дисекција, хематом или значаен пролапс на плакот;

Проценка на експанзија на стентот – постигнување на оптимална МСА според големината на крвниот сад и МСА во однос на дисталниот лумен на крвниот сад;

Намалување на мајорните несакани срцеви збиднувања (MACE) – Употребата на ИВУЗ го намалува бројот на пациенти со MACE: смртен исход, миокарден инфаркт, TLR.(4,5)

ЦЕЛИ НА ИСТРАЖУВАЊЕ

Примарна цел на истражувањето е да се компарира честотата во појава на збирните мајорните несакани срцеви збиднувања (MACE) помеѓу ИВУЗ-воденото и ангиографски воденото стентирање на долги коронарни лезии со употреба на зотаролимус - обложени стентови, во тек на едномесечно, шестмесечно и едногодишно следење на пациентите;

Материјали и методи

Изведена е проспективна студија во Специјална болница за превенција, третман и рехабилитација на за кардиоваскуларни заболувања "Св.Стефан" – Охрид во траење од една година.Во студијата ќе бидат вклучени 60 пациенти со ангиографски докажана коронарна артериска болест за перкутана коронарна интервенција: стентирање на долга коронарна лезија. Пациентите ќе бидат вклучени доколку имаат неостијална стеноза на коронарната артерија, поголема или еднаква на 20 mm во должина, со референтен дијаметар кој ќе дозволи имплантација на стентови со дијаметар ≥2.0 mm, без инволвираност на сигнификантна бочна гранка (дијаметар ≥2.0 mm). Исклучувачки критериуми ќе бидат: акутен миокарден инфаркт, кардиоген шок, ЛВЕФ<25%, напредната тешка валвуларна мана, напредната/тешка хронична бубрежна болест, крвавечки улкус на ГИТ, постоење на тотална оклузија, TIMI <3 по стентирањето, постоење на контраиндикација за користење на двојна антиагрегациона терапија (ацетил-салицилна киселина+клопидогрел). Пациентите ќе бидат поделени во две групи: I група: ангиографски-водено стентирање и II група: ИВУЗ-водено стентирање. Од нив 30 пациенти ќе бидат со ангиографски-водено стентирање и 30 со ИВУЗ-водено стентирање.

Иследувани беа елективни пациенти со стабилна ангина и пациенти со акутен коронарен синдром без СТ елевација, кај кои ангиографски е докажана КАБ (дијаметар стеноза на главната коронарна гранка над 70%), на бифуркации кои не го вклучуваат левото главно коронарно стебло, а се со клиничка експресија или јасно позитивен тест на оптеретување. Пациентите беа поделени во две групи: група со ангиографско-водено стентирање (n=30), и група со ИВУЗ-водено стентирање (n=30). И кај двете групи пред интервенцијата беше применувана квантитативна коронарна анализа (QCA) за мерење на должината на лезијата на главната гранка, проксималниот и дисталниот референтен лумен на истата гранка, како и луменот на бочната гранка. И во двете групи се употребуваа стентови обложени со зотаролимус (ZES). Кај пациентите со ангиографски-водено стентирање, процедурален успех беше дефиниран како <30% дијаметар стеноза споредена со дисталниот референтен лумен и отсуство на ангиографски евидентна дисекција. Кај ИВУЗ-воденатa групата се пристапуваше кон стент оптимизација според AVID критериумите. Двојна антиагрегациона терапија беше препорачана кај сите пациенти вклучени во студијата во траење од 12 месеци. Примарни иследувани исходи беа мајорните несакани кардијални настани (MACE): смрт, миокарден инфаркт и исхемија-водена реваскуларизација на целната лезија (TLR).

СТАТИСТКА

Анализата на податоците изведена е во статистички програми Statistica 7.1 for Windows и SPSS Statistics 23.0

РЕЗУЛТАТИ

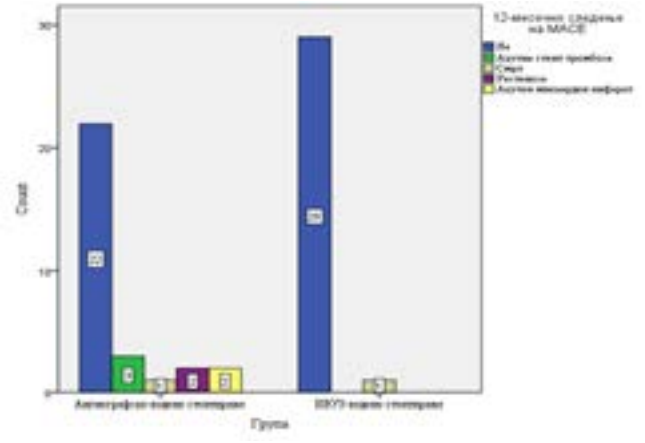
Податоците кои се однесуваат на 1-месечно следење на MACE кај стентираните пациенти Од 30 пациенти кај кои е изведено ангиографски-водено стентирање, кај 28(93,30%) не се регистрирани мајорни несакани кардиоваскуларни настани (MACE), а 2(6,70%) имале акутна стент тромбоза, додека во групата на ИВУЗ-водено стентирање, кај 30(100,00%) не се регистрирани мајорни несакани кардиоваскуларни настани (MACE). Во прикажаната кростабулација во релацијата група * 1-месечно следење на MACE за Fisher's Exact Test p>0,05(p=0,49) / Monte Carlo Exact Sig. (2-sided) нема значајна разлика помеѓу двете групи на стентирани пациенти во однос на 1-месечно следење на MACE. Резултатите од 1-месечно следење на збирните мајорните несакани срцеви збиднувања (MACE) за Fisher's Exact Test p>0,05(p=0,49) / Monte Carlo Exact Sig. (2-sided) се без значајна разлика помеѓу двете групи на стентирани пациенти, односно од 30 пациенти кај кои е изведено ангиографски-водено стентирање, кај 28(93,30%) не се регистрирани збирни мајорни несакани срцеви збиднувања (MACE), а 2(6,70%) пациенти имале збирни мајорни несакани срцеви збиднувања (MACE), додека во групата на ИВУЗ-водено стентирање, кај 30(100,00%) пациенти не се регистрирани збирни мајорни несакани срцеви збиднувања (MACE). На направена шест месечна контрола од 30 пациенти кај кои е изведено ангиографски-водено стентирање, кај 25(83,30%) не се регистрирани мајорни несакани кардиоваскуларни настани (MACE), 2(6,70%) имале акутна стент тромбоза, 1(3,30%) пациент имал смртен исход, кај 1(3,30%) пациент најдена е рестеноза а 1(3,30%) пациент имал акутен миокарден инфаркт, додека во групата на ИВУЗ-водено стентирање, кај 29(96,70%) не се регистрирани мајорни несакани кардиоваскуларни настани (MACE), а 1(3,30%) пациент имал смртен исход. Во прикажаната кростабулација во релацијата група

* 6-месечно следење на MACE за Fisher's Exact Test= 4,031 и p>0,05(p=0,357) / Monte Carlo Sig. (2-sided) / 0,344-0,369 / нема значајна разлика помеѓу двете групи на стентирани пациенти во однос на 6-месечно следење на MACE. Во евиденцијата на збирни мајорни несакани збиднувања (MACE) на шест месечна контрола во групата на ангиографски-водено стентирање, кај 25(83,30%) не се регистрирани збирни мајорни несакани срцеви збиднувања (MACE), а 5(16,70%) пациенти имале збирни мајорни несакани срцеви збиднувања (MACE) и во групата на ИВУЗ-водено стентирање, кај 29(96,70%) не се регистрирани збирни мајорни несакани срцеви збиднувања (MACE), а 1(3,30%) пациент имал збирни мајорни несакани срцеви збиднувања (MACE). И во оваа кростабулација за Fisher's Exact Test p>0,05(p=0,20) / Monte Carlo Exact Sig. (2-sided) нема значајна разлика помеѓу двете групи на стентирани пациенти во однос на збирните мајорните несакани срцеви збиднувања MACE. Во податоците за следење на MACE по 12 месеци од интервенцијата во групата на ангиографски-водено стентирање, кај 22(73,30%) не се регистрирани мајорни несакани кардиоваскуларни настани (MACE), 3(10,00%) имале акутна стент тромбоза, 1(3,30%) пациент имал смртен исход, кај 2(6,70%) пациенти изведена е рестеноза, а 2(6,70%) пациенти имале акутен миокарден инфаркт, додека во групата на ИВУЗ-водено стентирање, кај 29(96,70%) не се регистрирани мајорни несакани кардиоваскуларни настани (MACE), а кај 1(3,30%) пациент регистриран е смртен исход. Во прикажаната кростабулација во релацијата група * 12-месечно следење на MACE за Fisher's Exact Test= 7,052 и p<0,05(p=0,045) / Monte Carlo Sig.(2-sided) / 0,040-0,051 / постои значајна разлика помеѓу двете групи на стентирани пациенти во однос на 12-месечно следење на MACE.

Табела 1. 12-месечно следење на MACE

	12-месечно следење на MACE	Total						
	Не	Акутна стент тромбоза	Смрт	Рестеноза	Акутен миокарден инфаркт			
Група	Ангиографско-водено стентирање	Count	22	3	1	2	2	30
		%	73,3%	10,0%	3,3%	6,7%	6,7%	100,0%
	ИВУЗ-водено стентирање	Count	29	0	1	0	0	30
		%	96,7%	0,0%	3,3%	0,0%	0,0%	100,0%
Total		Count	51	3	2	2	2	60
		%	85,0%	5,0%	3,3%	3,3%	3,3%	100,0%

Графикон 1: 12-месечно следење на MACE

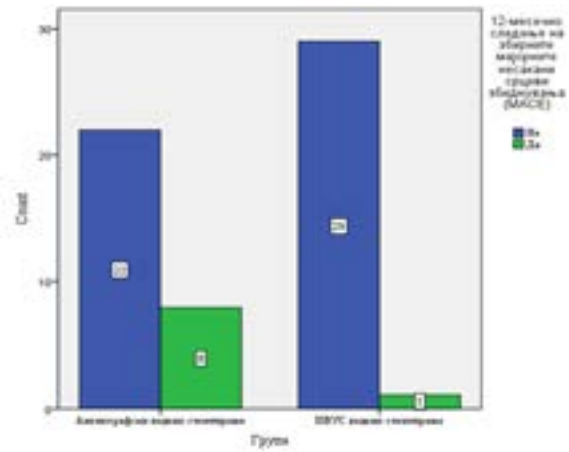


Во однос на 12-месечно следење на збирни мајорни несакани срцеви збиднувања од 30 пациенти кај кои е изведено ангиографски-водено стентирање, кај 22(73,30%) не се регистрирани збирни мајорни несакани срцеви збиднувања (MACE), а 8(26,70%) пациенти имале збирни мајорни несакани срцеви збиднувања (MACE), додека во групата на ИВУЗ-водено стентирање, кај 29(96,70%) не се регистрирани збирни мајорни несакани срцеви збиднувања (MACE), а 1(3,30%) пациент имал збирни мајорни несакани срцеви збиднувања (MACE) што резултира со значајна разлика помеѓу двете групи на стентирани пациенти во кростабулација во релацијата група * 12-месечно следење на збирни мајорни несакани срцеви збиднувања (MACE) за Fisher's Exact Test p<0,05(p=0,03) / Monte Carlo Exact Sig. (2-sided).

Табела 2: 12-месечно следење на збирните мајорните несакани срцеви збиднувања (MACE)

	12-месечно следење на збирните мајорните несакани срцеви збиднувања (MACE)	Total			
	Не	Да			
Група	Ангиографски водено стентирање	Count	22	8	30
		%	73,3%	26,7%	100,0%
	ИВУС водено стентирање	Count	29	1	30
		%	96,7%	3,3%	100,0%
	Total	Count	51	9	60
		%	85,0%	15,0%	100,0%

Графикон 2: 12-месечно следење на збирните мајорните несакани срцеви збиднувања (MACE)



ДИСКУСИЈА

Споредбата на резултатите помеѓу групата на ИВУС водена интервенција кај долги лезии, во споредба со групата на пациенти со ангиографски водено стентирње, резултираше со значително пониска стапка на збирни мајорни несакани срцеви настани 1 година по интервенцијата. Нашите резултати ја потврдија предноста на ИВУЗ-воденото стентирање на долги лезии со употреба на зотаролимус-обложени стентови во однос на ангиографски воденото стентирање, потенцирајќи ја зависноста на раните и доцните клинички исходи од употребата на ИВУЗ, споредено со коронарна ангиографија. Добиениот статистички значајно помал број на мајорни несакани срцеви збиднувања, вклчувајќи ги стент тромбоза (6), рестеноза (7), реваскуларизација на целна лезија, реваскуларизација на целна артерија поединечно, миокарден инфаркт и смрт (8) во групата на ИВУЗ водена ангиографија корелира со резултатите од IVUS-XPL студијата (9), која докажа дека користењето на ИВУЗ во стентирањето на долги лезии за два пати ја намалува појавата на несакани мајорни кардијални настани (MACE). Во групата на ИВУЗ-водено стентирање се доби подобро време на преживување без несакани настани, во споредба со групата на ангиографски воденото стентирање и се обезбедија корисни информации што доведуват до оптимално ширење на стентот за надминување на потенцијалните несакани настани кои би ги очекувале при имплантација на подолг ДЕС (10).

ЗАКЛУЧОК

Од резултатите добиени во нашето иследување може да се заклучи дека употребата на ИВУЗ во оптимизацијата на резултати при стентирање на бифуркациони лезии е следена со намалување на едно-годишните мајорни несакани кардијални настани (MACE) споредбено со ангиографски-воденото стентирање. Но секако, потребен е поголем репрезентативен примерок и кај двете иследувани групи за да се извлечат дефинитивни заклучоци по однос на претпоставените цели.

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Original scientific paper

NDIKIMI I KONTROLLIT TË DIABETIT NË CILËSINË E JETËS SI DHE NË PARANDALIMIN E SHFAQJES SË KOMPLIKIMEVE NGA DIABETIS

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ABSTRAKT

Diabeti paraqet një sfidë sistemet shëndetësore në botën perendimore dhe shtetet në zhvillim, kryesisht për shkak atë rritjes së obesitetit, popullatës së moshuar dhe mënyrës sedentare të jetesës. Ndryshimet e stilit të jetesës përfshijnë kujdes në dietë, përdorim të terapisë dhe monitorim të niveleve të glikemisë në kushte shtëpiake.

Qëllimi: Ky punim ka për qëllim të studioj faktorët që ndikojnë në cilësinë e jetesës së personave diabetik dhe komplikimeve të tij.

Materiali dhe metodat: Për qëllimin e studimit tonë kemi zgjedhur pyetësor për vlerësimin e kualitetit të jetës tek personat diabetik.. Pyetësori është aplikuar në mostër prej 79 pacientëve diabetik nga qyteti i Tetovës dhe fshatrave për rreth.

Rezultatet: Pasi që shkaktar kryesor i morbiditetit dhe mortalitetit të sëmundjes janë komplikimet e diabetit, Mesatarisht shumë ka ndikuar zhvillimi i komplikimeve të diabetit në kualitetin e jetës së këtyre pacientëve.

Përfundimi: Rezultatet e studimit tonë janë në përputhje me rezultatet e punimeve të mëparshme në këtë sferë. Sikurse edhe tek studimet tjera edhe tek studimi ynë diabeti melitus dhe në veçanti komplikimet e tij kanë ndikim të madh në kualitetin e jetesës së pacientëve diabetik.

Ky ndikim nuk ka dallim statistikor në mes popullacioneve të ndryshme demografike.

Fjalët kyçe: diabeti mellitus, faktorët e rrezikut, komplikime,

HYRJE

Diabeti paraqet një sfidë sistemet shëndetësore në botën perendimore dhe shtetet në zhvillim, kryesisht për shkak atë rritjes së obesitetit, popullatës së moshuar dhe mënyrës sedentare të jetesës. Paraqet një gjendje kronike që vendos kufizime serioze në aktivitetet e përditshme të pacientit. Duhet një edukim i zgjeruar dhe ndryshim sjelljesh për të menaxhuar këtë gjendje. Ndryshimet e stilit të jetesës përfshijnë kujdes në dietë, përdorim të terapisë dhe monitorim të niveleve të glikemisë në kushte shtëpiake. Pothuajse gjysma e pacientëve të diagnostikuar nuk arrijnë të mbajnë nivele të kënaqshme të glikemisë edhe përkundër ekzistimit të trajtimit efektiv të kësaj sëmundje. Si pasojë miliona njerëz me diabet janë me rrezik të rritur të zhvillimit të komplikimeve serioze të sëmundjes. Rreziku i komplikimeve është i ndërlidhur poashtu me faktorin gjenetik. Komplikimet e ndërlidhura me diabetin janë shkak kryesor morbiditetit, mortalitetit dhe kostos së kujdesit shëndetësor. Ato mund të ndahen në dy kategori: komplikime mikrovaskulare që përfshijnë neuropati, retinopati dhe nefropati si dhe komplikime makrovaskulare si insulti cerebrovaskular, sëmundjet kardiovaskulare dhe sëmundjet vaskulare periferike. Për shembull, retinopatia diabetike rezulton në humbjen e të pamurit. Vëmendje kanë edhe efektet makrovaskulare që rrisin rrezikun kardiak dhe cerebrovaskular. Shoqata Amerikane e Diabetit ka përllogaritur se përafërsisht 75-80% të pacientëve diabetik do të vdesin si rezultat i komplikimeve makrovaskulare të sëmundjes kryesore. Komplikimet e lartëpërmendura jo vetëm që shkaktojnë paaftësi fizike dhe shpenzime plotësuese, poashtu kompromitojnë kualitetin e jetës. Incidenca e komplikimeve diabetike është vërtetuar se luan

rol signifikant në kualitetin e jetës bazuar në shumë studime. Kontrolli i glikemisë në kualitetin e jetës në afat të shkurt kohor ende mbetet kontravers. Pasi që shumica e pacientëve mbeten të padiagnostifikuar për disa vite para se simptomet të paraqiten, disa prej tyre do të kenë tani më komplikime nga diabeti në momentin e diagnostifikimit të diabetit.

QËLLIMI

Diabeti si sëmundje padyshim që ndikon në stilin e jetesës. Ashtu siç kalojnë vitet me diabet ashtu edhe kualiteti i jetës së pacientëve është më i ulur. Poashtu prezenca e më tepër komorbiditeteve vështirëson kryerjen e obligimeve të përditsshme të pacientëve diabetik.

Ky punim ka për qëllim të studioj faktorët që ndikojnë në cilësinë e jetesës së personave diabetik dhe komplikimeve të tij.

MATERIALI DHE METODAT

Për vlerësimin e kualitetit jetesës është shfaqur nevoja për zhvillimin e veglave psikometrike për të vlerësuar kualitetin e jetës. Kështu, janë zhvilluar pyetësor të ndryshëm për të bërë matje të tilla. Sipas Snock dhe të tjerë. “nuk kemi standard të artë për vlerësimin e përgjithshëm të kualitetit të jetës, por duhen të bëhen tentime për zhvillim të testeve valide dhe të përshtatshme për popullacione të veçanta”.

Për qëllimin e studimit tonë kemi zgjedhur pyetësor për vlerësimin e kualitetit të jetës tek personat diabetik..

Pyetjet kanë qenë të formuluara në formën “Gjatë muajit të kaluar, sa shumë është ndikuar jeta juaj nga..?

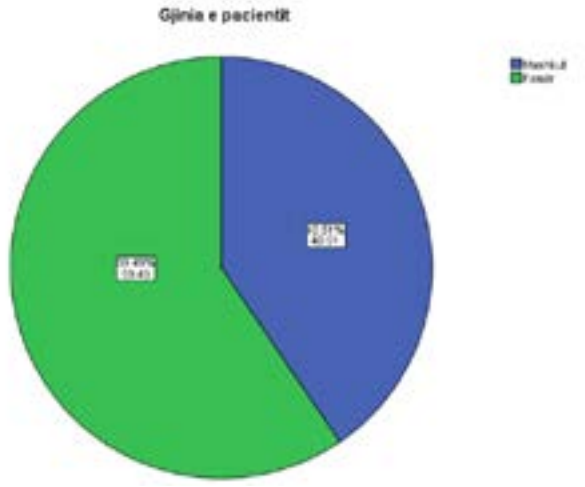
Pyetësori është aplikuar në mostër prej 79 pacientëve diabetik nga qyteti i Tetovës dhe fshatrave për rreth. Plotësimi i tij ka qenë anonim dhe pacientët e kanë plotësuar në kushte shtëpiake. Zgjedhja e pacientëve ka qenë tërësisht e rëndomtë.

Të dhënat janë përpunuar në programin statistikor IBM SPSS verzioni 25.

REZULTATET

Pacientët diabetik të mostrës kanë qenë përafërsisht me numra të përafërt të të dy gjinive tek mostra prej 79 pacientëve, meshkuj kanë qenë 32 (40,5%) ndërkaq femra 47 (59.5%).

Gjinia e pacientit					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Mashkull	32	40.5	40.5	40.5
	Femër	47	59.5	59.5	100.0
	Total	79	100.0	100.0	



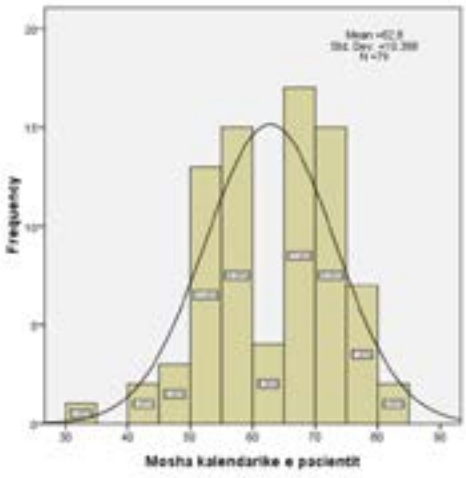
Pacientët e anketuar varësisht vendbanimit janë ndarë në pacient që jetojnë në vendbaim urban dhe rural. Kështu në vendbanim urban kanë qenë 36 (45.6%) ndërkaq rural 43 (54.4%).

Nga 79 të anketuarit, madje 64 (81%) kanë qenë të nacionalitetit shqiptar ndërkaq 15 (19%) kanë qenë maqedon.

Përdorues të alkoolit kanë qenë vetëm 2 (2.5%), ndërkaq 77 (97.5%) nuk kanë përdorur alkool.

Vendbanimi i përhershëm i pacientit					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Urban	36	45.6	45.6	45.6
	Rural	43	54.4	54.4	100.0
	Total	79	100.0	100.0	

Pacientët kanë qenë të moshave të ndryshme edhe atë prej 31 vjeç deri në 84 vjeç. Mesatarja prej 62.8 vjeç ndërkaq moda e moshës ishte 68 vjeç.

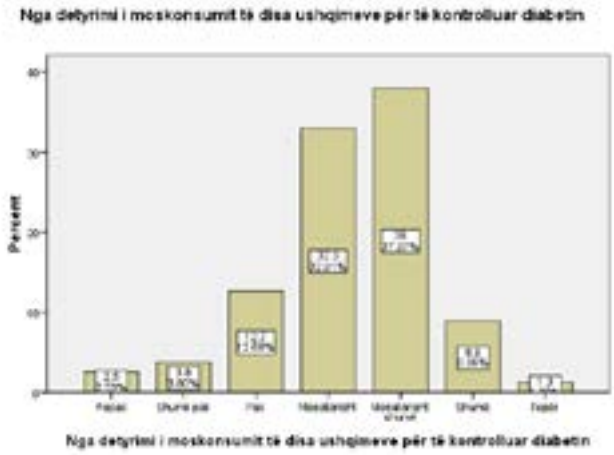


Në pyetjen sa shumë është ndikuar jeta juaj nga ndjekja e terapisë së përshkruar për diabetin.

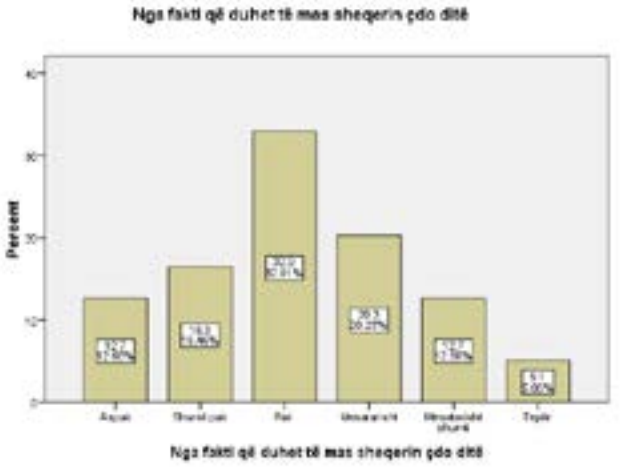
Shumica e pacientëve janë ndikuar mesatarisht.

Nga ndjekja e terapisë së përshkruar nga mjeku për diabetin					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Aspak	5	6.3	6.3	6.3
	Shumë pak	6	7.6	7.6	13.9
	Pak	18	22.8	22.8	36.7
	Mesatarisht	23	29.1	29.1	65.8
	Mesatarisht shumë	15	19.0	19.0	84.8
	Shumë	4	5.1	5.1	89.9
	Tepër	8	10.1	10.1	100.0
	Total	79	100.0	100.0	

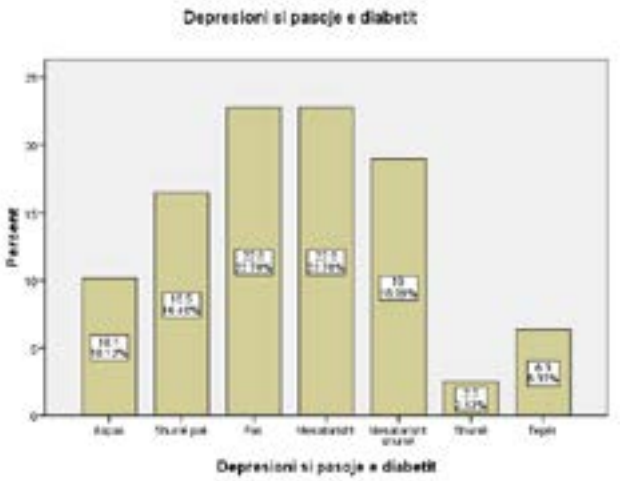
Nga detyrimi i moskonsumit të disa ushqimeve për të kontrolluar diabetin					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Aspak	2	2.5	2.5	2.5
	Shumë pak	3	3.8	3.8	6.3
	Pak	10	12.7	12.7	19.0
	Mesatarisht	26	32.9	32.9	51.9
	Mesatarisht shumë	30	38.0	38.0	89.9
	Shumë	7	8.9	8.9	98.7
	Tepër	1	1.3	1.3	100.0
	Total	79	100.0	100.0	



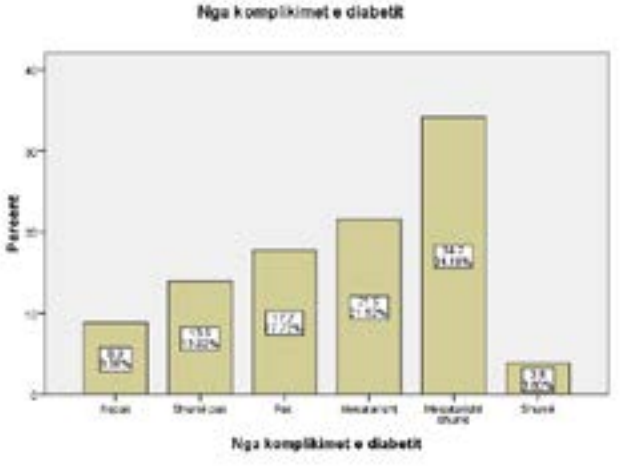
Nga fakti që duhet të mas sheqerin çdo ditë					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Aspak	10	12.7	12.7	12.7
	Shumë pak	13	16.5	16.5	29.1
	Pak	26	32.9	32.9	62.0
	Mesatarisht	16	20.3	20.3	82.3
	Mesatarisht shumë	10	12.7	12.7	94.9
	Tepër	4	5.1	5.1	100.0
	Total	79	100.0	100.0	



Depresioni si pasoje e diabetit					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Aspak	8	10.1	10.1	10.1
	Shumë pak	13	16.5	16.5	26.6
	Pak	18	22.8	22.8	49.4
	Mesatarisht	18	22.8	22.8	72.2
	Mesatarisht shumë	15	19.0	19.0	91.1
	Shumë	2	2.5	2.5	93.7
	Tepër	5	6.3	6.3	100.0
	Total	79	100.0	100.0	



Nga komplikimet e diabetit					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Aspak	7	8.9	8.9	8.9
	Shumë pak	11	13.9	13.9	22.8
	Pak	14	17.7	17.7	40.5
	Mesatarisht	17	21.5	21.5	62.0
	Mesatarisht shumë	27	34.2	34.2	96.2
	Shumë	3	3.8	3.8	100.0
	Total	79	100.0	100.0	



REZULTATET

Ky studim ka përfshirë pacient të të dy gjinive, të grupmoshave të ndryshme, etnive të ndryshme si dhe të vendmanimeve të ndryshme. Kryesisht nuk ekzistojnë dallime demografike në ndikimin e stilit të jetës nga diabeti mellitus.

Shumica e pjesëmarrësve në studim nuk janë konsumues të alkoolit dhe për këtë shkak përdorimi i alkoolit nuk pati ndonjë rëndësi statistikore.

Më shumë se gjysma e të anketuarve (57%) janë deklaruar se kanë limitime në konsumimin e ëmbëlsirave në muajin e fundit.

Ndjekja e terapisë së diabetit ka pasur ndikim mesatarisht shumë tek pacientët diabetik. Veçanarisht është i theksuar tek pacientët që janë me terapi me insulinë.

Detyrimi i moskonsumit të ushqimeve mesatarisht shumë ndikon në stilin e jetesës së këtyre pacientëve. Vështirësia për të mbajtur një dietë të mirë, ndikon në aspektin ekonomik të këtyre pacientëve.

Fakti që duhet matur sheqerin çdo ditë ka ndikuar shumë pak. Kjo mund të jetë nga shkaku se shumë pak pacientë nga të anketuarit tonë mund të kenë mundësi që të bëjnë matjen e diabetit në kushte shtëpiake dhe se shumica e tyre bëjnë matjen e nivelit të glikemisë vetëm gjatë kontrolleve rutine mjekësore.

Pasi që shkaktar kryesor i morbiditetit dhe mortalitetit të sëmundjes janë komplikimet e diabetit, mesatarisht shumë ka ndikuar zhvillimi i komplikimeve të diabetit në kualitetin e jetës së këtyre pacientëve.

PËRFUNDIMI

Rezultatet e studimit tonë janë në përputhje me rezultatet e punimeve të mëparshme në këtë sferë. Sikurse edhe tek studimet tjera edhe tek studimi ynë diabeti melitus dhe në veçanti komplikimet e tij kanë ndikim të madh në kualitetin e jetesës së pacientëve diabetik.

Ky ndikim nuk ka dallim statistikor në mes popullacioneve të ndryshme demografike.

Është shumë me rëndësi përfshirja e nivele të ndryshme të sistemit shëndetësor dhe edukim i vazhdueshëm i pacientëve për mbajtje të niveleve normale të glikemisë, me anë të dietave të ndryshme si dhe të gjithë terapinë aktuale që ekziston për të parandaluar zhvillimin e komplikimeve të sëmundjes.

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Original scientific paper

INFLUENCE OF GENDER, INHERITANCE FACTOR AND AGE IN GLAUCOMA OCCURENCE AND PROGRESS

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ABSTRACT

INTRODUCTION: Glaucoma, one of the leading causes of irreversible blindness in the elderly population worldwide, is a progressive optic neuropathy. Risk factors for glaucoma have been explored and published in many studies. Elevated intraocular pressure (IOP) is, as is well known, the highest risk for glaucoma. Studies show that reducing IOP reduces the risk of developing the disease or slows the progression of glaucoma. There is growing evidence that other risk factors such as age, sex, race, refraction, heredity, and systemic diseases play a role in the pathogenesis of glaucoma.

The risk factors for glaucoma can be divided into systemic and local. Systemic risk factors are blood pressure: hypotension or hypertension, vasospasm, diabetes, chronic heart disease, hypercholesterolemia, thyroid disease, etc. Local risk factors are parapapillary atrophy, intraocular pressure, papillary excavation, certain diseases of the anterior or posterior segment of the eye, central corneal thickness, fluctuations in IOP, etc.

RESOURCES AND METHODS: A case-control study was performed, which included patients aged 25 to 70.The study was conducted at the Clinic for Eye Diseases, in Skopje, in the Glaucoma Cabinet, in the period from 2015-2019.The study included 100 patients, who were divided into two groups. About the patients in the study, a comprehensive medical history was made, as well as a history of the condition, age, sex, family history, hereditary factor, and whether the patient was using anti glaucoma therapy.

RESULTS: In determining the significance of the contribution to the prediction of glaucoma, it was found that the age of the patients had the greatest influence (Wald = 5.05 / p <0.05 (p = 0.025), followed by the family history (Wald = 0.04 / p> 0 , 05 (p = 0.84) and the weakest is the influence of the sex of the patients (Wald = 0.01 / p> 0.05 (p = 0.94)

KEY WORDS:glaucoma,gender,age,inheritance factor

INTRODUCTION

Glaucoma, one of the leading causes of irreversible blindness in the elderly population worldwide, is a progressive optic neuropathy (1).

According to the European Glaucoma Association, glaucoma is a group of chronic progressive neuropathies most commonly characterized by morphological changes in the papillae of the optic nerve and retinal nerve fibers, without the presence of other eye diseases or congenital anomalies.

According to the American Academy of Ophthalmology, glaucoma is a group of conditions characterized by damage to the optic nerve and loss of nerve axons, through atrophy of ganglion cells and preservation of the neurofibrillary layer of the retina.

Because glaucoma ranks second on the list of ophthalmic diseases with the highest morbidity, there are many definitions that characterize its importance in the scientific world and in seeking opportunities for its treatment, and thus reducing the percentage of blindness that glaucoma can cause (2).

The global prevalence of glaucoma worldwide is expected to reach 80 million by 2020 (3).

According to Burr (4), population screening for glaucoma is not expensive, screening for risk factors is more expensive already, but it is especially important for the prognosis and choice of therapy. In the population with diabetes, heart disease, and heredity, screening has great effects on saving finances for the country up to over 40%.

The pathogenesis of glaucoma is still poorly understood. Increased intraocular pressure may be caused by increased ocular water production or decreased ocular leakage. There are several major theories about the initial mechanisms of POAG: "mechanical theory", "vascular theory", "excitotoxic theory" and "genetic theory".

The mechanical theory explains that increased IOP compresses the structures around the PNO, and disrupts axoplasmic nerve fiber transport. This leads to the death of retinal ganglion cells and their axons, resulting in thinning of the neuroretinal sheath and excavation of PNO (5). Based on this theory, lowering IOP would be an effective treatment to prevent further damage to the optic nerve (6).

Experience to date has shown that pharmacological or surgical interventions to reduce IOP slow the progression of visual field loss.

According to the vascular theory, glaucomatous optic neuropathy is the result of a reduced blood supply as a result of elevated IOP or certain systemic diseases such as increased blood pressure or vasospasm (7). Numerous scientific studies have found a correlation between arterial hypotension and increased IOP. Low blood pressure and increased IOP are thought to affect papillary vascularization and thus cause ischemia (8).

According to the excitotoxic theory, which is the most advanced, the etiopathogenesis of glaucoma is elaborated through elevated glutamate levels, which have been shown to be intravitreal and intraretinal. Numerous studies have confirmed the toxic effects of glutamate on ganglion cells. Glutamate binds to a specific receptor, through which ion channel calcium ions enter. If a certain level is exceeded, the uptake of calcium ions initiates a cascade of processes that result in cell death.

During the last decade, intensive work has been done on the study of the process of apoptosis and its increasingly reliable role as a mechanism for cell death in glaucomatous eyes. A number of authors and studies have identified various processes that speak in favor of apoptosis and are trigger mechanisms for the induction of programmed cell death, deficiency of trophic factors, ischemia, increased concentrations of glutamate, and disturbed nitric oxide metabolism (8).

The genetic theory is based on the hypothesis that mutations in certain gene loci may be responsible for some pathogenic mechanisms in glaucoma. In this context, family and racial predisposition could be due to genetic aberrations. The genetic theory supports the potential autoimmune pathogenesis of glaucoma (9,10,11).

The disease has, if left untreated or resistant to therapy, usually a bad ending with the loss of ganglion cells, gradual loss of vision and blindness.

Risk factors for glaucoma have been explored and published in many studies. Elevated intraocular pressure (IOP) is, as is well known, the highest risk for glaucoma (12). Studies show that reducing IOP reduces the risk of developing the disease or slows the progression of glaucoma (13). There is growing evidence that other risk factors such as age, sex, race, refraction, heredity, and systemic diseases play a role in the pathogenesis of glaucoma.

The risk factors for glaucoma can be divided into systemic and local. Systemic risk factors are blood pressure: hypotension or hypertension, vasospasm, diabetes, chronic heart disease, hypercholesterolemia, thyroid disease, etc. Local risk factors are parapapillary atrophy, intraocular pressure, papillary excavation, certain diseases of the anterior or posterior segment of the eye, central corneal thickness, fluctuations in IOP, etc.

The aim of the study is to determine the influence of hereditary factor and age on the occurrence and progression of glaucoma.

MATERILAS AND METHODS

A retrospective case-control study was performed, which included patients aged 25 to 70 years.

The study was conducted at the Clinic for Ophthalmological Clinic in Skopje, in the Glaucoma Cabinet, in the period from 2015-2019.

The study included 100 patients, who were divided into two groups:

The first group of respondents (group 1 / Patients with primary open-angle glaucoma) included: 60 patients diagnosed with glaucoma. Entry criteria for this group were the following:

- increased intraocular pressure (IOP) -over 24mmHg

without therapy;

- changes of the optic nerve papilla (PNO);
- vision field defect;
- anti glaucoma therapy.

The second group of respondents (group 2 / Control group) included: 40 patients without glaucoma. Entry criteria for this group were the following:

- patients without glaucoma;
- normal IOP;
- normal vision field;
- orderly finding of PNO (eyeball).

About the patients in the study, a comprehensive medical history was made, as well as a history of the condition, age, sex, family history, hereditary factor, and whether the patient was using anti glaucoma therapy.

The following statistical methods are used:

In the series with attributive features (systemic diseases) percentages of structure (%) are determined. Association & Differences - in attribute value series are tested with PearsonChi-Square / (p) and Fisher'sExactTest / MonteCarloSig primers. (2-sided) / (p). The predictive values of the analyzed risk factors for glaucoma prediction were analyzed using Univariate (Enter) and Multivariate Binary Logistic Regression Analysis (Wald, (Exp (B), 95% C.I., p) (Forward: Conditional).

Significance is determined by $p < 0.05$.

The data are presented in tabular and graphical form.

RESULTS

Prediction for glaucoma

1. Patient's age

Table 1 and Chart 1 show descriptive statistics of the age of patients.

The age of the patients varies in the interval 55.72 ±11.71 years, ±95.00% CI: 53.40-58.04; the minimum age is 28 years and the maximum age is 86 years.

Table 1. Age of patients

Variable	Valid N	Mean	Confidence -95,00%	Confidence +95,00%	Minimum	Maximum	Std. Dev.
Возраст	100	55,72	53,40	58,04	28	86	11,71

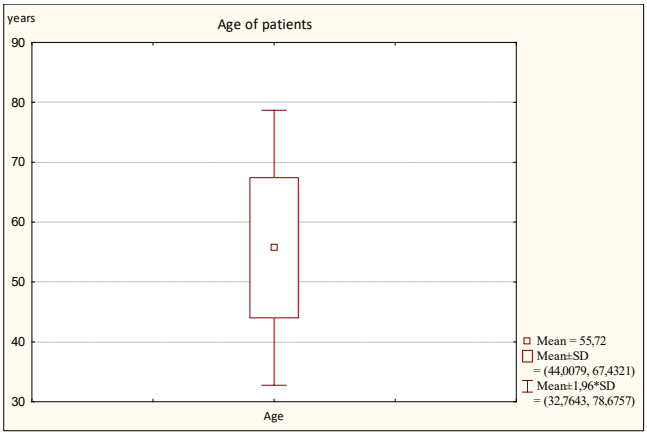

Chart 1

2. Gender of the respondents

Out of a total of 100 patients included in the study, 68 (68.00%) are women and 32 (32.00%) are men (Table 2 and Chart 2).

Table 2. Gender of the respondents

Category	Count	Cumulative Count	Percent	Cumulative Percent
Female	68	68	68,00	68,00
Male	32	100	32,00	100,00
Missing	0	100	0,00	100,00

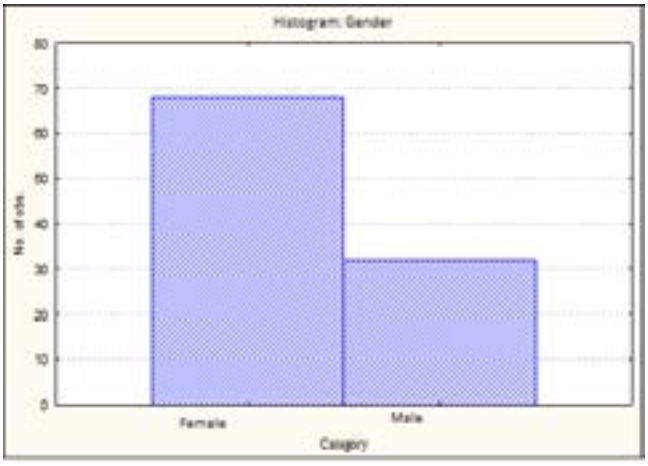

Chart 2

3. Family history

Out of a total of 100 patients included in the study, glaucoma was present in the family history in 25 (25.00%) patients and glaucoma was not present in the family history in 75 (75.00%) patients (Table 3 and Chart 3).

Table 3. Family history

Category	Count	Cumulative Count	Percent	Cumulative Percent
Inherited	75	75	75,00	75,00
Not Inherited	25	100	25,00	100,00
Missing	0	100	0,00	100,00

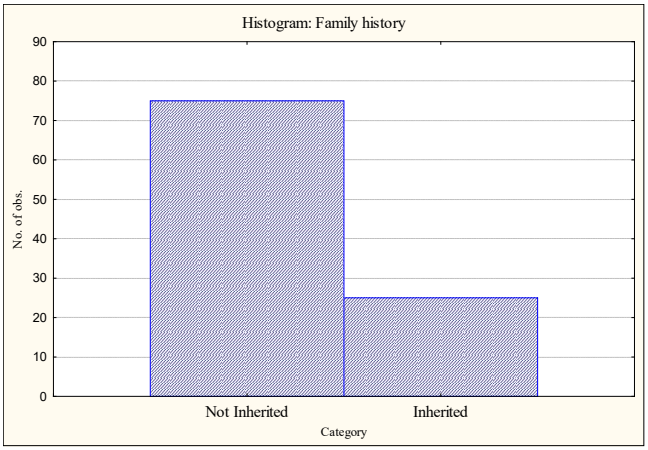

Chart 3

4. Glaucoma Prediction / Patient Age & Gender & Family History

In determining the predictive values of age of patients & gender & family history of glaucoma, the enter method was used. The global accuracy of this model for predicting glaucoma is 60.00%. The sensitivity is 83.30% and the specificity is 25.00%. (Table 4.).

Table 4. Predictive Values of Patient Age & Gender & Family History of Glaucoma / Discrimination Model

Observed			Predicted		
			Glaucoma		Percentage Correct
			No	Yes	
Step 1	Glaucoma	no	10	30	25.0
		yes	10	50	83.3
	Overall Percentage				60.0
a. The cut value is .500					

In determining the significance of the contribution to the prediction of glaucoma, it was found that the age of the patients had the greatest influence (Wald = 5.05 / p <0.05 (p = 0.025), followed by the family history (Wald = 0.04 / p> 0 , 05 (p = 0.84) and the weakest is the influence of the sex of the patients (Wald = 0.01 / p> 0.05 (p = 0.94) (Table 47.1).

Increasing the age of the patients by one year increases the risk of glaucoma by 4.30% (Exp (B) = 1,043), the effect of the age of patients is significant / 95% CI: 1.01-1.08 / p < 0.05.

Patients who have a family history of hereditary glaucoma (1) by 1,109 times (Exp (B) = 1,109) have a slightly higher risk of glaucoma than patients who do not have a family history of hereditary glaucoma, the effect of family history (1) is not significant / 95% Cl: 0.41-2.99 / p> 0.05.

Male / gender (1) by 1,036 times (Exp (B) = 1,036) have a slightly higher risk of glaucoma than female, the influence of the gender of the patients is not significant / 95% CI: 0.41-2.60 / p > 0.05.

Table 4.1 Binary Logistic Regression Analysis Glaucoma Prediction / Patient Age & Gender & Family History

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper	
Step 1a	Age	.042	.019	5.053	1	.025	1.043	1.005	1.082
	Gender(1)	.035	.470	.006	1	.940	1.036	.412	2.602
	Family history(1)	.103	.507	.041	1	.839	1.109	.411	2.993
	Constant	-1.956	1.063	3.383	1	.066	.141		

Variable(s) entered on step 1: Age, Gender, Family history.

The ROC area is 0.643 which means that in 64.30% / 95% CI: 0.533-0.753 / p <0.05 (p = 0.016) / of all possible pairs of which one patient is with glaucoma and the other is with no glaucoma, this model will determine a higher probability of glaucoma (Chart 4).

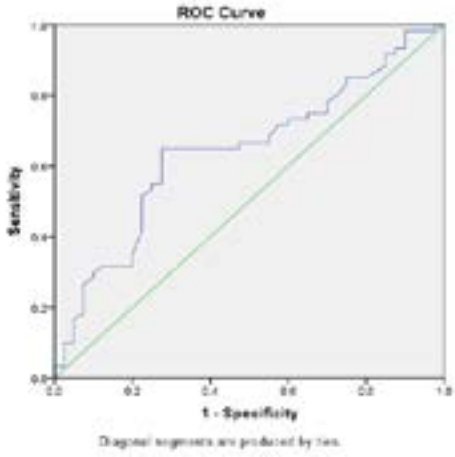

Chart 4

DISCUSSION

Glaucoma, one of the leading causes of irreversible blindness in the adult population worldwide, is progressive optic neuropathy. Primary open-angle glaucoma (POAG) is the most commonly reported type of glaucoma in prevalence studies based on the worldwide population. Increased intraocular pressure is a well-known major risk factor for POAG. In addition, there is evidence that other risk factors such as age, sex, race,

refractive error, heredity, and systemic factors may play a role in the pathogenesis of glaucoma.

The age of the patients is mentioned in many studies as a risk factor for the occurrence and progression of glaucoma (14,15).

The age of the patients in our study varies in the range 55.72 ± 11.71 years. It was found that by increasing the age by one year, the risk of glaucoma increases by 4.30%, significantly by p = 0.025.

Supporting the above are the results of SommerA, TielschJM, KatzJ, etal. where it is noted that primary open-angle glaucoma is an adult disease and increases with age (16).

Similar results have been obtained in several other studies (17,18,16). In the Barbados Eye Study (62), it has been found that with increasing age the chance of glaucoma increases (RR.1.04: 95% CI, 1.02-1.05 per year). In the Kandy Eye Study (64), the risk of glaucoma increases with age (p = 0.001), and patients over the age of 70 are six times more likely to develop glaucoma than those in the fourth decade (p = 0.003).

A study conducted in San Francisco, California (19) found that age was a major risk factor for glaucoma (p <0.001).

Another study was conducted at Yale University in the United States (20) to highlight the link between age and glaucoma. This study shows that age is a major risk factor for glaucoma. This leading cause of blindness has a higher prevalence in the elderly population. Tissue changes as a result of aging are thought to lead to faster disease development.

Usually there is no significant association of gender with glaucoma (18). In our study, of the total number of respondents, 32 (32.00%) are men and 68 (68.00%) are women. From the obtained results, men have 1.04 times slightly (p = 0.930) higher risk of glaucoma than women.

Hereditary factors play a major role in the onset and development of glaucoma (20,21,22). In our study, from the obtained results, it was determined that patients who have a family history of glaucoma have a slightly (p = 0.839) higher risk of glaucoma by 1.11 times than patients who do not have hereditary glaucoma in the family history.

Some studies have shown that there is a strong correlation between the hereditary factor and the occurrence of glaucoma (20) through certain dominant or recessive genes that are inherited. Performing these genetic inheritance screening tests can detect the disease early, even before the onset of glaucomatous lesions.

Other studies (22) suggest that there are three types of genes involved in the inheritance of the disease: primary open-angle glaucoma, primary closed-angle glaucoma, and pseudoexfoliative syndrome.

The results from the Barbados Eye Study (17) support our results, where a family history of glaucoma increases the risk of glaucoma (RR, 2.4; 95% CI, 1.30-4.6).

CONCLUSION

Based on the results of our study, the following conclusions were made:

1. There is no significant difference (p> 0.05) between the examined (group with glaucoma) and the control group (group without glaucoma) in relation to:

-distribution of gender,

-family history (glaucoma).

2. There is a significant difference between the examined and the control group in terms of the age of the patients;

3. In the Univariate Logistic Regression Analysis for glaucoma prediction, the age of the patients was significantly associated with glaucoma.

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Original scientific paper

ARTRITI URIK DHE BASHKËSHOQËRIMI ME DIABETIN MELIT

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ABSTRAKTI

Artriti urik, ose i njohur si "gout", është një tip i artritit që shkakton dhimbje intensive, ënjtje dhe ngurtësim të nyjeve. Zakonisht prek nyjen e gishtit të madhë të këmbës. Diabeti është faktor kryesues në barrën e sëmundjeve globale. Është vlerësuar se 387 milionë njerëz kanë pasur diabet në vitin 2014, kurse deri në vitin 2035 kjo shifër mund të shkojë në 592 milionë raste. Nivelet e ngritura të acidit urik në gjak, parashikojnë shfaqjen e diabetit të tipit 2. Qëllimi i punimit ka të bëjë me përshkrimin e lidhjes në mes artritit urik dhe diabetit, përmes gjetjes së rasteve me diabet në mes pacientëve të prekur me artrit urik, si dhe krahasimit ndërmjet grupmoshave dhe gjinisë së rasteve gout diabetike – gout jodiabetike. Punimi është i tipit deskriptiv, retrospektiv. Materiali është marrë nga Klinika e Reumatologjisë të QKUK-së. Të dhënat janë nxjerrë nga historitë e pacientëve të shtrirë në periudhën gjashtë vjeçare, respektivisht nga viti 2014 deri në 2019. Gjithsej janë 108 pacientë, me moshë nga 32 deri në 75 vjeç. Të dhënat janë paraqitur me anë të tabelave dhe grafikoneve. Për përpunimin e të dhënave janë përdorur madhësitë mesatare. Nga 108 pacientë gjithsej, 29 prej tyre ishin diabetik apo 26.85%, kurse 79 jodiabetik apo 73.15%. Nga 44 femra të prekura me gout, 13 prej tyre kishin diabet apo 44.83%, kurse 31 ishin jodiabetike apo 55.17%. Grupmosha më e prekur ishte ajo nga 50-59 vjet, me 15 raste diabetike gjithsej, apo 51.72% të krejt rasteve diabetike. Artriti urik bashkëshoqërohet me sëmundjen e diabetit. Të dy gjinitë kanë mundësi afërsisht të barabartë për të qenë gout të shoqëruar me diabet, mirëpo gjasa diçka më e lartë paraqitet te femrat. Grupmosha me artrit urik më e prekura nga diabeti është ajo 50-59 vjet. Grupmoshat femërore me artrit urik të prekura nga diabeti janë ato +50 vjet, kurse ato mashkullore janë 50-70 vjet. Me rritjen e moshës, gjasa për të qenë me artrit urik të bashkëshoqëruar me diabet, rritet.

Fjalët kyçe: Artriti Urik, Gout, Diabeti Melitus, Acidi Urik

HYRJA

Artriti urik, ose i njohur si "gout", është një tip i artritit që shkakton dhimbje intensive, ënjtje dhe ngurtësim të nyjeve. Zakonisht prek nyjen e gishtit të madh të këmbës. [1]

Diabeti është faktor kryesues në barrën e sëmundjeve globale. Është vlerësuar se 387 milionë njerëz kanë pasur diabet në vitin 2014, kurse deri në vitin 2035 kjo shifër mund të shkojë në 592 milionë raste. [2]

Shkenctarët nuk janë të sigurt saktësisht se pse ekziston lidhja në mes artritit urik dhe diabetit. Gout shkakton inflamacion në trup, andaj disa ekspertë besojnë se inflamacioni poashtu ka rol në shfaqjen e diabetit. Në anën tjetër, njerëzit me diabet të tipit 2 shpesh kanë vlera të larta të acidit urik në gjak, e cila mund të vie si pasojë e yndyrës së tepërt. Nëse ka mbipeshë, atëherë trupi prodhon më shumë insulinë. Kjo e bën më të vështirë për veshkët që të ekskretojnë acidin urik nga gjaku, gjë e cila mund të rezultojë me manifestimin e artritit urik. Nga një studim i cili njihet si Framingham Heart Study, projekt kërkimor rreth sëmundjeve të zemrës që filloi nga viti 1948, thuhet se personat me vlera të larta të acidit urik kanë gjasa më të mëdha për tu prekur me diabet të tipit 2, krahasuar me ata që nuk kanë vlera të larta të acidit urik. Më detajisht, për çdo 1 miligram për decilitër rritje në vlerat e acidit urik, rritet shanca për tu prekur

me diabet për 20%. [3]

Nivelet e ngritura të acidit urik në gjak, parashikojnë shfaqjen e diabetit të tipit 2. [4]

Gout është shkaktari më i shpeshtë i artriteve urike te meshkujt mbi moshën 40 vjeçare. Hiperurikemia është një nga simptomat e hiperinsulinizmit dhe sindromës metabolike. Nivelet e urikemisë janë në përpjestim të drejtë me shkallën e rezistencës së insulinës. [5]

Nga një studim i bërë te meshkujt me rrezik të lartë nga sëmundjet kardiovaskulare vie në përfundim se meshkujt me gout janë më të rrezikuar në shfaqjen e diabetit të tipit 2, sesa ata pa gout, të pavarur nga shkaktarët tjerë. [6]

Nga një studim i tipi case-control i bërë në Britani të Madhe (UK), vie në një përfundim se individët me diabet kanë rrezik më të vogël të shfaqjes së gout, sesa ata pa diabet, të pavarur nga faktorët tjerë. [7]

Diabeti melitus lidhet me çrregullime të eshtrave dhe të nyjeve, përfshirë neuroatropati, lëvizshmëri të limituar të nyjeve dhe hiperestezi. [8]

Afërsisht 90% e njërëzve me diabet të tipit 2 janë mbipeshë ose obezë. Personat obezë kanë katër herë më shumë shancë për të marrë gout, krahasuar me ata që janë në peshë normale. Pesha e tepërt e ngadalëson aftësinë e veshkave për të ekskretuar acidin urik. [9]

Një studim tjetër na sugjeron se gout i pavarur mund të jetë i lidhur me rritjen e rrezikut të shfaqjes së diabetit dhe atë me mundësi më të madhe të shfaqjes te femrat sesa te meshkujt. [10]

Lidhja në mes artritit urik dhe gout është shumë komplekse. Pacientët me gout kanë prevalencë të lartë të diabetit të tipit 2. Gout poashtu është faktor rreziku për shfaqjen e diabetit të tipit 2. Përderisa, pacientët me diabet kanë rrezik më të vogël të shfaqjes së gout. [11]

Në UK, gout prek 1 në 100 njerëz dhe është rreth 4 herë më i shpeshtë te meshkujt sesa te femrat. Studimet tregojnë se njerëzit me gout janë më të rrezikuar në shfaqjen e diabetit të tipit 2 sesa ata që nuk kanë gout. Një studim i bërë në shkollën mjekësore të Harvardit tregon se gout rrit rrezikun për 70% në shfaqjen e diabetit. [12]

Një studim i bërë në një grup veteranësh në Shtetet e Bashkuara (US), vie në përfundim se afërsisht 1 nga 11 raste të diabetit i atribohet pranisë së hiperurikemisë. [13]

Femrat me gout janë më të rrezikuara në shfaqjen e diabetit sesa meshkujt e prekur me gout. [14]

QËLLIMI

Qëllimi i punimit ka të bëjë me përshkrimin e lidhjes në mes artritit urik dhe diabetit melit, përmes gjetjes së rasteve me diabet në mes pacientëve të prekur me artrit urik, si dhe krahasimit ndërmjet grupmoshave dhe gjinisë së rasteve gout diabetike – gout jodiabetike.

MATERIALI DHE METODAT

Punimi është i tipit deskriptiv, retrospektiv. Materiali është marrë nga Klinika e Reumatologjisë të QKUK-së. Të dhënat janë nxjerrë nga historitë e pacientëve të shtrirë në periudhën gjashtë vjeçare, respektivisht nga viti 2014 deri në 2019. Gjithsej janë 108 pacientë, me moshë nga 32 deri në 75 vjet. Të dhënat janë paraqitur me anë të tabelave dhe grafikoneve. Për përpunimin e të dhënave janë përdorur madhësitë mesatare.

REZULTATET

Nga të dhënat e përpunuara, mbërritëm te këto rezultate:

Fillimisht, të dokumentuar ishin 108 raste me artrit urik, ku prej tyre 64 ishin meshkuj apo 59.26%

dhe 44 femra apo 40.74%. Mosha mesatare e të gjithë pacientëve ishte 57.68 vjet.

Tabela 1. Pacientët gout-diabetik dhe ata gout-jodiabetik

Prania e diabtetit	Numri total	%
Jo	79	73.15
Po	29	26.85
Gjithsej	108	100

Nga tabela 1 shihet se nga 108 pacientë të prekur me gout, sa ishin gjithsej, 79 prej tyre apo 73.15% nuk kishin diabet, kurse 29 nga ta apo 26.85% kishin të pranishëm diabetin.

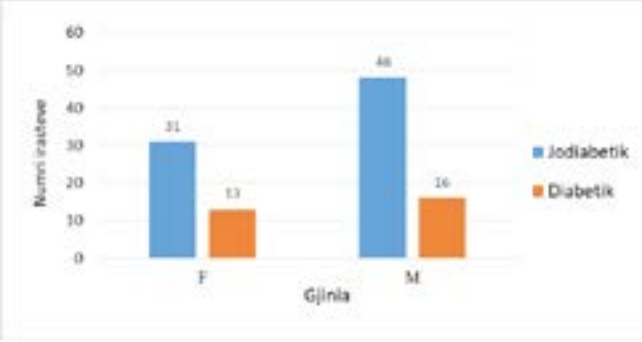
Grafiku 1. Pacientët gout-diabetik dhe ata gout-jodiabetik

Tabela 2. Pacintët me gout të shpërndarë sipas gjinisë, me dhe pa diabet

Gjinia	Jodiabetik	%	Diabetik	%	Githsej	%
F	31	39.24	13	44.83	44	40.74
M	48	60.76	16	55.17	64	59.26
Gjithsej	79	73.15	29	26.85	108	100

F – femra; M – meshkuj

Tabela 2 tregon se nga 79 jodiabetik gjithsej, 31 prej tyre ishin femra apo 39.24% dhe pjesa tjetër, 48, ishin meshkuj apo 60.76%. Sa i përket pacientëve të prekur me gout, të cilët ishin diabetik, nga 29 gjithsej, 13 prej tyre ishin femra apo 44.83%, kurse 16 ishin meshkuj apo 55.17%.

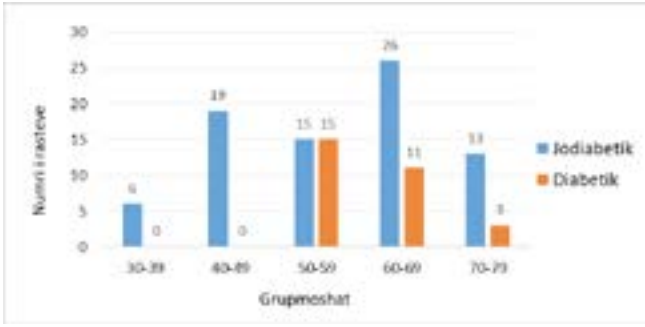


Grafiku 2. Pacintët me gout të shpërndarë sipas gjinisë, me dhe pa diabet

Tabela 3. Pacientë me gout të shpërndarë sipas grupmoshave, me dhe pa diabet

Grupmoshat	Jodiabetik	%	Diabetik	%	Gjithsej	%
30-39	6	7.59	...	...	6	5.56
40-49	19	24.05	...	...	19	17.59
50-59	15	18.99	15	51.72	30	27.78
60-69	26	32.91	11	37.93	37	34.26
70-79	13	16.46	3	10.34	16	14.81
Gjithsej	79	73.15	29	26.85	108	100

Nga tabela 3 shihet se grupmosha më e prekur nga diabeti ishte ajo nga 50-59 vjet me gjithsej 15 raste apo 51.72% të krejt rasteve diabetike. Grupmosha 30-39 vjet dhe ajo 40-49 vjet, nuk kishin asnjë rast diabetik.



Grafiku 3. Pacientë me gout të shpërndarë sipas grupmoshave, me dhe pa diabet

Tabela 4. Pacientët meshkuj të prekur me gout, të shpërndarë sipas grupmoshave, me dhe pa diabet

Meshkuj						
Grupmoshat	Jodiabetik	%	Diabetik	%	Gjithsej	%
30-39	6	12.5	...	...	6	9.37
40-49	13	27.08	...	...	13	20.31
50-59	11	22.92	10	62.5	21	32.81
60-69	13	27.08	6	37.5	19	
70-79	5	10.42	...	...	5	7.81
Gjithsej	48	75	16	25	64	100

Nga 64 meshkuj gjithsej, 48 prej tyre ishin jodiabetik apo 75%, kurse 16 nga ta kishin edhe diabet apo 25%. Grupmosha mashkullore më e prekur nga diabeti ishte ajo nga 50-59 vjet, me gjithsej 10 raste apo 62.5% të krejt rasteve mashkullore diabetike. Grupmosha 30-39 vjet, 40-49 vjet dhe ajo nga 70-79 vjet, nuk kishin asnjë rast diabetik.

Tabela 5. Pacientët femra të prekur me gout, të shpërndarë sipas grupmoshave, me dhe pa diabet

Femra						
Grupmoshat	Jodiabetik	%	Diabetik	%	Gjithsej	%
30-39	...	...	...	...	...	...
40-49	6	19.35	...	...	6	13.6
50-59	4	12.9	5	38.46	9	20.5
60-69	13	41.94	5	38.46	18	40.9
70-79	8	25.81	3	23.08	11	25
Gjithsej	31	70.45	13	29.55	44	100

Nga 44 femra gjithsej, 31 prej tyre ishin jodiabetike apo 70.45%, kurse 13 kishin diabet apo 29.55%. Grupmosha më e prekur femërore ishte ajo nga 50-59 vjet dhe nga 60-69 vjet, të dyja me nga 5 raste apo 38.46% të rasteve femërore diabetike. Grupmosha 30-39 vjet dhe ajo 40-49 vjet, nuk kishin asnjë rast diabeti.

DISKUTIMI

Në një studim të bërë në USA, pjesëmarrës ishin 35339 pacientë të prekur me gout, 72.4% e tyre meshkuj , mosha mesatare 62.7 vjet. Incidenca e rasteve diabetike te femrat dhe meshkujt ishte 10.1 dhe 9.5 raste për 1000 të prekur në vit. [10]

Nëse bëjmë krahasim me studimin tonë, ku pjesëmarrës janë 108 persona të prekur me gout, 59.26% meshkuj, mosha mesatare 57.7 vjet, vërehet një dallim i konsiderueshëm në parametra. Në studimin tonë, nga 108 pacientët gout pozitiv, 29 nga ta apo 26.85% kanë edhe diabet. Në pamundësi të matjes së incidencës, nuk mund të bëjmë një krahasim më të detajuar me punimin më lartë, mirëpo në punimin e mësipërm vërehet se incidenca te femrat është më e lartë sesa te meshkujt, kurse në punimin tonë shpërndarja sipas gjinisë e të prekurve me diabet është 13 femra (44.83%) dhe pjesa tjetër meshkuj, 16 (55.17%). Vërehet një numër më i madhë i rasteve mashkullore, mirëpo gjë e cila nuk është signifikante.

Hulumtimet e bëra thonë se 26% e pacientëve të prekur me gout, poashtu vuajnë edhe nga sëmundja e diabetit. [15]

Në studimin tonë, nga 108 pacientë me gout, 29 prej tyre kanë edhe diabetin apo 26.85%. Vërehet një përputhje e lartë me vlerat e studimin, gjë e cila e mbështet vlefshmërinë e studimin tonë.

Nga një studim i tipit case-control i bërë në Taiwan, Kinë, gjatë periudhës në mes viteve 1998-2010, 29765 pacientë u dokumentuan si të sëmurë me gout, përderisa 59530 persona tjerë ishin grup kontrolli. Nga 29765 të prekur me gout, 3940 prej tyre apo 13.24% ishin të prekur me diabet të tipit 2, kurse sa i përket grupit kontroll, 6334 prej tyre apo 10.64% e kishin të zhvilluar edhe diabetin e tipit 2. [14]

Në punimin tonë, i cili është i tipit deskriptiv, grupet kontrolle nuk na interesojnë. Sa i përket personave të prekur me gout, në punimin e mësipërm, gjithsej 29765, 3940 prej tyre apo 13.24% e kishin të zhvilluar edhe diabetin. Nëse bëjmë krahasim me punimin tonë, ku nga 108 persona të prekur me gout, 29 prej tyre janë diabetik apo 26.85%, vërehet një dallim në pjesëmarrje, gjë e cila mund të vie si pasojë e mungesës së rasteve në vendit tonë, apo edhe pjesëmarrja e vogël në vite (punimi jonë ka kohëzgjatje 6 vjeçare, përderisa i mësipërmi ka periudhë 13 vjeçare).

Në një punim kohort, me 54075 raste të gout gjithsej, 2000 prej tyre ishin incidencë e rasteve me diabet, apo 3.7%. Nga 54075 raste me gout, 45851 ishin meshkuj apo 84.8%, kurse pjesa tjetër femra, 8224 apo 15.2%. Nga gjithë femrat e prekura me gout, 305 prej tyre apo 3.71% ishin raste diabetike. Sa i përket meshkujve nga gjithë të prekurit me gout, 1695 prej tyre ishin raste diabetike apo 3.7%. [16]

Në krahasim me punimin tonë, ku nga 108 raste gjithsej, 29 prej tyre janë raste diabetike, apo 26.85%, punimi i mësipërm e ka shumë më të ulët prevalencën e rasteve, nëse e marrim si të tillë, me 3.7%. Në punimin e mësipërm 84.8% nga pjesëmarrësit ishin meshkuj, kurse në punimin tonë, 59.26% prej tyre janë të gjinisë mashkullore. Incidenca e rasteve te femrat nga punimi i mësipërm ishte 3.71%, kurse te meshkujt 3.7%, pothuajse e njëjtë në mes dy gjinive dhe komplet rasteve diabetike në kuadër të rasteve me gout. Në punimin tonë, prevalenca e rasteve diabetike në mes të prekurve me gout te femrat është 29.55%, kurse te meshkujt 25%. Dallimi në mes punimeve mund të vie për shkaqe të ndryshme, duke marrë parasysh edhe dallimin në tip të punimit dhe përfshierjes së rasteve.

Një punim i tipit meta-analizë, i përbërë nga 23 studime të ndryshme, me gjithsej 575284 pacientë të prekur me gout, arrin në përfundim se prevalenca e diabetit në tërë pacientët me gout është 16%. Me rritjen e moshës, rritet incidenca e rasteve diabetike në kuadër të rasteve të artritit urik. [17]

Në punimin tonë, prevalenca e rasteve diabetike në kuadër të pacientëve të prekur me gout është 26.85%. Sa i përket moshës, grupmosha më e prekur është ajo 50-59 vjet me 15 raste nga 29 raste diabetike gjithsej, apo 51.72%. Dallimi në pjesëmarrje të rasteve është i konsiderueshëm, mirëpo në të ndikojnë shumë faktor dhe signifikancën e tij nuk mund ta përcaktojmë. Mund ta mbështesim faktin se me rritjen e moshës, rritet edhe mundësia e rasteve me artrit urik për tu prekur me diabet, meqenëse edhe në punimin tonë mosha më e shtyrë ka pjesëmarrje të rasteve më të lartë.

PËRFUNDIMI

Pas analizës së rezultateve dhe krahasimit me punime tjera, kemi mbërritur në këto përfundime:

- Artriti urik bashkëshoqërohet me sëmundjen e diabetit, ku 26.85% e rasteve tona me gout janë edhe diabetik.

- Të dy gjinitë kanë mundësi afërsisht të barabarta për të qenë gout të shoqëruar me diabet, mirëpo gjasa diçka më e lartë paraqitet te femrat.
- Grupmosha me artrit urik më e prekur nga diabeti është ajo 50-59 vjet, ku në punimin tonë gjysma prej tyre janë diabetik.
- Grupmoshat femërore me artrit urik të prekura nga diabetiti janë ato +50 vjet, kurse ato mashkullore janë 50-70 vjet.
- Me rritjen e moshës, gjasa për të qenë me artrit urik të bashkëshoqëruar me diabet, rritet.

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Original scientific paper

THE PREDICTIVE (PROGNOSTIC) VALUE OF TMPRSS2-ERG IN PROSTATE CANCER SPECIMEN

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ABSTRACT

The incidence of prostate cancer is continually increasing due to the life span prolongation and the introduction of new diagnostic methods. Apart from the PSA, as the most widely used tumor marker, there are others, such as TMPRSS2-ERG fusion transcript which results of the predictive and prognostic value are still conflicting. Aim - The aim of this research was to analyze the presence of TMPRSS2-ERG fusion transcript in prostate cancer patients, and its predictive value for biochemical recurrence of the disease. Material and Methods - The research was a prospective clinical study that focused on random sample of 90patients with prostate carcinoma - study group. Real time PCR analysis for detection of the TMPRSS2-ERG fusion transcript was performed. Also data from the histopathology results of tissues, and of the level of PSA (prostate-specific antigen) in blood were used. Results - TMPRSS2-ERG fused transcript was detected in 33 (37,08 %) of the samples. There was no significant differences between patients with/without detected TMPRSS2-ERG fusion related to Gleason score and PSA level. TMPRSS2:ERG fussed transcript was significantly associated with recurrence of the disease Patients in the group with expression of TMPRSS2:ERG had 6.050 times more likely recurrence of the disease than ones without the expression of the TMPRSS2:ERG. Conclusion - The results from this research are in accordance with the values and results from analyses done in several research centres and ontological institutes. The findings in small scale studies encourage additional studies with more powerful clinical cohorts that will define the positive diagnostic and prognostic meaning of TMPRSS2-ERG fusion transcript.

Key words: TMPRSS2-ERG fusion ; prostate cancer ; recurrence

INTRODUCTION

It is tempting to judge the public health significance of a disease by its incidence or mortality, but when it comes to prostate cancer this dogma is confounded by the very high prevalence of occult disease. [1]

The incidence of prostate cancer cancer is continually increasing due to the life span prolongation and the introduction of new diagnostic methods, such as the PSA test (prostate – specific antigen test), transrectal ultrasonography and magnetic resonance [2–9].Only about half of patients diagnosed will develop significant symptoms, and <20% will die from their disease.

PSA, known as the most widely used tumor marker for the detection of prostate carcinoma, can be used for screening before the development of clinical disease, but its baseline values do not allow prognostic prediction of disease behavior. [5]

Apart from using the PSA, on its own or combined with its derivates, there are other markers which are used in diagnostic purposes at a greater or minor success rate. TMPRSS2-ERG fusion transcript leads to the androgen induction of ERG proto-oncogenes expression representing a high presence of oncogenes alteration among prostate tumour cells.This transcript has an

significant incidence in the human prostate cancer and can be detected in blood and tissue and also non-invasively in urine.[10]

Conflicting results about the prognostic and predictive value of TMPRSS2-ERG fusions have arisen, with some reports claiming a positive association with clinicopathologic features such as disease stage and metastases as well as disease recurrence [11], whereas others have found no association with these variables. [12, 13] The aim of this research was to analyze the presence of TMPRSS2-ERG fusion transcript in prostate cancer patients, and its predictive vallue for biochemical recurrence of the disease.

MATERIAL AND METHOD

The research was a prospective clinical study which was realized in the period of two years, 2018/2019, at the University Clinic of Urology – Skopje in cooperation with the Institute for Pathological Anatomy – Skopje and the Clinical Biochemistry at the Faculty of Medicine- Skopje; Institute for Radiotherapy and Oncology and the Research centre for genetic engineering and biotechnology "Georgi D. Efremov" at the MASA (Macedonian Academy of Sciences and Arts).

The research study employed random sample of 90 patients with prostate carcinoma. The inclusive criteria involved: men with prostate cancer belong to the age of ≥ 40 and ≤ 85, the socio- demographic features being irrelevant; PSA>4ng/ml and/or positive rectal toucher (suspect digito-rectal examination). Patients with other types of malignant diseases, severe general and locoregional disease, incurable condition, dementia, rational judgment disorder, more serious cardiovascular diseases and coagulopathy were excluded from this study.

For molecular analyses we used a prostate biopsy tissue or the operation material tissue. Histopathology results of tissues - Gleason score data, as well as data for the level of prostate specific antigen (PSA) in blood were analyzed for correlation with the fussed transcript, and also for biochemical recurrence (6 or 12 months after the operation or radiotherapy).

METHOD IMPLEMENTED

The samples of the prostate tissue were taken by a biopsy in accordance with the routine methods and procedures, i.e. at least 10-12"core" biopsies (+ 1 – 2 cylinders) 10 – 20 mm in length: 2 from the prostate apex, 2 from the base and 6-8 from the middle of the peripheral zone of the prostate (5-6 from both sides of the prostate). One additional cylinder from the suspect area was taken for molecular analysis. This cylinder was placed and submerged in 1,5 ml Eppendorf tube full of liquid nitrogen and it was snap-frozen and kept on a temperature of -80 degrees Celsius until the start of further analysis at the laboratory in MASA (Macedonian Academy of Sciences and Arts). If a certain sample of the bioptic material was inadequate (insufficiently long) the biopsy procedure in that region was routinely repeated. Immediately upon the biopsy procedure, the prostate tissue was placed in a 10% formalin container so as to prevent tissue autolysis. In addition, the material was processed in four different reagents, upon which it was moulded with paraffin, cut and finally processed in Hematoxylin and Eosin colors for histopathology and a "Gleason" assessment. The sample from the operative material was taken immediately after the prostatectomy, tissue was taken from the most suspected zone for the cancer presence and the procedure for its preparation and analyses was the same as for the biopsy specimen.

During the molecular analysis for TMPRSS2-ERG fusion, approximately 10mg of each tissue sample was used for total RNA extraction which was performed on an automated platform (MagCore®, RBC Bioscience, Taiwan) and a commercial kit (MagCoretriXact RNA Kit) which included DNase treatment for DNA elimination. For detection of the mutant and the wild-type alleles, a real time PCR analysis was performed using KiCqStart One-Step Probe RT-qPCR Kit (Sigma-Aldrich, Missouri, USA), TaqMan® fusion assay and a TaqMan® gene expression assay (Applied Biosystems™, Massachusetts, USA), following manufacturer's protocol. The fluorescent RT-PCR reaction was performed on 7500 Fast Real-Time PCR Systems using FAM dye for the detection of the fusion and VIC dye for the detection of the control transcript. The cycling conditions and threshold levels were set as recommended by the manufacturer. The fusion resulted in 106bp fragment containing TMPRSS2 exon 1 and ERG exon 4, while the control gene expression assay resulted in 79bp fragment containing exons 7-8 of the TMPRSS2 gene. This duplex assay has a declared detection limit of 0.05% for the detection of TMPRSS2-ERG exon1-exon4 isoform, however, this assay would also detect fusion transcripts involving other TMPRSS2 exons linked to the exons located 5' of the exon 4 from the ERG gene.

The implementation of this study was approved by the Ethics Commission of the Medical Faculty at "Ss. Cyril and Methodius" University – Skopje.

STATISTICS ANALYSIS

Data was statistically analyzed in SPSS software package, version 22.0 for Windows (SPSS, Chicago, IL, USA). The qualitative series were processed by determining the coefficient of relations, proportions, and rates, and were shown as absolute and relative numbers. Quantitative series were present as mean, median and standard deviation. To determine the association between qualitative variables Pearson Chi square test was used. Quantitative series were analyzed with measures of central tendency (average, median), as well as with dispersion measures (standard deviation, standard error). Normality of distribution was tested by Shapiro-Wilk W test. Mann-Whitney U Test was used for analysis of differences between the two independent numerical variables. Spearman coefficient was used to determine the correlation between recurrence of the disease and TMPRSS2. A two-sided analysis with a significance level of $p<0,05$ was used to determine the statistical significance.

RESULTS

TMPRSS2-ERG fused transcript was detected in 33 (37,08 %) of the patients(samples) in the study group (N=90) with prostate carcinoma (Table 1). There was one patient where the analysis was invalid. The PSA level in the study group (CaP) was 29,33±33,93ng/ml with min/max 4,3/152 ng/ml, and Median IQR=14 (9,15-38).Among patients were TMPRSS2-ERG transcript was not detected (N=56), average PSA level was 29,95±37,92ng/ml with min/max 4,5/ 152ng/ml and Median IQR=12,35 (8,39-28).For patients with detected TMPRSS2-ERG fused transcript, average PSA level was 27,43±37,92ng/ml with min/max4,33/116ng/ml and Median IQR=12 (7,71-23). We didn't find significant difference between patients with prostate cancer who were with/without detected TMPRSS2-ERG fused transcript related to PSA level(Mann-Whitney U Test: Z=-0,6158; p=0,5380).

Average Gleason Major, Gleason Minor and Gleason Score for patients with/without detected TMPRSS2-ERG fused transcript was 3,39±0,56 vs. 3,43±0,57; 3,48±0,57 vs. 3,52±0,66 and 6,88±0,78 vs.6,95±0,92 respectively. With nonparametric correlation we analyzed the association between TMPRSS2: ERG fusion transcript and Gleason Major, Gleason Minor and Gleason Score and found a non-significant linear negative weak correlation for Spearman Rank order correlations: R(89)=-0,029; p=0,7813 vs R(89)=-0,001; p=-0,9885 vs R(89)=-0,015; p=0,8891). For p> 0,05, TMPRSS2: ERG fusion transcript did not correlate with the height of Gleason Major, Gleason Minor and Gleason Score.

Table 1.Qualitative TMPRSS2:ERG RT-PCR in prostate cancer

Ca P	PSA	GMa1	GMin2	GS3	TMPRSS2–ENG Real-Time PCR	Ca P	PSA	GMa1	GMin2	GS3	TMPRSS2–ENG Real-Time PCR
Ca P - 1	9,7	3	3	6	Negative, type	Ca P – 46	57,0	4	3	7	invalid
Ca P – 2	32,0	4	4	8	Negative, type	Ca P – 47	14,0	3	3	6	Negative, type
Ca P – 3	16,5	4	5	9	Negative, type	Ca P – 48	100	4	4	8	Negative, type
Ca P – 4	84	3	4	7	Negative, type	Ca P – 49	7,4	3	3	6	Negative, type
Ca P – 5	8,3	3	3	6	Negative, type	Ca P – 50	65,0	4	3	7	Positive, type *
Ca P – 6	7,4	3	4	7	Positive, type *	Ca P – 51	44,0	3	4	7	Positive, type *
Ca P – 7	17,0	3	4	7	Negative, type	Ca P – 52	45,3	3	4	7	Positive, type *
Ca P – 8	45,0	4	4	8	Positive, type *	Ca P – 53	12,0	3	3	6	Negative, type
Ca P - 9	20,1	3	3	6	Negative, type	Ca P – 54	10,2	4	3	7	Negative, type
Ca P – 10	4,3	3	3	6	Positive, type *	Ca P – 55	58,0	3	3	6	Negative, type
Ca P - 11	5,2	3	3	6	Positive, type *	Ca P – 56	25,0	3	4	7	Positive, type *
Ca P - 12	9,1	4	3	7	Positive, type *	Ca P – 57	20,5	4	3	7	Negative, type
Ca P - 13	8,5	3	3	6	Negative, type	Ca P – 58	9,3	3	4	7	Positive, type *
Ca P - 14	14,0	4	3	7	Negative, type	Ca P – 59	37,0	3	4	7	Positive, type *
Ca P - 15	4,5	3	3	6	Negative, type	Ca P – 60	13,3	3	3	6	Negative, type

Ca P - 16	63,5	4	4	8	Negative, type	Ca P – 61	6,1	3	5	8	Negative, type
Ca P - 17	24,0	3	3	6	Positive, type *	Ca P – 62	8,2	3	3	6	Negative, type
Ca P - 18	9,4	3	3	6	Positive, type *	Ca P – 63	14,5	4	4	8	Negative, type
Ca P - 19	15,5	5	3	8	Positive, type *	Ca P – 64	68,9	4	3	7	Negative, type
Ca P - 20	18,0	3	3	6	Positive, type *	Ca P – 65	25,0	4	3	7	Positive, type *
Ca P - 21	9,7	3	4	7	Negative, type	Ca P – 66	12,0	3	4	7	Negative, type
Ca P – 22	18,0	3	3	6	Negative, type	Ca P – 67	42,1	4	3	7	Positive, type *
Ca P – 23	70,0	4	4	8	Negative, type	Ca P – 68	26,2	3	3	6	Positive, type *
Ca P - 24	22,3	4	4	8	Negative, type	Ca P – 69	10,6	3	3	6	Negative, type
Ca P - 25	9,4	4	3	7	Negative, type	Ca P – 70	10,5	3	4	7	Negative, type
Ca P – 26	45,8	4	5	9	Negative, type	Ca P –71	6,1	3	4	7	Positive, type *
Ca P - 27	12,7	3	3	6	Negative, type	Ca P – 72	10,3	3	4	7	Positive, type *
Ca P - 28	24,0	4	3	7	Negative, type	Ca P – 73	5,8	3	3	6	Positive, type *
Ca P – 29	94,0	4	4	8	Positive, type *	Ca P –74	11,7	3	4	7	Negative, type
Ca P – 30	12,2	3	3	6	Positive, type *	Ca P – 75	14,0	3	3	6	Positive, type *
Ca P - 31	6,1	3	3	6	Negative, type	Ca P - 76	9,7	4	4	8	Positive, type *
Ca P - 32	70,0	3	4	7	Positive, type *	Ca P - 77	14,3	4	3	7	Negative, type
Ca P - 33	116	4	5	9	Positive, type *	Ca P – 78	20,0	4	3	7	Positive, type *
Ca P - 34	7,0	4	3	7	Negative, type	Ca P – 79	5,4	3	3	6	Negative, type
Ca P – 35	6,2	3	3	6	Negative, type	Ca P - 80	38,0	4	3	7	Positive, type *
Ca P – 36	148	4	3	7	Negative, type	Ca P - 81	10,4	3	4	7	Positive, type *
Ca P – 37	150	4	3	7	Negative, type	Ca P - 82	11,0	3	3	6	Negative, type
Ca P – 38	4,7	3	4	7	Negative, type	Ca P - 83	23,0	4	4	8	Positive, type *
Ca P – 39	7,1	3	4	7	Negative, type	Ca P – 84	7,8	3	3	6	Positive, type *
Ca P – 40	90,0	5	4	9	Negative, type	Ca P – 85	11,6	3	3	6	Negative, type
Ca P – 41	7,6	5	3	8	Negative, type	Ca P – 86	10,0	3	4	7	Negative, type
Ca P – 42	8,0	3	4	7	Negative, type	Ca P – 87	11,0	3	3	6	Positive, type *
Ca P – 43	21,3	3	3	6	Negative, type	Ca P – 88	7,5	3	3	6	Negative, type
Ca P – 44	8,5	4	5	9	Negative, type	Ca P – 89	90,0	3	4	7	Negative, type
Ca P – 45	152	4	4	8	Negative, type	Ca P – 90	43,0	3	5	8	Negative, type

In this part of the research we made an analysis of the patients in CaP group in the relation of the recurrence of the disease with an additional analysis according to expression of TMPRSS2:ERG fussed transcript.

Recurrence of the disease was seen at 17 (18,89 %) patients with prostatic cancer (CaP group). In 2 (11,76%) of them, radiotherapy was applied. Average level of PSA in patients with prostatectomy, without radiotherapy was 0,51 +/- 0,39 ngr/ml with min/max value from 0,22/1,80 ngr/ml. All of the had PSA value above the cut-off PSA β0,2 ngr/ml. In patients who had received radiotherapy, average value of PSA was 6,75 +/- 6,43 ngr/ml, with min/max value of 2,2 / 11,3 ngr/ml. In 7 (53,85%)patients recurrence of the disease occurred after 6 months, while in 6 (46,15%) patients, the recurrence occurred after 12 months.

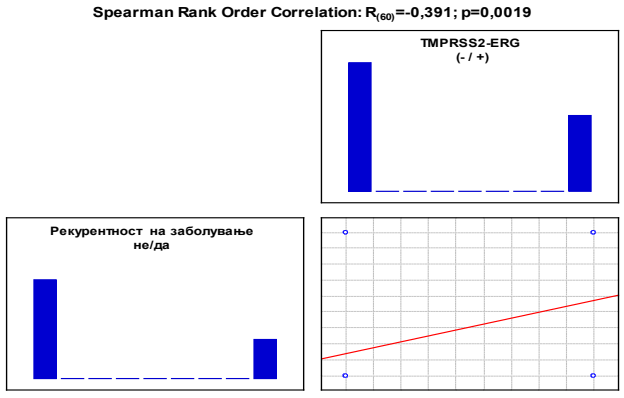
Table 2. Recurrence of the disease

He		Recurrence of the disease		
		Да	p	
TMPRSS2:ERG (N=60)	Negative, type	33 (84,62%)	6 (15,38%)	X2=9,201; df=1; p=0,0024*
	Positive, type	10 (47,62%)	11 (52,38%)	

For pβ 0,05, TMPRSS2:ERG fussed transcript was significantly associated with recurrence of the disease (Pearson Chi-square test: X2=9,201; df=1; p=0,002) Recurrence of the disease was seen in 11 (52,5 %) in patients with expression

of TMPRSS2: ERG. Patients in the group with expression of TMPRSS2: ERG had 6.050 times more likely recurrence of the disease than ones without the expression of the TMPRSS2:ERG.

For additional observations we applied a nonparametric correlation analysis (Spearman Rank Order Correlation). We saw that between TMPRSS2: ERG fussed transcript and the recurrence of the disease (prostatic cancer), there was a significant positive linear correlation for Spearman Rank Order Correlation: R(60)=-0,391; p=0,0019. With positive expression of TMPRSS2: ERG fussed transcript, recurrence of the disease was significantly higher.



Graphic 1. Correlation of recurrence of the disease with TMPRSS2: ERG in CaP group

DISCUSSION

Some researchers showed that aberrant expression of the TMPRSS2: ERG in prostate of some animals may cause prostatic intraepithelial neoplasm (PIN). Some authors pointed out that this genetic aberration may induce other genomic changes, as excessive genetic expression, deletion of PTEN, PI3K or to affect the transmission of the signal in androgenic receptor (AR), which makes promotion of genesis of the cancer in the manner of progression of the disease, migration and invasion of cancer cells. [14-18] This studies allows functional insight in the role of TMPRSS2: ERG in prostatic cancer.

In our research, the TMPRSS2-ERG fusion transcript was detected in 33 (37,08%) out of 90 patients with prostate carcinoma (with one being invalid). This finding is in accordance with the values and results from analyses done in several research centers. In studies and research done at the ontological institutes in European genetics centers the significant proportion of prostate cancer with TMPRSS2-ERG genetic rearrangements and alterations has been confirmed.

Mehra et al. found that TMPRSS2-ERG mRNA expression was present in 10 of 27 (37%) of hormone-refractory metastatic prostate cancer patient samples[19], and in the research of cases defined as localized prostate cancer, Liu B et al. concluded that TMPRSS2-ERG fusion was positive in 28.0% (14/50). [20]

TMPRSS2-ERG, can occur in approximately 50% of prostate cancer cases. [21] This fusion event most often arises from deletion of an interstitial fragment of chromosome 21, resulting in the androgen responsive promoter and 50 end of TMPRSS2 driving the expression of the ERG oncogene. [21] Fusion frequency more than 50% has been cited also by Soller and his associates, but this high discrepancy is due to the small numbers of cases (n=18) and/or the use of included PCR. [22] The reasons why frequency of genetic fusion varies between different studies are complex. Most likely because of the raise, methodology of sample obtaining, sensitivity of applied technology, and number of samples included in the study, criteria used for determination of positivity and patients (samples) of different parts of the country. [23]

Association between TMPRSS2-EEG genetic fusion and clinical outcome of prostatic cancer is not clearly determinate yet. Some studies show that this genetic fusion is not significantly related with the clinically-pathological parameters of the tumor. [24, 25] Other studies showed that presence of the fusion has correlation with advanced Gleason scores and clinical stadiums of the disease. [25]

Font-Tello and al. determine results that TMPRSS2 – ERG is positively associated with the results of Gleason and their serum level of PSA, in both local and total carcinoma samples, but that correlation was weak. [25] Expression of specific fusion of mRNA is correlated with the appearance of more aggressive disease. This may be used as a tool for planning the individual definitive treatment of each patient. [26]

TMPRS2-ERG fusion transcript is significantly associated with the recurrence of the disease. The patients from the group with expression of TMPRSS2-ERG fused transcript were 6,050 times more likely to have recurrence of the disease than the patients without expression of TMPRSS2-ERG.

In study group of 108 patients undergone radical prostatectomy was concluded that time of recurrence of the disease is way shorter in patients that has high expression of TMPRSS2-ERG. [27]

Researches for prostatic cancer are offering perspective way of identifying patients with unfavorable prognosis, who need radical treatment or other types of therapy that can influence the quality of life. [27] In according with this potentially meaning of TMPRSS2-ERG transcript, Petterson et al. in their study are analyzing if the patients with prostatic cancer who has the fusion, are more likely to have carcinoma with more aggressive pathological characteristics, and manifest progression of the disease. [28]

Many analyzes are implemented to estimate the fusion of these genes in different subtypes and groups of prostatic carcinomas, to discover their role in detection and prediction of aggressive forms of the disease. [29] According to the results of Rajput et al., TMPRSS2-ERG is more often detected at moderate to weak differentiated forms of tumors, (in 35 out of 86 patients - 40,7%), than in well differentiated forms. [29]

COCLUSION

The findings in small scale studies encourage additional studies with more powerful clinical cohorts that will define the positive diagnostic and prognostic meaning of TMPRSS2-ERG fusion transcript, perhaps enriched with results of genetic transcript in blood and urine, offering additional information for further managing of prostate cancer.

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Original scientific paper

RESULTS FROM POST - MARKETING OBSERVATIONAL STUDY FOR THE ASSESSMENT OF SAFETY OF INTRAVENOUS IBANDRONIC ACID IN POSTMENOPAUSAL WOMEN

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ABSTRACT

Our study was non interventional, observational, open, uncontrolled and prospective- retrospective study, multicentre and one branch - during 2009-2011 at secondary and tertiary medical level. 5 medical centres and two clinics from N. Macedonia were included. The study entered 611 pts, but finished 153 pts. 146 were bisphosphonate naive, 7 had previous received peroral bisphosphonate therapy. In our group of patients 36 side effects were registered in 31 patients. 35/36 appeared during first 7 days of application,15/36 did not appeared after fist application, 28/36 were with mild intensity and 5 were with moderate intensity and 2 were SAERS.

We analyzed review database (2009 to 2011), from the perspective of recent studies. And to point out, that DXA results, together with CMAJ guidelines and FRAX questionnaire, were not changed during last 10 years. Both of them (CMAJ and FRAX), together or without DXA, are solid foundation to begin antiresorbtive bisphosphonate therapy. DXA finding of osteoporosis, sex, and presence of one major or two minor risk factors was the basis of initiating the therapy. All of our patients were female. With the major risk factors 2,1 present in 129 (84%) from 153 patients. In 123 (80,09%) we have registered more than 1 minor risk factors (1,7).

Intravenous bisphosphonate therapy, is still most useful steadily in the last decade. It is due to the simple dosing regimens, the adherence, excellent compliance and persistence accurate for certain group of patients. This therapy have few adverse effects.

Key words: Osteoporosis, Risk factors, adverse effects

INTRODUCTION

Landmark Consensus Development Conference described osteoporosis as: "A systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture." Osteoporosis is a chronic condition. Therefore patients require long-term protection and treatment. Indeed, many patients are treated for 5 years or more. The chosen treatment should provide protection from low energy fracture, as well as reduction new ones. Ibandronate has shown continuous vertebral antifracture efficacy in a lot of studies (13). Two separate meta analysis confirmed protection of nonvertebral fractures with Ibandronate. (14). There were a lot of studies which shows that 3 mg i.v.ibandronate injection /3months, has showed increase of BMD after 2 years compared with the beginning 2 years ago (15).

The prime goal of our study was to record the adverse effects of i.v.ibandronic acid given intermittently, during one year. Report SAE (fill full SAE questionnaire). The

evaluation form which was fulfill on the first visit, did not estimate any other interventions out of clinical. We have followed them with intent to record eventually possible appearance of adverse effect. Also to copy with them. The end of study showed that manifested adverse effects were very similar to the side effects that occur in patients on oral therapy with bisphosphonates. So, this study provides systematized collecting, following and analysing the data, as well as documentation of our experience with adverse effects with i.v.ibandronic acid during one year. In 2011 we have used Canadian guidelines where bisphosphonate therapy is recommend for patients with osteoporosis (T-score of ≤ -2.5SD in the spine, femoral neck, total hip, or distal 33% radius). But it was recommended also for the patients with low bone mass (T score ≤ -1,5 SD) and presence of one major or two minor clinical risk factors for osteoporosis. The second target of our study was to note the presence of clinical risk factors (CRF-s).. Bisphosphonates, as any other medication, have some adverse effects(19). They have a relatively good safety record and are tolerated by the majority of patients, but serious adverse events can be recorded sometimes. During the follow up in our study, 10 patient appeared adverse effect (mostly fly-like) (2 of them has serious adverse effect(death), which were not connected with the given medication. For them, we have fulfil SEARS questionnaire and send it to authorities.

Fracture Risk Assessment Tool (FRAX®), was included in the initial evaluation for osteoporosis. It is still actual (American College of Endocrinology: Clinical practice guidelines for diagnosis and treatment of menopausal osteoporosis 2016(5) and is composed with data about: age, sex, high (cm), weight - BMI kg/m2, long lasting glucocorticoid use, history of parent fracture, presence of sec.osteoporosis, excessive use of alcohol (more than 3 units /day), current cigarette smoking, and RA. We can use it with or without BMD .

Canadian guidelines divides CRFs in major and minor CRFs(Clinical Risk Factors). Major CRF-s were: age>65 years, gender (woman), vertebral compression fracture (loss of 10 % of high as young, family history of osteoporotic fracture(maternal loose high), chronic corticoid therapy (more than 3 months), malabsorption-(GI disorders), primary hyperparathyroidism, osteopenia on RTG, hypogonadisms (menopause), early menopause(<45 years). In the group of minor risk we are: rheumatoid arthritis, history of hyperthyroidism, chronic therapy which reduces bone mass (glucocorticoids, anticonvulsive, proton pump H2 blockers), low dietary calcium intake, smoking, excessive caffeine intake, excessive alcohol intake, BMI less than 18 kg/m2, high loss (> 10% of their high at age 25). Older algorithms indicates that prevention of fractures, is better targeted on the basis of fracture probability using multiple risk factors, rather than BMD alone (6,7). We have extended both questionairs with : presence of diabetes mellitus, longer immobilisation, level of education, and physical activity

Data analyzing were done with Statistic for windows.

MATERIALS AND METHODS

Our study was non interventional, observational, open, uncontrolled and prospective- retrospective study, multicentre, one branch. It was conducted- during 2009-2011 at secondary and tertiary medical level. In this study, i.v. ibandronateis does not constitute a research product, because it is used within its registered indications. The recomended dose was in Macedonia 3 mg during 15-30 seconds, every 3 months. All patients were woman with menopause. 8 Medical centres were included in study (Skopje, Tetovo, Struga, Veles, Shtip, Bitola, Ohrid,Strumica). DXA measurements were done at the clinic of Endocrinology diabetes and metabolic disorders and Clinic for Orthopaedic surgery. At the beginning of the study 611 pts.were reported. For 161 one visit was registered, 2 visits for 106 pts , 3 visits for 82 pts. 4 visits were completed for 215 pts, but 153lists were submitted,evaluated and statistical processed.

Exept DXA finding of osteoporosis(T score≤ -2,5SD), we have used CMAJ and FRAX questionaire for starting the therapy together with low BMD (T score between -1,5SD and -2,5SD) and presence of one major or at least 2 minor risk factors .

Data which were taken account in the group of major risk factors were: Age > 65 years, vertebral compression fragility fracture after age 40 (lost of high and plane RTG), family history of osteoporotic fracture (especially maternal), systemic glucocorticoid therapy > 3 months, malabsorption syndrome (Gastro Intestinal Disorders), primary hyperparathyroidism, osteoporosis apparent on x-ray film (osteopenia), hypogonadism (menopause), early menopause. Data related to minor risk factors were taken as follows: rheumatoid arthritis, past history of hyperthyroidism, chronic use of concomitant therapy: antacid (H2blockers), heparin, anticonvulsive therapy. All of them has a reduction effect BMD- bone mineral density.

Low dietary calcium intake (less than 1000mg calcium/day - diary or supplementary), smoker, excessive alcohol intake (more than 3 unites/day), excessive caffeine intake(more than 5 cup coffee/day). We have consider weight as: low BMI- less than 18 kg/m2, normal between 18-24 kg/m2 and overweight and obese >30 kg/m2 and high loss > 10% of high at age 25 (in centimeters).

FRAX questionnaire was very similar and good portion of its readings are incorporated in CMAJ guidelines: age, sex, weight, high (BMI), premenopausal fracture, parent fracture (hip), curent smoking, glukokortikoid use, RA, secondary osteoporosis, femoral neck BMD (with or without it). We have extended both questionairs with : presence of diabetes mellitus, level of education and physical activity.

I.v.Ibandronate is administered quarterly (16,17,18). After starting the therapy, appearance of adverse effects was recorded and followed from the beginning of the study and quarterly. Type and intensity of the adverse effect were categorized as mild, medium or severe. Connection with the therapy was: probably, there is, there is not.

The end point of the therapy was without sequels, mild, or severe adverse effects (SAE). The notes about presence seriousness averse effect:were marked as: yes or no. If adverse effects appeared we had: follow them, give therapy (usually NSAR or other analgetics), or patient was withdrawn from the study.

RESULTS

Patients who had DXA eneterance data within a range of osteoporosis were 53: T-scor of L1-L4 and total hip. L1-L4 total was average 0,78913gr/cm2, with SD ±0,09383 and for 48 pts total hip BMD was average 0,769167gr/cm2, with SD ±1,0300.

Other patients came to our outpatient's clinics just for screening, with pain body ashes, or joint or muscle pain, thinking that they have pain due to osteoporosis. For the second group, after fulfil the questionnaire, DXA measurement was done. They had low BMD (T score -1,5SD or less).

After making a decision, we had started with medication, taking account presence of contraindications: hypersensitivity or hypocalcaemia.

Usually, mild adverse effect occurred within first 3 days after first therapy, with duration of maximum 7 days. They happened to 36 (23%) of patients. They had flu like symptoms (acute phase reaction or influence - like symptoms), which were mild to moderate with no withdrawal. In 36 adverse effects appeared first 7 days of application in 31 patients (20,20%), in 15/35did not appiered after first application. From 28/36 reported mild adverse effects (77%), 5 (14%) were moderate adverse effects and 2% were with SAERS. From those 36pts - 8complained of muscle pain (myalgia) and joint pain (arthralgia), on bone ashes complained 8 pts. Mild febricity had 6pts, fatigue-2, spine and hips pain had 6 pts, on body ashes and fatigue complain 4 pts, nausea and urge to vomit happened to 1, local phlebitis 1, chest pain 1pts . SAER"s were reported from investigators, but according to their opinion, considered unrelated to treatment (both were Chronic Heart Disease , and one of them was with lethal end). Adverse effects were addressed by the principles of good clinical practice.

Regarding the presence of Clinical Risk factors (CRFs) from FRAX and CMAJ, the following parameters were taken account for starting the therapy:

Age -is the most important clinical risk factor for osteoporosis. <45 year were 3 (2%), 45-55 were 19(12,4%), from 55-65 were 60 (39,2%), from 65-75 years were 56 (36,6% pts), over 75 years old were 15 (9,8%). Patients age range was 39-92years (SD 64±9). Over 55years were 87% of our group of 153 pts. There is statistical significant association between presence of clinical risk factor for osteoporosis p<0,05 and the age group 65-75years

Sex is the second main factor for osteoporosis. All of our patients were female.

During first examination itself, there was 9pts (5,88%) with vertebral low energy compression deformity - (osteoporotic fracture).

Low energy fracture as adult (after 40) reported 10 (6,5%). Those 10 patients reported totally 28 fractures, usually multiple.

Family history of osteoporosis reported 22 (14,2%) of the patients (data about obvious high loss of their first relatives, usually mother)

34 (22%) has lost 10% of their height, in settlement when they were 25 years and 7 (4,5 %) reported longer immobilisation.

Systemic Glucocorticoid therapy > 3 months: We have registered 7 (4,5%) patients who have received systemic prednisolone(or its equivalent), more than 3 months.

Chronic diseases: gastro enterological disorders (gastroenteritis or dyspepsia,) were significantly more frequent, compared to other chronic diseases they had: 93 (61%) gave information about some kind of gastrointestinal disturbances, haematological -2 (1%), HOPD had 17 (11%), endocrinological: diabetes 8(5,2%) and rheumatologically disease had 44 (29%). 48 (31%)pts. did not gave data about chronic diseases.

Hipogonadismus(menopause)All the patients from our group were menopausal (17,5.± 8,2 years menopausal) and average 9,3 years without cycles . 145-(94,8%) patients were in natural menopause, 8 had medical induced menopause.

Osteoporosis on RTG (RTG specialist for any level of-osteopenia give a diagnose osteoporosis), had 65,3% (100).

The average age of menopause was 46,8 years. The youngest patient was 32years, and the oldest was 55 years(considered late menopause) ± SD 5,09

Early menopause Oonly 2 (1,3%) women were under 45years. The youngest woman with early menopause was 38 year.

Taking into account presence of minor risk factors:

RA : Patients with RA were 28,4%(44), and with diabetes mellitus were 32,9%(51). There is statistical significant difference of P ≤0,05 for presence od RA or/and diabetes mellitus, in relation of presence of other minor clinical risk factors.

Chronic concomitant therapy : 65 (42,4%) of patients did not report use of any kind. From the rest 88pts.77(88%) has a therapy for reduction of gastric acidity (proton pump blockers), on thyrosupresive therapy were 3, on glucocorticoid therapy 13 (due to RA or HOPD), 9 are on some kind of immunosuppressive therapy(5) or metatrexat (3), anticoagulant 3, 3had any kind of chronic therapy

Low dietary calcium intake: only 8 (5,2%) have been used supplementary therapy at the beginning of the study with Ca - (1000-1200 mg), and only 5(3,2%) have been used vitamin D-400-800IU/day. And, at the end of the study, levels of Vitamin D and Calcium in patients were nearly the same like at the beginning of the study.

Normal BMI is between 18-24 kg/m2. 38 (25%)of our patients had normal weigh. Low BMI (< 18 kg/m2) had only 1% (2). The other 61 were overweight (39,6%) and obese 52 (34,4%) were with BMI>30kg/m2.

Smokers were 33 (21,3%) patients.

Excessive coffee intake: more than 5 cups of coffee - reported 2pts (7,7%).

34 (21,9%) has lost 10% of their their high at 25 years. Losing the high usually due to reducing of the high of vertebral bodies, which is a result of bone mass reduction.

Analysis of blood test show no significant association between the kidney functioning and receiving a therapy (e-GFR and albumin creatinine ratio).

DXA finding of osteoporosis, sex, and presence of one major or two minor risk factors was the basis of initiating the therapy. 2,1 of major risk factors were present in 129(84%) from 153 patients. In 123 (80,09%) we had registered more than 1 minor risk factors (1,7).

53,5% from all patients included in the study, had primer education, secondary school has finished 32,4%, and 14.1% of the patients were with high education. So there was a difference wetween a group with high and those with primary and secondary school finished p=0,0000 and p=0,0122. Most of our patients are not high aducated. Significcant corellation was found between physically nonactive patientsv.s. active patients p=0,0000 (most of the patients in our group were no active)

DISCUSSION

Osteoporosis is a growing major public health problem with impact on quality and quantity of life that cross medical, social, and economic lines.Very high socio-economic impact of osteoporosis is due to increased incidence of the disease, mortality and fracture-related costs. Progressive bone loss has been called “the silent epidemic” or “silent thief”. In our paper, the patients who have been choose to put on i.v. bisphosphonates therapy were patients with Type 1 osteoporosis, menopausal, who cannot tolerate oral bisphosphonate, or in whom oral bisphosphonates are contraindicated due to upper GI disorders (dyspepsia, gastroenteritis) and patients whose mental or physical status do not allow them to receive per oral therapy. As a clinician, working in every day practice, we know that BMD assessment only partially provides information about bone strength. On one hand BMD is a measure of bone mass, and on the other hand, bone fragility is dependent also on its microarchitecture quality which is determined by all the features (microarchitecture, micro damages and remodeling rates in bone) that influence a bone’s ability to resist fracture(9).

Bone quality describes the characteristics that influence bone strength, which is the maximum load that the bone can sustain before fracture. (10,11) Indeed, many patients this days are treated for 5 years and more.

The World Health Organization (WHO) and the International Osteoporosis Foundation (IOF) advice that fracture risk should be expressed as a short-term absolute risk. The absolute risk of fracture is relative to age and life expectancy which is in our group 15years, as well as sex, smoking, alcohol intake, glucocorticoid therapy, and DXA of the hip (if it is available) We have taken account that presence clinical risk factors FRAX(Fracture risk Assessment Tool), with or without DXA of the hip and total lumbar BMD. We had expanded FRAX questionaire with CMAJ (4) and extend them, as the prediction of osteoporosis and osteoporotic fractures (12). And start with the therapy.

Ibandronate has shown continuous vertebral antifracture efficacy in a lot of studies (13). Two separate meta analysis confirmed protection of nonvertebral fractures with Ibandronate. (14). There were a lot of studies which shows that 3 mg i.v.ibandronate injection /3months, has showed increase of BMD after 2 years compared with the beginning 2 years ago (15). I.v.Ibandronate was administered quarterly (16,17,18).

Bisphosphonates, as any other medication, have some adverse effects(19). They have a relatively good safety record and are tolerated by the majority of patients, but serious adverse events can be recorded sometimes. In our group, reported adverse effects were very similar with daily Ibanadronate - BONE study (20, 21, 22). Usually most common mild and moderate adverse effects are robustly observable in clinical trials.

The most appropriate therapy for our group of patients, considering our opinion and patients preference, was i.v. ibandronat acid. Especially for those one who cannot tolerate oral bisphosphonates, in whom oral bisphosphonates are contraindicated, who are unable to follow oral therapy recommendation for oral drug use, or those one who prefer this kind and frequency of therapy taking account their mental structure or physical condition. It has the list unwonted effect on GI tract (MOBILE study) and has extended antifracture efficacy on vertebral and non vertebral fractures (13, 14, 23, 24.) Also, we suggested this kind of therapy for women, who have stopped per oral bisphosphonetes due to the GI intolerance (22, 26). I.v .bisphosphonates are specially suitable for older patients who receive multiple medications (22). (LasterA, et al. Bone mineral res 2006;(Abstract SU326), (26).

Total 153 has finished the study. All patients who were included, were menopausal.There were not withdrawal from the therapy, although GI adverse events can lead to discontinuation (27).

Adverse effects were registered in totally 36 pts. 35/36 they were noticed first 7 days after first application, and 15/36 after other applications. 5 pts had adverse effects with moderate intensity, 28/36 were with mild intensity. Mild adverse effect occurred within first 3 days after first therapy, with duration of maximum 7 days. They happened to 36 (23%) of patients. Flu like symptoms (acute phase reaction or influence - like symptoms), or they were mild to moderate with no withdrawal. In 35 of those 36 pts. symptoms appeared first 7 days of application: 28(77%) of them were mild, in 5(14%) they were moderate and 2pts(5%) had SAERS. From those 28 with mild adverse effects - 8 complained of muscle pain (myalgia) and joint pain (arthralgia), on bone pain complained 8 pts (lumber and hip). With mild febricity were 6 pts, fatigue had 2, nausea and vomiting 1, local phlebitis 1, and chest pain 1. The rest 2 cases end the study with lethal outcome "SAER"s were reported from investigators, but according to their opinion, considered unrelated to treatment (both had Chronic Heart Disease with lethal end).

In this context, our attention was focused on identification of CRFs among patients where: oral therapy is contraindicated due to comfortable of dose regiment, with gastrointestinal disturbance, for those receiving a lot of medications, or for patients in whom this form of therapy is necessary due to their current physical and mental condition, or in patients who prefer this kind of application. (28). We have taken account that absolute risk of fracture is relative to age and life expectancy, as well as the current relative risk, i.e., the probability over a 10-year interval (29.) Low BMD alone is a poor predictor of fracture in men and women, indicating the need for more tools that predict fracture risk independent of, or in addition to, BMD. Measurement of skeletal mass with Dual Energy Absorptiometry method is the golden standard for diagnose (30).

In Canadian guidelines (4) FRAX is incorporated (1,2) . There are more than 100 guidelines those days, which recognize FRAX as a tool for estimating fracture probability and propose that pharmacological treatment

should be indicated for people with "rather high" fracture risk, but not to identify intervention thresholds (31, 32). FRAX questionnaire. (1,2,27) calculates the 10-year probability of major osteoporotic fracture (clinical vertebral, hip, forearm, or humerus) and the 10-year probability of hip fracture in men and women based on easily obtained clinical risk factors and bone mineral density (BMD) of the femoral neck (optional).The National Osteoporosis Foundation updated its U.S. guidelines in February 2008 to incorporate FRAX and recommends that all postmenopausal women and men aged ≥50 years with a hip or vertebral fracture, and T-score ≤ −2.5SD at the femoral neck or spine (excluding secondary causes) or low bone mass (T-score between −1.0 and −2.5) and a 10-year probability of hip fracture ≥3%, or of major osteoporosis-related fracture ≥20% . They should be considered candidates for drug therapy like it is point out in Guidelines American College of endocrinology clinical practice guidelines from 2016 (28).The use of fracture risk assessment tools that include clinically relevant risk factors are being those days increasingly incorporated into osteoporosis screening and treatment guidelines. From 2009-2011we have used both guidelines. The diagnostic DXA criteria established by the WHO and recommended by the AACE 2019 were and applies only to the axial measurements (i.e. lumbar spine, femoral neck).

Those patients who had osteoporosis (eneterance data within a range of osteoporosisT score ≥

-2,5SD for L1-L4 and total hip. L1-L4 was 0,78913gr/cm2 with SD ±0,09383 and for 53 pts total hip BMD was 0,769167gr/cm2with SD ±1,0300, for 48pts.

All patients had gone under questionairres and reported 1 major or 2 minor risk factors. We took presence of risk factors aditive and they were not considered indenpendently of one to anoughter. 100 patiets have done testing for BMD (bone minerl density) - concerning the guidelines which are still actual (29, 34,35). They had osteopenia with T score from -1,5 SD to -2,5 SD. All the patients in our group were woman.

Age: Over 87% of the patents were over 55 years old, and 2 % were les than 4years with early menopause. Age of menopause, together with osteopenia confirmed with DXA helped us with making a decision for starting the therapy.

Gastrointestinal disturbances (dyspepsia, gastroenteritis) were present statistical significantly. From 87 (57%) with GI disturbances, 77(88%) has a therapy for reduction of gastric acidity. Antacids (H2 blockers) are well known factor for reduced BMD. (35).

Fragility fracture after 40 had 10pts who had reported totally 28 low energy un vertebral fractures.Numerous studies show that a history of fragility fractures a great predictor of osteoporotic fractures (29, 37,38)

Family history of osteoporosis: patients did not know what is osteoporosis at that time, so they have reported dowager hump or remarcable lost of the high of their mothers.

Chronic use of glucocorticoid therapy more than 3 months in our group were 7 (4%).The use of glucocorticoids is an important cause of osteoporosis and fractures according to numerous trials. (28,38). But, except glucocorticoids, a lot of other medications like :thyroid hormones, antipsychotics, antihypertensive, proton pump blocators, immunosuppressives, anticonvulsive and anticoagulant therapy - lead to reduced bone mineral density (BMD) - increasing the risk of osteoporosis and osteoporotic fractures (29)

Osteopenia on RTG (osteoporosis with or without a difference in cranial caudal high on x-ray), had 100(65%)

Hypogonadismus (menopause): Menopause-related bone loss begins 3 to 5 years before the last menstrual period and continues for 3 to 5 years after the cessation of menses. It occurs at an average rate of 1 to 2% per year. (39,40). The woman in our group were 17,5± 8,2 years menopausal. 145(95%) patients were in natural menopause. Menopause was in only 6(4%) medical induced. Menopause that occurs before a woman < 45 as early or premature menopause. If a woman is 55 or older and still hasn't begun menopause, doctors considered it late-onset menopause. According to the Center for Menstrual Disorders and Reproductive Choice, the average age for menopause is 51. Menopause can be natural or surgically induced and long lasting menopause, leads to an increased risk of mortality and fragility fractures because these women are exposed to a hypogonadal state for a longer time (42). Menopause is one of the most important risks for osteoporosis. Crucial role is estrogen decrease, which leads to increased resorption. (9, 28, 43,44). World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis (Report of a WHO Study Group. World Health Organ Tech Rep Ser 1994; 843: 1-129 [PMID: 7941614]). We considered 55 years and older as in late menopause.

RA : In our study, there was a signifucan correlation

between presence od chronic disease: D.M and RA.The number of patients with RA were 44 (28,4%), and diabetes mellitus had 51% of patients wich is similar to the data of WHO (42). There was statically significant difference for RA (28,4%) and for diabetes(32,95%), with p<0,05, and presence of other minor risk. factor.

Smokers were 33 pts (21,4%). Cofein excess intake -reported only 12 pts (7.7%)

BMI : Most of our patients were overweight or obese which is not in agreement with numerous studies wich shows that osteeoporosios is more common in thinner woman.

Haigh loss:34 (21,9%)of the patients has lost 10% of their their high in settlement when they were 25 years, and 7 pt.s reported longer immobilisation.

53,5% of our patients have primer education, secondary school has finished 32,4%, and 14.1% of the patients were with high education. So there was a difference wetween a grup with high and those with primary and secondary school finished p=0,0000 i p=0,0122. We have find the data of reaserch in where women with lower education thinks more of their health and goes to visit doctors.That is not the case in China for exapmle. (45)

Significcant corellation was found between physically non active patients than active patients p=0,0000 wich correlates with data which we had find in literature. (46).

As far as suplement therapy in our study, there was not statistical difference between calcium level at the beginning and at the end of the study which means that patients did not receive supplementation of calcium which was suggested to them at the beginning of the study. Lack of vitamin D is important risk factor for osteoporosis. All of our patients were vitamin with vitD insufficiency or deficiency at the beginning of the therapy, and insufficiency at the end of the following period. Vitamin D deficiency and bone fragility are common in some countries such as Iran, where conservative cultural codes encourage body coverage and so limit sun exposure (47). In our country a lot of people, including our senior patients, usually do not go outside during summer, and, do not care about supplementation with vitamin D.

During the follow up period there was no change in renal function (following urea creatinine and electrolytes) as confirmed by data from literature (48,49)

CONCLUSION

Osteoporosis has been defined as a systemic disease which affects the skeleton and is characterized by low bone mass, deterioration of microarchitecture of bone tissue and bone fragility increase with consequent susceptibility to fracture (29). The occurrence of osteoporotic fractures is growing in several world areas as a consequence of the increased longevity of the population. Indeed, the number of hip fracture worldwide has reached 1.7 million by 1990 (51) In 2050, hip fractures could exceed 21 million (52,53)

The annual number of hip fractures grows significantly with the sustained getting older of the people. In our study, average age was 64± 9 years and the range was 39-92years. It is estimated that this demographic trend could induce a global increment of hip fractures from about 2 million in 1990 to a projected 6 million in 2050 (50,51). So, taking account that earlier diagnosis and prevention of fractures should decrease the medical, social and economic burdens of this disease we have made a decision of starting the therapy taking account BMD and a number of CRFs. The interesting point was that all of our patients gave a date related to reduction of the pain (usually back or lumbar pain) during the first quarter of the therapy, which was very interesting. (53). Extended antifracture efficacy on vertebral and nonvertebral fractures with I.v. Ibandronate was confirmed in number of studies (9,23,24) .

We have chosen menopausal patients who are either naïve on bisphosphonates, or those one who were on peroral therapy with high compliance rate. (22). I.v Ibandronat is especially suitable for older patients who receive multiple medications (22). Gastrointestinal disorders were very often result of age pain killers and multi medication therapy: NSAR, other kind of pain killers, glucocorticoid , thyroid hormones, antipsychotics, antihypertensive, proton H2 pump blockers, anticoagulant therapy which lead to reduced bone mineral density (BMD) increase the risk of osteoporosis (29) . Low BMD alone is a poor predictor of fracture in men and women, indicating the need for more tools that predict fracture risk independent of, or in addition to, BMD. Measurement of skeletal mass with Dual Energy Absorptiometry method is the main one for making a diagnose (gold standard)

Mild adverse effect occurred within first 3 days after first therapy, with duration of maximum 7 days. They happened to 36 (23%) of patients. Flu like symptoms (acute phase

reaction or influence - like symptoms), or they were mild to moderate with no withdrawal. 31(20,2%). 35 of those 36 pts. appeared first 7 days of application: 28(77%) of them were mild, 5(14%) were moderate and 2(5%) were with SAERS. They appeared after first time of application during first 3 days and lasted less than 7 days. Patients were alarmed for possible occurrence the appearance of these side effects. From those 28- 8 patients complained of muscle pain (myalgia) and joint pain (arthralgia), on bone pain complained 8 pts (lumber and hip), mild febricity had 6pts, fatigue -2, nausea and vomiting 1, local phlebitis 1, chest pain 1 . The rest 2 cases end the study with lethal outcome (cardiac arrest). "SAER"s were reported from investigators, but according to their opinion, considered unrelated to treatment). Adverse effects were addressed by the principles of good clinical practice.

Concerning the safety laboratory: KS, renal safe: eGFR and albumin/creatinine clearance, there was no change at the beginning and at the end of the study like in other studies (17).

Advantages of this study were: advantage is that they are giving an overview from everyday practice. Patients we very satisfied with the dose regiment and fell comfortable.

Disadvantages of the study were that there was diversity in following and the lack of data. i.v form of ibandonic acid is safe and comfortable for every day practice. Our experience confirms that i.v. given bisphosponate therapy is especially comfortable for patients who are older, with a lot of concomitant chronic diseases, with multiple medication therapy and with gastrointestinal disturbances.

The average life expectancy in N.Macedonia is 75 years. 131 of our group were over 50 years. So they had expected lifespan at least 25 years and it is long .The should live without fractures and with good quality of life. Out duty, as doctors is to enable it to them.

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Original scientific paper

NIVELI I ACIDIT FOLIK DHE HOMOCISTEINËS TE PACIENTËT DIABETIK

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ABSTRAKTI

Hyrje: Hiperhomocisteinemia ka efekt në funksionin dhe integritetin e endotelit, kështu që është një faktor rreziku për aterosklerozën, sëmundshmërinë dhe vdekshmërinë. Acidi folik luan një rol të rëndësishëm në remetilimin (cikli metionin–folat) e homocisteinës dhe kështu është i aftë të ulë nivelet e ngritura të saj.

Qëllimi i studimit: Qëllimi i këtij studimi është matja e nivetit të acidit folik dhe homocisteinës te pacientët diabetik dhe vlersimi i efektit terapeutik të acidit folik në nivelin e homocisteinës te këto pacientë.

Materiali dhe metoda: Në këtë studim kohort-prospektiv i cili është realizuar në laboratorin Biokimik Diagnostik në Spitalin Klinik të Tetovës janë përfshirë 45 pacientë diabetik dhe 25 jo daibetik të cilët janë marrë si grup kontrollë. Për matjen e parametrave si glukoza, HbA1c, acidi folik dhe homocisteina nga pacientët eshtë marrë gjak venoz.

Rezultatet: Niveli homocisteinës të matur para trajtimit me acid folik është dukshëm më i lartë te pacientët diabetik, vlera mesatare 22.148±10.051 te pacientët diabetik të trajtuar me hipoglikemik oral dhe 17.135±6.50 te pacientët diabetik të trajtuar me insulin. Pas trajtimit me acid folik niveli i acidit folik eshtë ulur 21.35% në grupin e pacientëve diabetik të trajtuar me hipoglikemik oral dhe 14.66% në grupin e pacientëve diabetik të trajtuar me insulin.

Konkluzioni: Niveli i homocisteinës është më i lartë te pacientët diabetik, krahasuar me pacientët jo diabetik dhe nivel më i lartë është gjetur në gupin e pacientëve diabetik të tajtuar me hipoglikemik oral. Pas trajtimit me acid folik, niveli i homocisteinës ulet, ulje e cila është më e theksuar te pacientët diabetik të trajtuar me hipoglikemik oral.

Fjalët kyçe: acidi folik, homocisteina, pacientë diabetik.

HYRJE

Homocisteina është aminoacid i cili u zbulua në vitin 1932 nga Vigneaud dhe formohet si produkt i transmetilimit të metioninës që është një aminoacid esencial. Hiperhomocisteinemia (vlerat më të larta se 15 mikromol për litër) zakonisht gjendet në më shumë se 60% e pacientëve që kanë një formë të sëmundjes vaskulare, ndërsa prevalenca e saj në popullatën e përgjithëshme vlersohet të jetë rreth 1%. Hiperhomocisteinemia ka efekt në funksionin dhe integritetin endotelial, kështu që është një faktor risku për aterosklerozën, sëmundshmërinë dhe vdekshmërinë [1,2].

Plazma/Serumi human përmban formën e oksiduar dhe të reduktuar të homocisteinës. Forma e reduktuar ose sulfudrile e homocisteinës quhet homocistein, ndërsa forma e oksiduar ose disulfide homocistin. Në plazmën humane, 98-99% e homocisteinës totale bën pjesë në formën e oksiduar dhe atë 80-90% është e lidhur me proteina, kryesisht me albumina dhe 5-10% e formës tjetër të oksiduar: homocistin dhe disulfidi i përzier, cistein-homocistein. Vetëm 1% e formës së reduktuar ndodhet e lirë. Termi homocistein totale (tHcy) paraqet shumën e katër formave që ndodhen në plazëm/serum [3].

Duke marrë parasysh studimet e homocisteinës totale

(tHcy) te pacientët diabetik, hiperhomocisteinemia duket se shoqërohet me manifestime klinike të makroangiopatisë [4] dhe retinopatisë proliferative [5], derisa studijues të tjerë kanë gjetur nivele të larta të tHcy vetëm te pacientët me shenja klinike të nefropatisë diabertike [6].

Acidi folik luan një rol të rëndësishëm në remetilimin (cikli metionin–folat) e homocisteinës dhe kështu është i aftë të ulë nivelet e ngritura të saj [7]. Metionina është një nënprodukt i sintetizuar pasi folati zvogëlon nivelet e homocisteinës në gjak; 5-10-MTHF (5-10-metil-tetrahidrofolat) dhuron një grup metil në një enzimë, metil-tetrahidrofolat reduktaza (MTHFR), dhe më pas kalon në 5-metil THF [8]. Metil-THF e konverton vitaminën B12 në metil-B12 (metilkobalamin). Metil-B12 e konverton homocisteinën në metionin në reaksionin e katalizuar nga homocistein metiltransferaza [9].

Acidi folik është një përcaktues i rëndësishëm dietik i homocisteinës; furnizimi ditor me 0,5 deri 5,0 mg acid folik zakonisht e ul nivelin e homocisteinës në plazëm me rreth 25 përqind [10].

QËLLIMI I STUDIMIT

Qëllimi i këtij studimi është matja e nivetit të acidit folik dhe homocisteinës te pacientët diabetik dhe vlersimi i efektit terapeutik të acidit folik në nivelin e homocisteinës te këta pacientë.

MATERIALI DHE METODA

Në këtë studim kohort-prospektiv i cili është realizuar në laboratorin Biokimik në Spitalin Klinik të Tetovës në periudhën kohore Nëntor 2019-Nëntor 2020 janë përfshirë gjithsej 70 pacientë tek të cilët janë gjetur vlera të rritura të MCV >99 fL, prej të cilëve 45 pacientë diabetik (23 trajtohen me hipoglikemik oral dhe 22 insulin) dhe 25 pacientë jo daibetik të cilët janë marrë si grup kontrollë. Nga studimi janë përjashtuar pacientët të cilët vuajnë nga insuficienca renale, sëmundje malinje dhe sëmundje autoimmune. Pacientët u përfshinë në studim pasi plotësuan një dokument të pëlqimit.

Për matjen e parametrave biokimik dhe hematologjik nga pacientët është marrë gjak venoz (pas 12 orësh gjendje urie, pas 15 minuta pushim, në pozitë ulur) 3 ml me antikoagulant K3EDTA ku është matur HbA1c dhe 6 ml gjak në epruvetë për përfitimin e serumit ku janë matur parametrat biokimik si glukoza, acidi folik dhe homocisteina. Niveli i glukozës në serum është matur me anë të aparatit Siemens RXL me anë të metodës spektrofotometrike, niveli i homocisteinës në aparatin Immulite 2000 me anë të metodës elektrohemiluminiscente (ECLIA), ndërsa acidi folik me anë të metodës direkte hemiluminiscente (DCLIA) në aparatin Advia Centaur.

Vlerat referente për parametrat e realizuar janë: Glukoza në serum 3,5-6,1 mmol/L; HbA1c 4,5-6,2%; Acidi folik >5, 38 ng/mL dhe homocisteina 5-12 µmol/L. Të gjithë pacientët e përfshir në studim janë pacientë të cilët janë trajtuar me acid folik për 8 javë. Matja e parametrave si HbA1c, glukozës,acidit folik dhe homocisteinës është realizuar para dhe pas trajtimit me acid folik.

Përpumimi statistikor i të dhënave është realizuar me anë të programit statistikor IBM SPSS, version 26. Për variablat u përcaktua vlera mesatare, devijimi standard, p-vlera dhe koeficienti i Pearson-it. Vlera e $p<0.05$ është vlersuar si statistikisht e besueshme.

REZULTATET

Në këtë studim morën pjesë 70 pacientë. Shpërndarja e pacientëve në studim është paraqitur në figurën 1.

Fig. 1 Shpërndarja e pacientëve të përfshirë në studim

Mosha mesatare e pacientëve në grupin kontroll (pacientë jo diabetik) është 56.280±9.172, në grupin e pacientëve të trajtuar me hipoglikemik oral 61.478±12.471 dhe 57.090±9.012 në grupin e pacientëve të trajtuar me insulin. Në studim morën pjesë 34 meshkuj dhe 36 femra (tabela nr 1).

Tabela nr.1 Karakteristikat e pacientëve të përfshir në studim

	Grupi kontroll	Pacientët diabetik të trajtuar hipoglikemik oral	Pacientët diabetik të trajtuar me insulin
Mosha	56.280±9.172	61.478±12.471	57.090±9.012
M:F	13:12	11:12	10:12
Glukoza	5.816±0.768	11.595±4.827	11.290±4.704
HbA1c	5.40±0.367	8.609±1.732	7.731±1.471
Acidi folik	9.781±2.831	7.067±3.495	7.584±1.948
Homocisteina	14.083±3.508	22.148±10.051	17.135±6.50

Vlera mesatare ± devijimi standard

Nga tabela nr.1 mund të shihet se vlera e HbA1c është në përqindje më të lartë tek pacientët diabetik të trajtuar me hipoglikemik oral, vlera mesatare 8.609±1.732. Gjithashtu niveli i homocisteinës të matur para trajtimit me acid folik është dukshëm më i lartë te pacientët diabetik, vlera mesatare 22.148±10.051 te pacientët diabetik të trajtuar me hipoglikemik oral dhe 17.135±6.50 te pacientët diabetik të trajtuar me insulin.

Tabela nr.2 Krahasimi i koncentrimit të parametrave të analizuar në mes grupit kontroll dhe pacientëve diabetik te trajtuar me hipoglikemik oral

	Grupi kontroll	n	Pacientë diabetik të trajtuar me hipoglikemik oral	n	p
Glukoza	5.816±0.768	25	11.595±4.827	23	<0.0001
HbA1c	5.40±0.367	25	8.609±1.732	23	<0.0001
Acidi folik	9.781±2.831	25	7.067±3.495	23	0.0048
Homocisteina	14.083±3.508	25	22.148±10.051	23	0.0005

Vlera mesatare ± devijimi standard; p-sinjifikanca statistikore

Nga përpunimi statistikor i parametrave të analizuar te pacientët diabetik të trajtuar me hipoglikemik oral dhe grupit kontroll të cilët janë paraqitur në tabelën nr.2 mund të shihet se egziston dallim sinjifikant statistikor për të gjithë parametrat e analizuar.

Tabela nr.3 Krahasimi i koncentrimit të parametrave të analizuar në mes grupit kontroll dhe pacientëve diabetik te trajtuar me insulin

	Grupi kontroll	n	Pacientë diabetik të trajtuar me insulin	n	p
Glukoza	5.816±0.768	25	11.290±4.704	22	<0.0001
HbA1c	5.40±0.367	25	7.731±1.471	22	<0.0001
Acidi folik	9.781±2.831	25	7.584±1.948	22	0.0038
Homocisteina	14.083±3.508	25	17.135±6.50	22	0.0476

Vlera mesatare ± devijimi standard; p-sinjifikanca statistikore.

Nga tebela nr.3 vërehet se egziston dallim sinjifikant statistikor për të gjithë parametrat e analizuar, në mes pacientëve diabetik të trajtuar me insulin dhe grupit kontroll.

Tabela nr. 4 Korrelacioni i homocisteinës dhe parametrave të tjerë

	Grupi kontroll		Pacientë diabetik të trajtuar me hipoglikemik oral		Pacientë diabetik të trajtuar me insulin	
Korelacioni	r	p	r	p	r	p
Gl. vs Hcy	0.333	0.104	0.090	0.684	-0.133	0.554
HbA1c vs Hcy	0.381	0.060	0.125	0.571	0.432	0.045
Ac. Folik vs Hcy	0.359	0.078	-0.222	0.309	0.003	0.989

r-korelacioni i Pearsonit; p-sinjifikanca statistikore

Të dhënat për koeficientin e korrelacionit, ndërmjet nivelit të homocisteinës dhe parametrave të tjerë si glukoza, HbA1c dhe acidi folik janë paraqitur në tabelën nr. 4, ku vërehet se egziston korrelacion pozitiv jo sinjifikant në grupin e kontrollit. Në grupin e pacientëve të trajtuar me hipoglikemik oral vërehet korrelacion pozitiv jo sinjifikant me mes glukozës, HbA1c në lidhje me nivelin e homocisteinës, ndërsa korrelacion negativ jo sinjifikant në mes acidit folik dhe homocisteinës. Nga përpunimi i të dhënave në grupin e pacientëve të trajtuar me insulin vërehet se egziston korrelacion negativ jo sinjifikant në mes glukozës dhe homocisteinës, korrelacion pozitiv sinjifikant në mes HbA1c dhe homocisteinës ndërsa korrelacion pozitiv jo sinjifikant në lidhje me koncentrimin e acidit folik dhe homocisteinës.

Tabela nr.5 Niveli i homocisteinës para dhe pas trajtimit me acid folik

	Niveli i Hcy para trajtimit me acid folik	Niveli i Hcy pas trajtimit me acid folik	p
Grupi kontroll	14.083±3.508	11.488±3.148	0.0132
Pacientët diabetik të trajtuar me hipoglikemik oral	22.148±10.051	17.419±5.022	0.0497
Pacientët diabetik të trajtuar me insulin	17.135±6.500	14.658±5.833	0.1906

Vlera meratare ±devijimi standard; p-sinjifikanca statistikore

Nga tabela nr. 5 shihet se ka dallim sinjifikant statistikor te pacientët jo diabetik (grupi kontroll) para dhe pas trajtimit me acid folik , p=0.0132 (niveli i acidit folik eshtë ulur 18.43%). Në grupin e pacientëve diabetik të trajtuar me hipoglikemik oral gjithashtu vërehet dallim

statistikor sinjifikant , p=0.0497 (niveli i acidit folik eshtë ulur 21.35%). Dallim sinjifikant statistikor nuk vërehet në grupin e pacientëve diabetik të trajtuar me insulin ku p=0.1906 (niveli i acidit folik eshtë ulur 14.66%).

KONKLUZIONI

Nga ky studim mund të konkludojmë se niveli i homocisteinës është më i lartë te pacientët diabetik, krahasuar me pacientët jo diabetik dhe nivel më i lartë është gjetur në gupin e pacientëve diabetik të tajtuar me hipoglikemik oral.

Te pacientët me diabetik, esull edhe pas ngarkimit të organizmit me metionin, është gjetur se niveli i homocisteinës në plazëm është dukshëm më i lartë në krahasim me njerzit e shëndoshë [11]. Dy studime tregojnë se plotsimi i furnizimit me folate zvoglon difunksionin endotelial te diabeti melitus tip 2 që shoqërohet me hiperinsulinemi [12,13]. Pas trajtimit me acid folik, niveli i homocisteinës ulet, ulje e cila është me e theksuar te pacientët diabetik te trajtuar me hipoglikemik oral. Plotësimi i acidit folik duhet të rekomandohet te çdo pacient që ka nivel të rritur të homocisteinës [14] dhe acidi folik duhet të administrohet së bashku me metforminën në diabetin tip 2 [15].

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Profesional paper

ВЛИЈАНИЕ НА ФАКОЕМУЛЗИФИКАЦИЈАТА ВРЗ КОРНЕАЛНИОТ ЕНДОТЕЛ

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АБСТРАКТ

Цел на трудот: да се посочи влијанието на факоемулзификацијата со примена на техниката Divide and conquer, врз морфологијата и функцијата на ендотелните клетки, како и на нејзините предности и недостатоци.

Вовед: Со развојот и усовршувањето на факоемулзификацијата, оперативниот зафат на катаракта веќе не е само метод за отстранување на заматената леќа, туку техника која се карактеризира со минимална инвазивност и минимални компликации и предизвик за хирурзите за добивање максимална постоперативна видна острина. Веќе неколку години наназад се прават истражувања за влијанието на фако методата врз корнеалниот ендотел со цел подобрување на техниките и добивање на подобар постоперативен исход. Меѓутоа и покрај напорите, декомпензацијата на ендотелот постоперативно, останува една од почестите постоперативни компликации.

Методи: проспективна анализа на пациенти кои се испратени на Клиниката за очни болести- Скопје, за оперативен зафат на катаракта. Сите пациенти се над 60 години, групирани според возраст и пол. Сите пациенти се со сенилна катаракта, групирани според зрелост во три групи (нон матурна, матурна и хиперматурна). Кај пациентите е направена спекуларна микроскопија со пахиметрија, рефракција, одредување видна острина, мерење на тонус и преглед на фундус, предоперативно, 7 дена после операција и 1 месец после операција. При анализа на спекуларната микроскопија земени се во обзир вредностите на : густина на ендотелни клетки на 1мм квадратен, коефициент на варијација, хексагоналност и централна корнеална дебелина. Сите пациенти се оперирани на Infinity phaco систем, со техниката Divide and conquer, од ист хирург.

Резултати: густината на ендотелните клетки е значајно намалена постоперативно, и тоа за 18% во првите 7 дена и за 33.3 % после 1 месец. Коефициентот на варијација на клетките е зголемен за 11 % во првите 7 дена, а хексагоналноста е намалена за 26% првите 7 дена. Постоперативно централната дебелина на рожницата е зголемена за 2.10 % и се враќа во нормала (+0.07%) во следниот месец. Во однос на пол, кај мажите е поизразено губењето на ендотелни летки, а по однос на возраст, кај пациентите во 7ма декада губењето е 21.3 % по 1 месец, а кај пациентите над 70 години е 36. 9 %. И во однос на видот на катаракта, кај хиперматурните катаракти губењето на ендотелни клетки е за 3 % повеќе отколку кај матурните и нематурните катаракти.

Заклучок: факоемулзификацијата влијае на морфологијата и функцијата на ендотелните клетки. Тоа се согледува постоперативно преку променетите параметри: густина на ендотелните клетки, полиморфизам и полимегатизам. Исто така ова влијание е поизразено со напредната возраст и кај пациенти со хиперматурна катаракта.

Клучни зборови: факоемулзификација, ендотелни клетки, спекуларна микроскопија, Divide and conquer

ВОВЕД

Катарактата е една од водечките причини за превентивно слепило ширум светот. Со напредокот на технологијата, операцијата на катаракта веќе не е само зафат за отстранување на заматената леќа, туку техника со максимална безбедност, минимална инвазивност и се стремеж за постигнување на максимална видна острина. Овие цели се остварени преку креирање минимален рез, со тоа намален постоперативен астигматизам, контрола на флуидите за време на операција и енергијата при фако, се со цел помала инфламација и побрзо опоравување. Проблемот кој сеуште постои е губењето на ендотелни клетки и декомпензација на рожницата. (1) Со развојот на новите технологии, факоемулзификацијата стана најкористена метода за екстракапсуларна екстракција на леќа. Меѓутоа и покрај сите усовршувања, оштетувањето на корнеалниот ендотел сеуште е сериозна компликација. Ефектите на иригационио притисок, покачената температура во предна комора

како и формирањето на слободни радикали се фактори кои доведуваат до оштетување на ендотелот. (2) Користениот ултразвук предизвикува кавитација на водениот раствор и директна дезинтеграција на водената молекула, создавајќи една од најпотентните реактивни кислородни видови- хидроксил радикалите. Хидроксил радикалите настануваат повеќе при користење на аеробни раствори, а се намалуваат при користење на балансиран солен раствор (BSS) кој содржи бикарбонати, декстроза и глутатион (BSS plus). Ендотелното оштетување може да се јави и заради други фактори како што се дисторзија на рожницата, при аспирација на нуклеарни фрагменти, контакт со IOL, но и јатрогено со инструмент. (3) (4)

Корнеалниот ендотел е единечен слој на ендотелни клетки на внатрешната страна на корнеата. Ендотелните клетки кои имаат улога на бариера и пумпа, се важни за одржување на транспарентност на корнеата. (5) Нивниот број изнесува од 4000 до 5000 клетки на милиметар квадратен при раѓање и се намалува со возраста, за да кај адулти изнесува 2000 до 3000 клетки на милиметар квадратен. Ендотелните клетки се нерепликативни и нивното губење се надоместува преку миграција, издолжување и зголемена хетерогеност на клетките, заради компензација. Критична бројка за да настане декомпензација на рожницата е под 500 клетки на милиметар квадратен. (5)(6)

Неколку студии покажуваат дека одредени ризик фактори предоперативно и интраоперативно го зголемуваат ризикот од губење на ендотелни клетки за време на факомулзификација, како што е постара возраст, тврд нуклеус, голема ултразвучна енергија, продолжено време на операција, применетата техника и голем волумен на инфузијата-иригацијата. Факоемулзификацијата се изведува во ограничен затворен простор, затоа влијание, во однос на механичкото и термалното оштетување на ендотелот, имаат анатомскиот фактор, како што е длабочината на предна комора, како и техниката на работа на самиот хирург. Според друга студија пак, (Hwang и сор., 2015) длабочината на предна комора нема влијание во однос на губење на ендотелни клетки. Сепак овие студии немаат земено во предвид други фактори како што се кумулативната расипна енергја (CDE), времетраење на ултразвук (UST) и балансираниот солен раствор (BSS) како ризични кофактори. Оштетувањето на ендотелните клетки може да доведе до декомпензација на рожницата особено кај високо ризичните групи, затоа мерењето на ендотелни клетки предоперативно е значаен прогностички фактор за исходот од оперативниот зафат и ефектот врз постоперативната видна острина. (7) (8)

Нормално ендотелните клетки се намалуваат со годините за 5-6 % на секои 10 години (9), додека постоперативно, во различни конфликтни извештаи, губењето на ендотелни клетки варира помеѓу 7% за конвенционалните методи и 11,6% за бимануелното фако. (10)

Губењето на ендотелните клетки е главно поврзано со зголемената кумулативната расипна енергија - Cumulative dissipated energy (CDE), продолжено време на аспирација и зголемена количина на флуид што се користи за време на хируршката процедура. Кај тврдите нуклеарни катаракти и кај торзионото фако, има потреба од многу повеќе енергија , затоа што торзионата сила сама по себе не е доволна и со тоа консеквентно се зголемува CDE што може да заврши со поголемо губење на ендотелни клетки. (11)

МАТЕРИЈАЛИ И МЕТОДИ

Во нашата студија беа вклучени 23 пациенти, оперирани и следени на Клиниката за очни болести- Скопје. Од вкупниот број на пациенти, 12 беа жени и 11 мажи. Сите на возраст над 60 години. Пациентите беа поделени во групи, според возраст : пациенти на возраст од 60-70 години, 70-80 години и над 80 години. Пациентите беа групирани и според зрелоста на катарактата: пациенти со нон-матурна, матурна и хиперматурна катаракта. Кај секој пациент беше одредена видна острина, мерење на тонус (Topcon CT- 80 computerized tonometer), преглед на фундус, направена спекуларна микроскопија со централна корнеална дебелина (Tomey specular microscope EM-3000), и рефрактометрија (Nidek ARK-1S), предоперативно, 7 дена после операција и 1 месец после операција. При анализа на спекуларната микроскопија земени се за анализа вредностите на CD (cell density- густина на ендотелни клетки на 1мм квадратен), CV (coefficient of variation – коефициент на варијација), 6A - хексагоналност и CCT (централна корнеална дебелина). Варијациите на ендотелните клетки се анализирани и по групи врз основа на возраст и пол. Сите пациенти се оперирани на Infinity phaco систем, во периодот од јануари 2020 до март 2020 година, со техниката Divide and conquer, од истиот офталмохирург.

РЕЗУЛТАТИ

Од анализата на податоците може да се заклучи дека постоперативно има значајно намалување во густината на ендотелните клетки, како и варијација во форма (плеоморфизам) и големина (полимегатизам) на клетките, со тоа што поголемо губење на ендотелни клетки имаше во групата мажи и кај пациенти над 70 години. Просечно намалување на CD кај мажи изнесува 38% после 1 месец од операција, додека кај жени 28.7 %. Коефициентот на варијацијата на клетките- CV, кај мажите е зголемен за 14.6 %, а кај жените за само 1.6 %. Хексагоналноста исто така има поголеми промени кај машката популација со намалување од 14.7 %, додека кај жените за 8.09%. Централната корнеална дебелина и кај двете групи не е знчајно променета, постоперативно корнеалната дебелина е зголемена за 0.8% кај мажи и за 0.9% кај жени. (табела 1, 2 и 3, графикон 1и 2).

Мажи/возраст	CD preop	CD 7d	CD1m	CV preop	CV 7d	CV 1m	6A preop	6A 7d	6A 1m	CCT preop	CCT 7d	CCT 1m
60-70 години	2420.6	1981.3	1443.4	41.4	45.3	42.9	43.3	37.5	40.6	550.7	557.9	547.7
70-80 години	2422.9	1883.7	1450.4	41.7	45.8	42.8	42.9	36.4	42.7	551.5	559.9	552.2
80-90 години	2246	1983	1495	36	45	51	49	43	32	509	530	524
Средна вредност	2363.167	1949.333	1462.933	39.7	45.36667	45.56667	45.06667	38.96667	38.43333	537.0667	549.2667	541.3
			38%			14.60%			14.70%			0.80%

Табела1. Анализа на спекуларна микроскопија кај мажи во различни возрасни групи (просечни вредности), предоперативно, по 7 дена и по 1 месец. (CD - cell density- густина на ендотелни клетки на 1мм квадратен, CV - coefficient of variation – коефициент на варијација, 6A- хексагоналност и CCT -централна корнеална дебелина)

Жени/возраст	CD preop	CD 7d	CD1m	CV preop	CV 7d	CV 1m	6A preop	6A 7d	6A 1m	CCT preop	CCT 7d	CCT 1m
60-70 години	2362.3	2086.9	2199	41.7	45.7	39	41.1	36.8	34	554.3	569.2	542
70-80 години	2379.7	1832.9	1422.2	42	45.3	44.5	42.7	36.2	40.9	549	558.2	546.7
80-90 години	2380.3	1843.2	1461.4	42.3	45.5	44.6	42.3	36.1	41	550.9	559.7	550.5
Средна вредност	2374.1	1921	1694.2	42	45.5	42.7	42.03333	36.36667	38.63333	551.4	562.3667	546.4
			28.70%			1.60%			8.09%			0.90%

Табела2. Анализа на спекуларна микроскопија кај жени во различни возрасни групи (просечни вредности), предоперативно, по 7 дена и по 1 месец

Просек заедно ма	2367.852	1937.19	1366.839	40.68571	45.42381	38.81408	43.76667	37.85238	33.72254	543.2095	554.881	475.551
		18%	33.30%		11.27%	8%		26%	3.90%		2.10%	0.07%

Табела 3. Просек на променетите вредности кај мажи и жени заедно.

Графикон 1: графички приказ на податоците од спекуларна микроскопија кај мажи.

Графикон 2: графички приказ на податоците од спекуларна микроскопија кај жени.

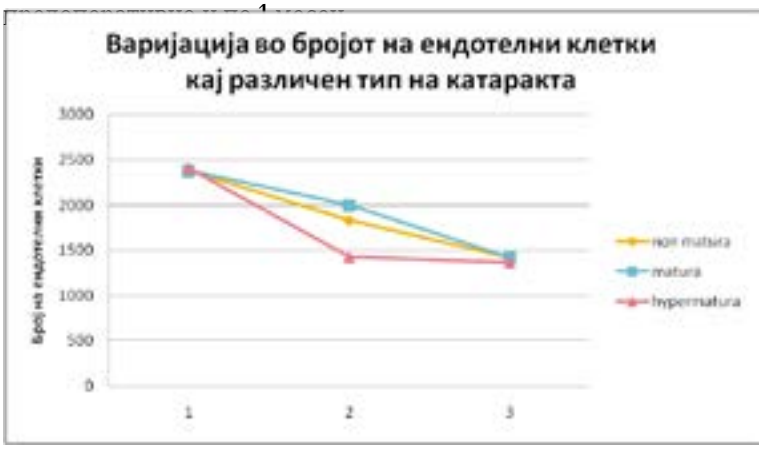
Разлика во варијацијата се покажа и кај различните типови на катаракта. Очекувано кај нон матурните катаракти, намалувањето во густината на ендотелните клетки, како и промена во коефициентот на варијација и хексагоналност, е помала за разлика од матурните и хиперматурните катаракти, иако разликата е само 3%. (табела 4 и 5, графикон3)

Катаракта	CD preop	CD 7d	CD1m	CV preop	CV 7d	CV 1m	6A preop	6A 7d	6A 1m	CCT preop	CCT 7d	CCT 1m
non matura	2379.7	1833	1422.2	42	45.3	44.5	42.7	36.2	41	549	558.2	546.7
matura	2381.3	1997.8	1418.6	42.1	47.4	44.4	42.6	37	40.7	550	560	548.9
hypermatura	2410.8	1428	1367.1	41.9	54	43.4	42.1	39	40.8	550.5	559.1	548.2

Табела4. Анализа на спекуларна микроскопија кај различни типови на катаракта (просечни вредности), предоперативно, по 7 дена и по 1 месец

Тип на катаракта	preop	1m	Процент
non matura	2379.7	1422.2	40.20%
matura	2381.3	1418.6	40.40%
hypermatura	2410.8	1367.1	43.30%

Табела.5. процентуално намалување на густината на ендотелни клетки кај различен тип на катаракта,



Графикон3. Графички приказ на намалување на густината на ендотелни клетки кај различен тип на катаракта, предоперативно (1), по 7 дена (2) и по 1 месец (3).

Различно намалување се забележува и во различните возрасни групи, што исто така е очекувано, и изнесува 21.3% кај пациентите од 60-70 години, 36.9 % кај пациентите од 70-80 години и 36.1 % кај пациентите од 80-90 години. (табела 6).

Возраст	preop	1m	Процент
60-70 години	2391	1824.7	21.30%
70-80 години	2312.8	1458.6	36.90%
80-90 години	2313	1478	36.10%

Табела 6. Просек во намалувањето на густината на ендотелни клетки кај мажи и жени заедно, во различни возрасни групи, предоперативно и по 1 месец.

Графикон 4. Графички приказ на варијациите на спекуларна микроскопија кај различен тип на катаракта.

Беше направена анализа и на видната острина постоперативно и корелацијата со густината на ендотелни клетки. Изненадувачки е што кај одредени пациенти чија густина на ендотели клетки беше под 800/мм2, имаа добра видна острина од 0.8 уште првите 7 дена, кај двајца пациенти не можеше да се направи спекуларна микросопија заради едем на рожницата. Најниската видна острина изнесуваше 0.25 и 0.3 бк (без корекција), кај две пациентки кај кои имаше постперативен астигматизам од -2.5 и -3.00 диоптрии соодветно. И двете пациентки имаа астигматизм од -1.75 диоптрии предоперативно. Видната острина кај двете пациентки со корекција изнесува 0.5 по Снелен.

Графикон 5. Корелација меѓу видната острина и густината на ендотелни клетки.

Просечната видна острина предоперативно изнесуваше 0.14 (BCVA) по Снелен. Постоперативно 7 дена просечната видна острина изнесуваше 0.75 бк, и 1 месец постоперативно 0.77 без корекција и 0.81 со корекција (BCVA).

ДИСКУСИЈА

Постоперативните копликации кај факоемулзификацијата сеуште остануваат предизвик, особено губењето на ендотелни клетки и едем на рожницата. Влијание имаат различни фактори како техниката на работа,

длабочина на предна комора, иригационен притисок, создавање топлина и слободни радикали. (1) (2) Едни од компликациите при факоемулзификација за време на операција на катаракта се инцизиона изгореница или контрактура од топлината предизвикана со фрикција како резултат на ултразвучното движење на типот. Причини за да настане изгореница се сметаат: позиција на иглата, низок прилив (flow) и несоодветно подесување на ултразвукот. Друга студија (Han и сор., 2009) ја истражува разликата во продукцијата на топлина меѓу лонгитудиналното и торзионото фако и е заклучено дека торзионата факоемулзификација резултира со создавање помала температура за разлика од лонгитудиналото фако, кое ја зголемува температурата за 41.5 степен целзиусов повеќе од торзионото. (12)

Во една студија (Chen и сор, 2015) правена во Хонолулу, САД направена е споредба меѓу двата фако системи, Centurion и Infiniti, и е заклучено дека Centurion фако системот бара помалку енергија за отстранување на катаракта, со просечна редукција на енергијата од 38 % по хирург во споредба со Infiniti фако системот. А и кај двата системи, кумулативна расипна енергија и за системот Infiniti и Centurion варирала директно со возраста на пациентот, зголемувајќи се во просек од 2,38 проценти-секунди, на секои 10 години. (13) Се смета дека ова намалување настанува заради самата апоптоза на клетките и/или некроза од оксидативно оштетување индуцирано од светлина. (6) Според документите на Алкон, 2015 година, хендписот на системот Инфинити има еден недостаток, имено при значителни движења со типот се индуцира фрикција (триење) долж резот, што резултира со стромални промени на место на инцизијата. Новиот shaft friction phacoemulsification ги минимизира овие стромални промени со намалување на количеството на енергија која се пренесува на сливот и на инцизиниот порт и овој дизајн имено освен што го подобрува термалниот профил , ја зголемува и ефикасноста на сечењето (cutting efficiency). (13)

Во друга студија (Storr и сор, 2008) направена е споредба меѓу техниката phaco chop и divide and conquer, во однос на влијанието на различната техника врз корнеалниот ендотел. За време на операцијата анализирани се времетраењето, фако енергијата, иригациониот волумен и степенот на тврдост на јадрото. Мерена е густината на ендотелни клетки, варијација на клетките по големина, процент на хексагналност и централната корнеална дебелина и се заблежувани 3 и 12 месеци постоперативно. Резултатите покажале значајно помала фако енергија користена за време на phaco-chop техниката за разлика од divide-and-conquer. Постоперативно двете групи имале пад во клеточната густина, немало сигнификантна разлика во варијацијата на клеточна големина, процент на хексагоналност или централна корнеална дебелина. Видната острина значајно била подобрена кај двете групи. Било забележано поголемо губење на ендотелни клетки кај пациенти со помала аксијална должина. Заклучено е дека сепак техниката phaco-chop е помалку штетна по еднотелот на корнеата заради користење на помалку енергија, меѓутоа и кај двете техники е сепак мало губењето на ендотелни клетки. (14)

Во студија (Bourne и оср, 2004) правена за споредба на факоемулзификацијата во однос на ECCE, најдено е дека нема значајна разлика во вкупното губење на ендотелни клетки меѓу двете техники, додека кога се работи за пациенти со тврда катаркта, губењето на ендотелни клетки е 52.6 % кај фако наспроти 23.1 % кај ECCE. Што сугерира дека кај тврдите катаракти можеби факото не е метода на избор. (15)

Анализа на пациенти со унилтерална факоемулзификација и интракапсуларна екстракција, покажала намалување на бројот на ендотелни клетки за 33.8 % (ECD) кај факоемулзификација. Додека пациентите со интракапсуларна екстракција имале намалување во бројот на ендотелни клетки за 14.9%, што укажува на тоа дека факоемулзификација е потрауматска за корнеалниот ендотел за разлика од интракапсуларната екстракција. (16)

Во споредба на торзионо со лонгитудинално фако, во една студија (Takahashi и сор.,2002) која вклучува 50 очи, заклучено е дека нема статистички важна разлика во бројот на изгубени ендотелни клетки и централната густина на ендотелните клетки, постоперативно кај двете методи. (17)

Истражувано е експериментално на зајаци , формирањето на слободни радикали како фактор за постоперативни компликациии и дали одреден хијалуронат со различна специфична тежина може да влијае на нивно создавање. Оштетувањето е мерено преку евалуација на централната корнеална дебелина со пахиметрија, а инфламацијата преку мерење на леукоцити и простагландин E2 (PGE2) и

евалуација на активноста на миелопероксидаза во увеално ткиво. Заклучено е дека хијалуронатот го намалува формирањето на слободни радикали за 58-60%, намалувајќи го задебелувањето на корнеата за 76-80% и губитокот на ендотелни клетки за 54-61%, без разлика на различната специфична тежина на хијалурнатот.(18)

Исто така правена е анализа на статусот на корнеалниот ендотел после факоемулзификација и постоперативното опоравување кај пациенти со дијабет и пациенти без дијабет. Заклучено е дека без разлика на гликемиската контрола т.е и кај добра гликемиска регулација, кај пациентите со дијабет има поголемо оштетување на ендотелот после операција и многу поспоро постоперативно опоравување.(19)

Споредувајќи ја пахиметријата и бројот на ендотелни клетки пред и после операција, направена е анализа за дејството на континуираната инфузија во предна комора (continuous anterior chamber infusion- CACI) и е заклучено дека транзицијата од конвенционална во бимануелна факоемулзификација не го зголемува оштетувањето на ендотелот. (20)

Слободните радикали се една од причините за оштетување на ендотелот. Водородниот пероксид врши физиолошки и анатомски оштетувања на ендотелот што резултира со стромален едем на корнеа. (21)

Намалување во бројот на ендотелни клетки е нормално со зголемување на возраста. Нагло намалување на бројот настанува постоперативно кај сите направени студии. (9) Исто така одредени студии покажуваат дека губењето на ендотелните клетки продолжува до една година постоперативно, со губење на ендотелни клетки од 3.5-5.7% после 12 месеци. (22). Различни студии даваат различни податоци за намалување на ендотелните клетки. Намалувањето на ендотелните клетки варира од 5.2–9.1% после 2 месеци од операција и за 4.5–7.9% после 3 месеци од операција. (23)(24)

ЗАКЛУЧОК

Факоемулзификацијата иако развиена метода сеуште има свои предизвици. За да се добие добра видна острина постоперативно, мора да се внимава на многу фактори, а еден од нив е густината на ендотелните клетки. На губењето на ендотелни клетки влијаат различни фактори вклучувајќи ја и техниката на работа. Важно е и користењето на соодветен солен раствор и хијалуронат при работа. Треба да се обрне внимание и на длабочината на предна комора, како и манипулациите во истата за време на фако. Видната острина постоперативно е во корелација со намалениот број на ендотелни клетки. Губењето на ендотелни клетки зависи и од типот на катаракта и можеби кај тврдите катаракти е добро да се размисли да се работат со техниката ECCE, со цел заштита на ендотелот. Спекуларната микроскопија е важен дел од предоперативната подготовка, заради навремено известување на пациентите за постоперативниот исход и опоравување, особено кај постари пациенти, пациенти со дијабет и пациенти со тврда катаракта.

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Profesional paper

VALUES OF PAPP-A, ASSOCIATED WITH PREMATURE BIRTH

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ABSTRACT

Summary: Children born prematurely are at higher risk of mortality, morbidity and impaired motor and cognitive development in childhood than prematurely born babies.

Objective: To establish the relationship between the corresponding levels of pregnancy-related plasma protein-A (PAPP-A) and the frequency of premature birth.

Materials and methods: The study is prospective. The data was collected through monitoring patients through a questionnaire and sonographic examination at 11-13 gestational weeks. The study excluded all known risk factors for preterm birth, such as previous preterm births, pregnant women with gestational diabetes, preeclampsia, hypertension, placenta previa, hydramnion, multiple pregnancies, smoking, structural and chromosomal abnormalities of the fetus and planned preterm birth. The data from the measured values of PAPP-A and the frequency of premature birth in 636 pregnant women were analyzed.

Results: PAPP-A levels are a statistically significant factor for preterm birth. It is expected with a 95% probability in the population with PAPP-A values below 0,515 that the cases with premature birth will be from 7 to 14 times more.

Conclusions: Pregnant women with PAPP-A level less than 10th per cent are significantly associated with an increased risk of preterm birth.

Keywords: First-trimester screening, Pregnancy-associated plasma protein-A (PAPP-A), Preterm birth, Pregnancy outcomes.

INTRODUCTION

In daily practice, the study of pregnancy-related plasma protein-A (PAPP-A), in combination with the β-fraction of human chorionic gonadotropin (β-hCG) and ultrasound measurement of NT between 11 and 13 years plus 6 days of pregnancy is widely used as a biochemical screening to calculate the risk of Trisomy 21 and other aneuploidies (1). The marker PAPP-A is produced in the syncytiotrophoblast of the placenta and is a major source of circulating plasma protein-A in the maternal serum (2). It helps to create a free insulin-like factor (IGF), which plays an important role for the trophoblast invasion in uterine decidua (3). Low levels of PAPP-A in the maternal serum lead to low levels of IGF, which can lead to abnormal trophoblast development and hence to various adverse complications of pregnancy, such as abortion, fetal developmental delay (IUGR), more frequent development of preeclampsia (PE), premature birth and oligohydramnios. Because PAPP-A serum marker screening is used worldwide to rule out fetal aneuploidy, low levels have been found to be associated with premature birth and other adverse effects of pregnancy (4, 5). Children born prematurely are at higher risk of mortality, morbidity and impaired motor and mental development in childhood than those born at term.

There are currently some differences in the definition of preterm birth. According to the Ministry of Health, a premature (untimely, embryonic) birth is the birth of a

fetus with a birth weight of 800-2499 grams, including/or at gestational age of 26 and/or less than 37 completed gestational weeks, regardless of whether it is alive or dead. Premature birth is also established if the body weight of the fetus is below 800 grams and the age is below 26 gestation weeks, provided that it was born alive and lived for at least 3 days.

The most widely used and accepted definition of preterm birth is that of the World Health Organization (WHO), which defines preterm birth as any birth before 37 full weeks of pregnancy or less than 259 days from the first day of a woman's last menstrual period (LMP). This is further divided on the basis of the gestational age (GA):

- extremely premature (up to 28 weeks);
- very premature (28 to 32 weeks);
- moderate or late premature birth (32 to 37 weeks of pregnancy).

The limitation of the WHO definition is that there is no boundary between miscarriage and the birth of a viable fetus, which complicates the assessment of premature birth. According to WHO data from 2015, about 10-15% of premature babies are born annually (15 million premature babies), and almost 1 million of them die due to complications related to early birth.

Data from 184 countries on all continents show that the percentage of premature births varies from 5 to 18% and the poorer a country is, the more premature births. Data for Europe from 2013 are for a level of prematurity from 5.5 to 11.5% (6).

According to the data from the Association of Neonatology, the average percentage of premature births in Bulgaria in recent years ranges between 9.5 and 10.5%. In addition, in most previous publications, the presence of other predisposing factors for preterm birth is not strictly controlled. We conducted this study to determine the strength of the relationship between PAPP-A levels and the development of "ideopathic preterm birth" (preterm birth without other predisposing factors and causes) using our own reference range.

AIM

To establish the strength and the relationship between the corresponding levels of pregnancy-related plasma protein-A (PAPP-A) and the frequency of premature birth.

OBJECTIVES

To establish the values of PAPP-A leading to premature birth.

MATERIALS AND METHODS

The study covered 636 consecutive singleton pregnancies in women undergoing screening in the first trimester. The duration of pregnancy during the blood test was calculated on the date of the last regular menstruation and was confirmed by ultrasound examination of the parietal-sacral length (CRL). This study excludes all known risk factors for preterm birth, such as previous preterm births, gestational diabetes, preeclampsia, hypertension, placenta previa, hydramnion, multiple pregnancy, smoking, structural and chromosomal abnormalities of the fetus and planned preterm birth.

Patients have given informed consent to the use of their data. The venous blood was tested in a laboratory using the DELFIA Xpress system (Perkin Elmer, Waltham, MA, USA). PAPP-A values were modified as MoMs (multiples of mediane).

All pregnant women with a PAPP-A level below 0.5 MoM in the first trimester during the biochemical screening were selected in a separate target group, while women with normal levels at the same gestational age were used as a control group. The selected group of pregnant women with PAPP-A levels below 0.5 MoM is based on reports in the literature of a more common adverse pregnancy outcome at these levels (4, 5, 7). Information on the course of pregnancy and childbirth is obtained from the protocols of women's consultations (LC) and maternity wards.

Statistical analysis was performed using IBM SPSS version 25.0.

Disease with a 95% confidence interval was calculated.

ROC analysis was used and a ROC curve was constructed to determine the diagnostic efficacy of low PAPP-A levels in predicting birth problems. ROC analysis determined the cut-off value, with the maximum amount of sensitivity and specificity. Logistic regression was used, the odds ratio was calculated to assess the prognosis of problems in the course of pregnancy in cases with low PAPP-A with 95% confidence intervals. Significance level $P < 0.05$ was established.

RESULTS

A total of 636 pregnant women were studied for a period of 5 years - from 2014 to 2019. Of the 636 women who gave birth, in 104 pregnant women (16%) the PAPP-A values were below 0.515 MoM. (Figure 1).

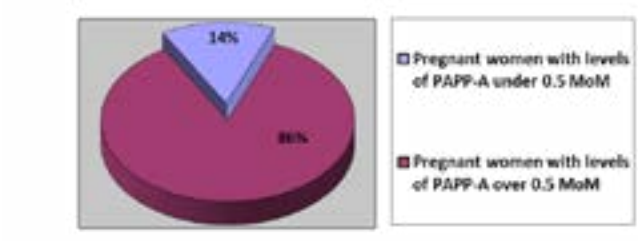

Fig.1 Frequency of pregnant women with low levels of PAPP-A

Out of 104 pregnant women with low levels of PAPP-A (MoM <0.515), 39 women had an unfavorable pregnancy outcome, such as: pregnancy loss, premature birth, preeclampsia, hypertension and retarded fetus birth.

In the control group of pregnant women with normal PAPP-A levels (MoM> 0.515), who were 532 women, these complications occurred in 39 pregnant women (Table 1).

Table 1. Complicated pregnancy and childbirth at low PAPP-A levels and in the control group.

Total number of pregnant women– 636			
With level of PAPP-A<0,515 MoM – 104 pregnant women		With level of PAPP-A>0,515 MoM - 532 pregnant women	
Complicated pregnancy and birth	Normal pregnancy and birth	Complicated pregnancy and birth	Normal pregnancy and birth
46	58	39	493
44,23%	55,77%	7,33%	92,73%

In the target group (PAPP-A <0.515 MoM) in 55.77% of the cases healthy full-term babies were born and in 44.23% there were complications of pregnancy and childbirth, such as premature birth, hypertensive diseases – preeclampsia or gestational hypertension (PE or PIH), young children of gestational age (SGA), fetal loss. In the control group, 92.73% of healthy full-term babies were born and all such complications were 7.33%. These differences were statistically significant (P <0.0001).

The distribution of the various complications of pregnancy in pregnant women with low levels of PAPP-A and in the control group are illustrated in Figure 2 and Figure 3.

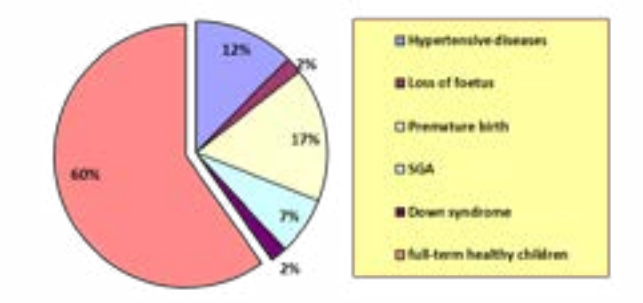

Fig.2 Pregnancy complications in pregnant women with PAPP-A level ≤ 0.5 MoM

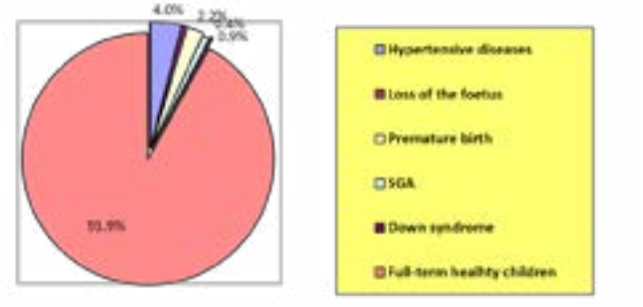

Fig.3 Complications of pregnancy in the control group - PAPP-A over 0.5MoM

The two figures show that the largest share of complications of pregnancy are: premature birth, PE and PIH, SGA and others (trisomy 21; fetal loss after 12 weeks of gestation).

There are 627 pregnant women with live births. Of these, 29 children were born prematurely (4.62%).

Of the pregnant women with preterm birth, 12 were with PAPP-A <0.5 MoM and 17 with PAPP-A> 0.5 MoM. The results of the percentage distribution of preterm infants are shown in Table 2.

Table 2. Distribution of premature births according to the level of PAPP-A

PAPP-A<0,515 MoM, N = 99	PAPP-A>0,515 MoM, N=528
Number of pregnant women with premature birth 12	Number of pregnant women with premature birth 17
12,12%	3,21%

The table shows that the level of PAPP-A is definitely different for the two groups and this difference is statistically significant (P <0.0001). PAPP-A levels are a statistically significant factor for preterm birth.

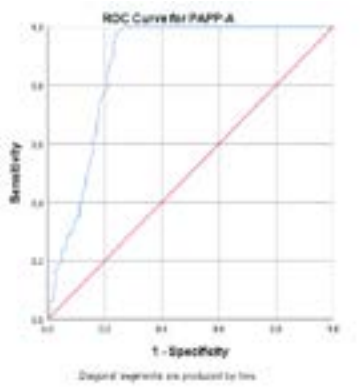

Fig. 4 Predicted PAPP-A levels <0.515 for complications during pregnancy (the area below the ROC curve 0.870).

In many studies, different authors report different cut-off values for the PAPP-A level expressed in MoM. Most opinions are grouped around a cut-off below 0.4 MoM. (8, 9) From the ROC analysis of our data, the breakpoint, cut-off is 0.515 MoM (Figure 4).

Because the study is a slice, it is possible to calculate the incidence of „preeclampsia“ and it is 5.7% with a 95% confidence interval (3.9; 7.5%).

It is expected with a 95% probability in the population with PAPP-A values below 0.515, the cases with premature birth to be from 7 to 14 times more.

DISCUSSION

Pregnant women with PAPP-A levels below the 10th percentile are associated with a significantly increased risk of preterm birth (4, 5, 7). According to some authors, the study of the level of serum PAPP-A independently performs poorly as a screening test for premature birth. The prognostic value is improved by the inclusion of additional factors (10, 11, 12).

According to the results of the study presented here, its significance is greater if only the cases of „idiopathic premature birth“ are taken into account.

CONCLUSION

This study excludes all known risk factors for preterm birth and the results give us reason to conclude that the level of PAPP-A is an independent risk factor for ideopathic premature birth.

Measurement of the sonographic length of the cervix (CL) is known to be the most useful tool for assessing the risk of spontaneous preterm birth in asymptomatic women in the middle of the pregnancy (13).

Cases of low levels of PAPP-A in the first trimester may focus the attention on tracking the relevant pregnant women and measuring the length of the cervix. Other biochemical and genetic factors (alpha-fetoproteins, insulin-like growth factor IGFBP-1, progesterone receptors, etc.) may be studied in pregnant women with low levels of PAPP-A and a shortened cervix.

This can help clinicians monitor and prevent preterm birth in cases with low levels of PAPP-A, regardless of other risk factors. Although the main purpose of using first-trimester serum indicators is to screen for aneuploidies, they are informative and are likely to be very useful in predicting preterm birth.

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Profesional paper

USE OF PRESEPSIN FOR DIFFERENTIAL DIAGNOSIS OF CARDIOGENIC PULMONARY EDEMA AND PNEUMONIA IN EMERGENCY DEPARTMENT. A PILOT STUDY.

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ABSTRACT

Objective of research: Shortness of breath may be the symptom for many diseases. When the causes of dysponea are evaluated, it may be observed that two-thirds of all cases are caused by cardiac and pulmonary causes. It may be difficult to make a differential diagnosis of these two diseases in some patients, especially for elderly patients and patients suffering from diabetes, immunosuppression, malignant and comorbid diseases. The aim of this study was to determine whether presepsin has a significant role in differential diagnosis of pneumonia and pulmonary edema.

Methods: This observational study was conducted at the Emergency Department of Zonguldak Bülent Ecevit University.

Patients who were admitted to the emergency department and who were diagnosed with pneumonia or cardiogenic pulmonary edema were included in the study. Plasma presepsin levels were measured in both patient groups.

Results: A total of 32 patients, 16 of whom were diagnosed with pneumonia and 16 were diagnosed with cardiogenic pulmonary edema, were included in the study. The level of presepsin was significantly higher in the pneumonia group.

Conclusion: The differentiation of cardiogenic pulmonary edema and pneumonia is closely related to the correct or wrong treatment. The use of specific biomarkers that are specific to infection may be helpful in the diagnosis, when differential diagnosis cannot be achieved clinically. In this study, we evaluated the availability of presepsin for this purpose and found that the level of presepsin was significantly higher in the pneumonia group.

Keywords: Presepsin, Differential Diagnosis, Pneumonia, Cardiogenic Pulmonary Edema

INTRODUCTION

Dyspnoea refers to difficulty breathing and it is one of the most common causes of application to emergency department. It does not have a single pathogenesis; however, it may be caused by several diseases. Two thirds of patients applying to emergency department with complaints of dyspnoea have cardiac or pulmonary origin [1]. 130 million people apply to emergency department per year due to complaints of pneumonia or acute decompensated heart failure [2]. Emergency physicians can make the diagnosis by evaluating this group of patients with anamnesis, physical examination, laboratory tests, and, if necessary, imaging methods. However, anamnesis, physical examination and laboratory findings may not be very sensitive and specific to achieve a diagnosis in diabetic or elderly patients, or patients with immunosuppression

or with many underlying diseases [1].

Patients with cardiogenic pulmonary edema (CPE), which occurs unilaterally in 2.1% of cases, may be mistakenly diagnosed with pneumonia. There is an increased risk of death in these patients because of inappropriate treatment due to misdiagnosis [3].

Cluster of differentiation 14 (CD14) is one of the leucocyte differentiation antigens [4]. The CD14 molecule is a glycoprotein receptor that is attached to the cell surface and has two soluble forms [4-6]. Both forms play role in the recognition of lipopolysaccharide pattern and in cell activation [5]. CD14 is mostly found in monocytes, macrophages, neutrophils, B lymphocytes, chondrocytes, dendritic cells, and intestinal epithelial cells. The soluble form of CD14, known as Soluble CD14 subtype (sCD14-ST), is called as presepsin. Presepsin, which exists in lower concentrations in serum of healthy individuals, is significantly increased during inflammation [7].

The aim of our study was to determine whether as an inflammatory biomarker, presepsin has a significant role in the diagnosis of pneumonia or CPE.

METHODS & MATERIAL

This observational prospective study was performed at Emergency Department of Zonguldak Bülent Ecevit University. All patients were informed of the nature of the study and signed an informed consent form. The study was approved by the Ethics Committee of Zonguldak Bülent Ecevit University (No: 2015/02 and Date:20/05/2015).

Study design and population

Patients who were admitted to the Emergency Department of Zonguldak Bülent Ecevit University Medical Faculty with complaints of shortness of breath, cough, and production of sputum between 01.06.2015- 01.12.2015 and who were diagnosed with pneumonia or cardiogenic pulmonary edema were included in the study.

Based on the clinical symptoms and physical examinations, laboratory tests, imaging methods, and echocardiographic findings, the patients were diagnosed with pneumonia or cardiogenic pulmonary edema.

Diagnosis of pneumonia:

Pneumonia was diagnosed in patients presenting with complaints of cough fever and purulent sputum with unilateral crackles, rales or bronchial breath sounds and egophony on physical examination, unilateral infiltrate on chest imaging, elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin and leukocytosis on complete blood count

Diagnosis of cardiogenic pulmonary edema:

Cardiogenic pulmonary edema was diagnosed in patients presenting with complaints of edema, dyspnea, and fatigue with bilateral crackles, rales on physical examination, elevated B-type natriuretic peptide levels on blood and cardiac chamber enlargement, interstitial or alveolar edema on chest imaging, structural or functional impairment of ventricular filling or ejection of blood on echocardiography.

A total of 32 patients, 16 of whom were diagnosed with pneumonia and 16 diagnosed with cardiogenic pulmonary edema, were included in the study.

The exclusion criteria include:

-Age <18 years old,

-Evidence of an immunocompromision (e.g., malignancy),

-Pregnancy,

- Those with malignancy,

- Those with inflammatory diseases,

- Those with kidney failure.

In addition to the standard tests required for the diagnosis, sedimentation, C-reactive protein (CRP) and Presepsin levels were investigated in both pneumonia and cardiogenic pulmonary edema groups as common tests.

Measurements of presepsin, CRP and Sedimantaion

Blood samples were obtained by vein puncture into ethylene diamine tetra acetic acid (EDTA) blood collection tubes at admission before the administration of any medication. Blood samples were recovered by centrifuging at 3000 rpm for 5 minute. The serum was collected after centrifugation and stored at –80ºC until analysis up to 6 months. Plasma presepsin concentrations were measured using an automated chemiluminescent enzyme immunoanalyzer, PATHFAST system (LSI Medience Co., Tokyo, Japan).

Plasma CRP level was measured by Roche Diagnostic brand Cobas 600 device using the same brand commercial kit which was operated with turbulent method.

Automatic Westergren measurement for sedimentation (Vacuplus ESR -120): citrated samples (1.5 cc) were mixed

manually then the tubes were placed in the device. This device kept samples at a 26°C stable temperature, and the reading was made in 30 minutes with Infrared method.

STATISTICAL ANALYSIS

Statistical analysis was performed by using the SPSS (version 13; SPSS Inc., Chicago, IL) software. All data were summarized and displayed as mean ± standard deviation for the continuous variables and as number of individuals plus the percentage in each group for categorical variables. Comparisons of variables were obtained using Fisher's exact test, chi-square test, Student's t-test, Wilcoxon rank sum test, Pearson's test and Jonckheere–Terpstra test as appropriate. All the above analyses were considered significant at $p < 0.05$ (two tailed).

RESULTS

Subjects characteristics

A total of 32 patients, 16 of whom were diagnosed with cardiogenic pulmonary oedema and 16 with pneumonia, were included in the study. Of the patients in the cardiogenic pulmonary edema group, 7 (43.7%) were female and 9 (56.3%) were male. In the pneumonia group, 6 (37.5%) of the patients were female and 10 (62.5%) were male. The average age was 72 ± 12.9 years in CPE patients, and it was 48 ± 18.2 years in pneumonia patients ($p<0.001$).

Comparison of CPE and pneumonia patients

When we compared the complaints of the patients in both groups, it was found that the complaints of dyspnea and edema in the legs were significantly higher in the CPE group, while the complaints of cough and sputum production were significantly higher in the pneumonia group (Table 1).

Fever and respiratory rate were significantly higher in the pneumonia group, when the vital signs were evaluated. Heart rate was higher in the patients in the cardiogenic pulmonary edema group (Table 1).

When we compared both groups in terms of comorbid diseases, chronic heart failure and coronary arterial disease were more frequent in the CPE group than in the pneumonia group (Table 1).

PAAC graphy and echocardiographic findings of the patients are shown in Table 2.

When the laboratory findings of both groups were compared; urea, creatinine, AST and lactate levels were significantly higher in the CPE group. There was no significant difference between haemoglobin, ALT, WBC and CRP levels. Sedimentation and Presepsin levels were significantly higher in pneumonia group ($p=0.035$, $p<0.001$) (Table 3).

The median level of presepsin was 690 pg/ml (range: 251–6359) in pulmonary edema group (n = 16), and it was 1507 pg/ml (range: 407–11803) in pneumonia group (n = 16).

The presepsin level of pneumonia group was higher than the CPE group ($P<0.001$).

The most suitable cut-off value for presepsin was determined by drawing ROC curves. For our optimal cut-off value of 1344, our sensitivity value is 81.3%, our specificity is 93.8%, (+) Predictive value is 92.9%, (-) Predictive value is 83.3% and our AUC (Sh) is 0.871 (0.072) and it was found to be statistically successful in dividing the groups ($P<0.001$). ROC curves of patients with pneumonia against CPE patients are shown in Figure 1. Distribution of presepsin in CPE and pneumonia patients are shown in Figure 2.

DISCUSSION

Cardiogenic pulmonary edema and pneumonia are two important diseases that include completely different treatment protocols and may lead to an increase in mortality, if not diagnosed early and treated. Clinical examination, laboratory tests and imaging methods are sometimes insufficient for the differential diagnosis of both conditions. Inflammatory biomarkers, such as CRP, WBC, procalcitonin, may not be useful for differentiation, as both diseases result in membrane damage, release of cytokines, increased pulmonary capillary permeability, and accumulation of neutrophils into the damaged area [8,9,10]. In such cases, more specific biomarkers are needed for rapid diagnosis and treatment. In our study, we aimed to evaluate the effectiveness of presepsin in the differential diagnosis of cardiogenic pulmonary edema and pneumonia, and it was found that the presepsin was significantly higher in the pneumonia group compared to the CPE group ($p <0.001$). It was considered that the increase of presepsin, especially in infection is not clear; but its release is related to phagocytosis of microorganisms and the release of lysosomal enzymes [11]. There are also studies showing that the presepsin levels are significantly higher in the cases, when they are accompanied by infection when compared to noninfective inflammatory processes [12]. In another study, it was concluded that

presepsin can be used to monitor the treatment process as well as the diagnosis of pneumonia [13].

In the study conducted by Romualdo et al. in the emergency department, the median presepsin values were determined to be 493 (290-586) pg/ml in patients without infection, 666 (434-1103) pg/ml in patients with infection, and 1115 (614-2337) pg/ml in patients with sepsis [14]. In our study, the median value of presepsin in CPE patients was found to be 690 pg/ml (range: 251-6359) and it was 1507 pg/ml (range: 407-11803) in pneumonia patients. In the study conducted by Carpio et al. in the emergency department, the median values of presepsin at the zero-hour were found to be 304 (175-477) pg/ml in SIRS patients, 544 (457-688) pg/ml in sepsis patients, and 2037 (1482-3668) pg/ml in severe sepsis patients [15]. Most of the studies related to presepsin were performed on sepsis patients and it was found that they were superior to conventional biomarkers and blood culture for the diagnosis of sepsis [13,15,16].

While the presepsin values of healthy volunteers was 60.1-365 pg/ml in a study [7]; it was found to be 189 (92.7-398) pg/ml (17), 259 (11-425) pg/ml (18), 130 (58-339) pg/ml [15], 128 (101.5-176.5) pg/ml [19] in other studies. The different reference range of presepsin in different studies may limit its use. For this reason, the reference range should be generated by multi-center studies.

This study shows that presepsin may be a new biomarker that can be used in the early differential diagnosis of pneumonia and cardiogenic pulmonary edema. However, larger studies are needed to show the cut-off levels of presepsin to be used in the differential diagnosis of pneumonia and CPE.

Limitations

The low number of patients and the lack of a control group of healthy volunteers were the limitations of our study.

In addition, in our study, we diagnosed pneumonia by clinical laboratory and imaging methods. Another limitation is that our diagnosis has not been confirmed with sputum culture.

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Table 1: Application Complaints and Demographic Data of Patients with Cardiogenic Pulmonary Edema and Pneumonia

	Cardiogenic Pulmonary Edema	Pneumonia	P Value
Case amount	16	16	
Patient demographics			
Male sex	9 (56.3%)	10 (62.5%)	1.000
Female	7 (43.7%)	6 (37.5%)	1.000
Average age ±SD.	72 ± 12.9	48 ±18.2	<0,001
Complaints			
Dyspnea	14(87.5%)	6(37.5%)	0.011
Edema in the legs	6(37.5%)	-	0.018
Chest pain	3(18.8%)	3 (18.8%)	1.000
Weakness	1(6.3%)	-	1.000
Cough	-	12(75.0%)	<0.001
Purulent sputum	-	5(31.3%)	0.043
Vital Findings			
Pulse	112 ± 20.1	86 ± 15.4	<0.001
Systolic Tension	127 ± 28.1	120 ±15.1	0.380
Respiratory rate	21 ± 5.6	27 ±5.8	0.003
Body temperature	36.5 ± 0.8	37.4 ± 0.8	0.005
SO2	91 ± 6.6	93 ± 5.4	0.373
Co-morbidities			
Hypertension	8 (50%)	3 (18.8%)	0.137
Diabetes mellitus	4 (25%)	1 (6.3%)	0.333
Chronic heart failure	8 (50%)	1 (6.3%)	0.015
COPD	5 (31.3%)	6 (37.5%)	1.000
Coronary artery disease	6 (37.5%)	-	0.018

SD: standart deviation, SO2: oxygen saturation COPD: chronic obstructive pulmonary disease

Table 2: Imaging findings

	Cardiogenic Pulmonary Edema	Pneumonia	P Value
X-ray			
Infiltration	4 (25.0%)	14 (87.5%)	0.001
Pleural effusion	5 (31.3%)	4 (25.0 %)	1.000
Cardiomegaly	11 (68.8 %)	2 (12.5%)	0.004
Increase in Bronchovascularity	6 (37.5%)	2 (12.5%)	0.220
Echocardiography			
Systolic dysfunction	13 (813%)	-	<0.001
Diastolic dysfunction	7 (43.8%)	1 (6.3 %)	0.037
Heart valve dysfunction	13 (81.3 %)	2 (12.5%)	0.001

Table 3: Laboratory findings in patients with cardiogenic pulmonary edema and pneumonia and the outcome of patients

	Cardiogenic Pulmonary Edema	Pneumonia	P Value
Laboratory parameters			
Hemoglobin	12.55 (10.30-15.50)	13.70 (9.40-14.70)	0.149
Urea	60.50 (31.00-418.00)	29.50 (13.70-158.00)	<0.001
Creatinine	1.40 (0.40-4.80)	0.85 (0.50-7.00)	0.001
AST	39.50.(16.00-728.00)	25.50 (15.00-93.00)	0.043
ALT	30.50 (13.00-1468.00)	26.00 (8.00-99.00)	0.254
Lactate (mmol/L)	2.00 (0.70-7.00)	1.00 (0.50-1.60)	<0.001
WBC	10.60 (6.10-29.90)	9.75 (2.00-63.30)	0.867
CRP	6.60 (1.80-97.00)	9,55 (1.90-116.00)	0,515
Sedimentation	25.50 (6.00-52.00)	40.50 (11.00-69.00)	0.035
PRESEPSβN (pg/ml)	690 (251-6359)	1507 (407-11803)	<0.001
Result			
Discharged	1 (6.3%)	12 (75.0 %)	<0.001
Hospitalization	2 (12.5%)	3 (18.8 %)	
Intensive Care Hospitalization	12 (75.0%)	1 (6.3%)	<0.001
Died	1 (6.3 %)	-	

AST: aspartate aminotransferase, ALT: alanine aminotransferase, WBC: White blood cell, CRP: C-reactive protein

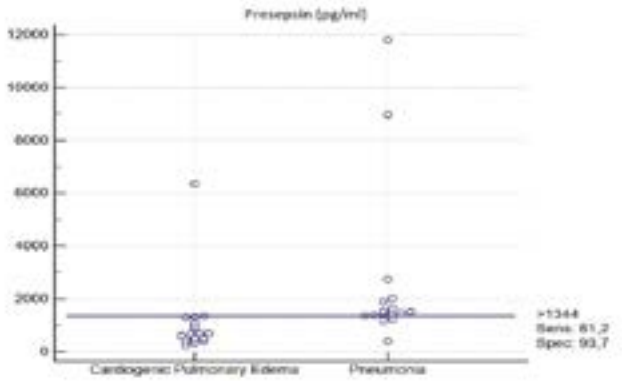

Figure 1: ROC curves of patients with pneumonia against CPE patients

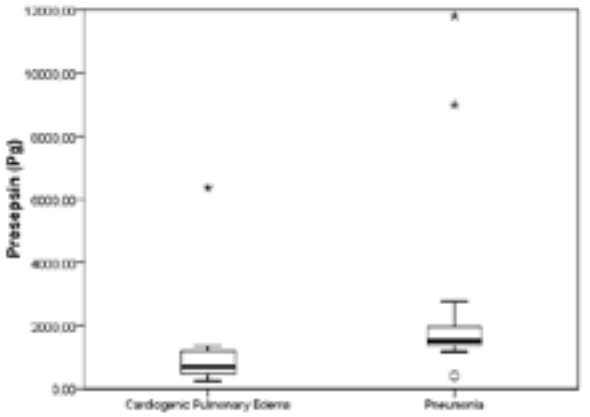

Figure 2: Distribution of presepsin in CPE and pneumonia patients

Profesional paper

ОПЕРАТИВЕН ТРЕТМАН НА СКРШЕНИЦИ НА ТАЛУС – 3 ГОДИШНО ИСКУСТВО НА КЛИНИКАТА ЗА ТРАУМАТОЛОГИЈА ПРИ ЈЗУ ТОАРИЛУЦ

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АПСТРАКТ

Скршеници на талусот се несекојдневни, претставуваат околу 0,1% од сите скршеници. По калканеусот, талусот е најчесто скршена коска од тарзусот. Фрактурите на вратот се околу 50% од сите фрактури на талусот, односно 45% според студијата на Elgafy et al (2000). Менаџирањето на овие фрактури е голем предизвик од повеќе аспекти. Анатомска редукција на скршеници на талус е неопходна поради тоа што поголемиот дел од површината е зглобна и оптеретувачка површина. На клиниката за Трауматологија во периодот 2017 до 2020 година, беа хирушки третирани 14 скршеници на талус. Од нив 10 беа машки пациенти, а 4 женски пациенти. Средна возраст на пациентите беше 44 години. Во оваа студија беа вклучени само пациенти кои ги исполнија инклузионите услови, оперативно третирани скршеници и потпишана согласност за учество во истражувањето. Кај сите пациенти се направи крвава репозиција и остеосинтеза со шрафови или реконструктивна плочка. Постоперативно сите пациенти беа имобилизирани со гипс имобилизација во тек на следните 14дена.

Сите пациенти постоперативно беа на терапија со LMWH, антибиотска терапија во тек на 5 дена и аналгетска терапија. Од 14 испитаници, одличен резултат имаше кај 2-ца пациенти, а добар резултат кај 8 пациенти, незадоволителен резултат кај 3-ца пациенти и лош кај еден пациент. Оваа повреда е многу ретка за да се изнесат и споредат поголеми студии. Сепак сите поголеми студии од референтни траума центри водат кон истиот заклучок, а тоа е дека менаџментот на овие фрактури е комплексен, зависи многу од постигнување на апсолутна анатомска редукција, но исходот сепак и тогаш може да не е задоволителен поради сложената биологија на оваа тарзална коска.

Клучни зборови: талус, оперативен третман, незадоволителен исход;

ВОВЕД

Скршеници на талусот се несекојдневни, претставуваат околу 0,1% од сите скршеници. По калканеусот, талусот е најчесто скршена коска од тарзусот. Фрактурите на вратот се околу 50% од сите фрактури на талусот, односно 45% според студијата на Elgafy et al (2000). (1) Менаџирањето на овие фрактури е голем предизвик од повеќе аспекти. Анатомска редукција на скршеници на талус е неопходна поради тоа што поголемиот дел од површината е зглобна и оптеретувачка површина. Доколку не се постигне анатомска редукција, процентот на постеоперативна асептична остеонекроза и посттрауматски остеоартрит се зголемува значајно, а како причини можеме да ги наведеме:

1.Анатомски карактеристики

Анатомски на талусот разликуваме тело, глава и врат. Талусот се зглобува со тибијата, фибулата, и калканеусот преку неговото тело,а преку главата со навикуларната коска. На оваа коска нема никакви мускулно-тетивни припои. Биомеханичката улога на

оваа тарзална коска е пренос на силите од подколеница кон стопало и обратно.

2.Специфична васкуларизација

Исто така и крвоснабдувањето на талусот е специфично, бидејќи скоро 60% од неговата површина е рскавична, само мал дел од него може да е перфориран од крвни садови. Постои прстен од крвни садови околу главата и вратот на талусот, составен од предна и задна тибијална артерија и перфорантни перонеални артерии. Доколку тие зони на влез на нутритивните артерии се нарушени, лесно може да настапи аваскуларна некроза(2). Најчест механизам за настанување на овие фрактури е присилена дорзофлексија со аксијално оптеретување. Придружни фрактури може да се бималеолрните скршеници, поточно фрактурите на медијалниот малеол.

ЦЕЛ НА ТРУДОТ

Целта на трудот е да се прикаже оперативен третман на скршеници на талусот кај пациенти, и тоа за период од три години, како искуство на Клиниката за Трауматологија при ЈЗУ ТОАРИЛУЦ.

МАТЕРИЈАЛИ И МЕТОДИ

На клиниката за Трауматологија во периодот 2017 до 2020 година, беа хирушки третирани 14 скршеници на талус. Од нив 10 беа машки пациенти, а 4 женски пациенти. Средна возраст на пациентите беше 44 години. Во оваа студија беа вклучени само пациенти кои ги исполнија инклузионите услови, оперативно третирани скршеници и потпишана согласност за учество во истражувањето.

Под инклузиони фактори спаѓаат:

1. Да нема повеќе од 2 коморбидитети

2. Да не е отворена фрактура

3. Да нема претходен инвалидитет на повредениот екстремитет

4. Повредаа да не е придруна состојба при политраума

Сите скршеници беа класифицирани по Hawkins класификација(3). Според неа скршениците се поделни во 4 групи и тоа:

1. Тип 1, недислоцирани фрактури

2. Тип 2 , дислокација на скршеницата со дислокација на субталарниот зглоб

3. Тип 3, дислокација на скршеницата со субталарна луксација и луксација на скочниот зглоб

4. Тип 4, дислокација на скршеницата со субталарна луксација, луксација на скочниот зглоб и талонавикуларна дислокација.

Halvorsen et al, во нивната студија издадена 2013 година, образложиле како се менува процентот на аваскуларна некроза на талусот во однос на тоа кој тип по Hawkins е скршеницата. По проследени 848 пациенти, заклучиле дека кај тип 1 инциденацата на настанување аваскуларна некроза изнесува 5,7%, кај тип 2 е 18,4%, за тип 3 се зголемува на 44,7%. За Hawkins тип 4 не може да се донесе заклучок од студијата, поради раритетот на повредата.(4).

Според горенаведената класификација со тип 1 иследуваме 2 пациенти (1 маж, 1 жена), со тип 2, 9 пациенти (1 жена, 8 мажи) и со тип 3 , 3 пациенти (2 жени и 1 маж). Калсификацијата се направи на база на снимки од компјутерска томографија, направена кај сите пациенти.

Од 14 пациенти, 5 имаа придружена скршеница на медијалниот малеол.

Кај сите пациенти се направи крвава репозиција и остеосинтеза со шрафови (слика бр 2) или реконструктивна плочка (слика бр.1). Постоперативно сите пациенти беа имобилизирани со гипс имобилизација во тек на следните 14 дена. Кај тројца пациенти се направи ревизија, поради несоодветната примарна редукција видена на контролните снимки на КТ скен.

Сите пациенти постоперативно беа на терапија со LMWH, антибиотска терапија во тек на 5 дена и аналгетска терапија.

Пациентите амбулантски се следеа на 14-тиот ден постоперативно, 1-виот месец, 3-тиот месец и 6-тиот месец. На сите контроли, со исклучок на првата (на која се вадеа конци од оперативна рана), се правеше контролна рентгенска графија. На амбулантаската контрола на 6-тиот месец кај сите се правеше објективно и функционално тестирање на фукцијата на зглобот. За таа примена го одбравме Kitaoka score унифициран од American Orthopaedic Foot and Ankle Society. (5) Според него се евалуираа следните девет параметри:

1.болка, (без болка, блага болка, средна болка, перзистентна болка)

2.функција(од без ограничување до одење со помагало)

3. Изодена дистанца (помалку од 1 километар до повеќе од 6 километри)

4. Терен (рамен, скали, планински)

5. Абнормалности при одење

6. Сагитално движење (екстензија и флексија)

7. Еверзија и инверзија

8. Стабилност на стопало (антеропостериорно, варус/валгус)

9. Алајмент на стопало и скочен зглоб

Максимален скор на Kitaoka score ситемот е 100 бода, од одличен(100-85), добар(85-65), незадоволителен(65-45) и лош(>45).(6)

Од 14 испитаници, одличен резултат имаше кај 2-ца пациенти (86,5 среден бод), а добар резултат кај 8 пациенти (68 среден бод), незадоволителен резултат кај 3-ца пациенти (среден бод од 48,5) и лош кај еден пациент (38 бода).

Рани компликации кои ги воочивме беа постоперативни проблеми со кожа(зони на некроза во предел на оперативна рана) кај 4 пациенти.

Како доцни компликации со кои се соочивме е посттрауматскиот остеоартрит (6 пациенти) и аваскуларна некроза (4 пациенти).

ДИСКУСИЈА

Оваа повреда е многу ретка за да се изнесат и споредат поголеми студии. Сепак сите поголеми студии од референтни траума центри водат кон истиот заклучок, а тоа е дека менаџментот на овие фрактури е комплексен, зависи многу од постигнување на апсолутна анатомска редукција, но исходот сепак и тогаш може да не е задоволитен поради сложената биологија на оваа тарзална коска.

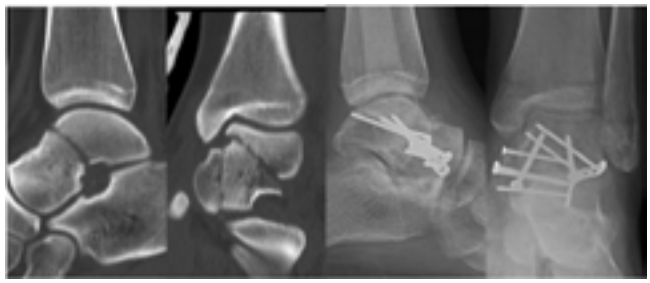
Fournier со неговите соработници во 2014 година направил мултицентрична студија од 114 случаеви на фрактури на талус оперирани во различни центри. (7) Резултатите се поразувачки од аспек дека најголем процент, 40% се незадоволителни, а само 10% одлични. Кај 39 од случаевите имало појава на аваскуларна некроза, а посттрауматски остеоартрит во 74% од случаевите.

Barnett со соработници во 2017 година од нивната студија го потврдуваат гореизнесеното на Fournier со неговите соработници. Но потенцираат дека времето е златен фактор во третманот на овие фрактури. Доколку е фрактуриран дел од талусот кој е нутритивен , истата треба да се оперира во првите 24 часа. (8)

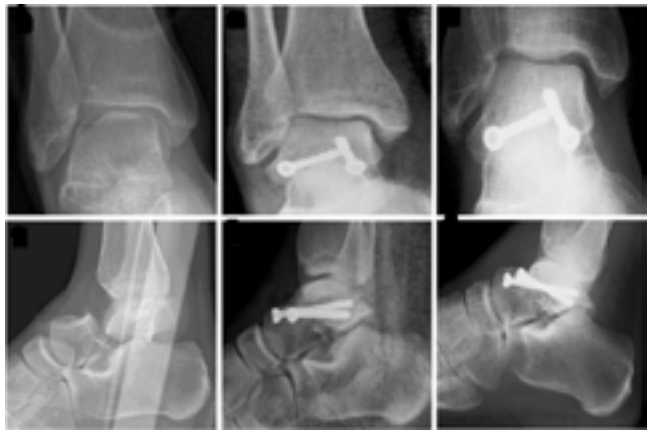
ЗАКЛУЧОК

На нашата клиника не се зема во предвид дека исходот од третманот на одредени типови на фрактури на талус зависи правопропорционално од времето на извршување на операцијата. Анатамоска редукција е задолжителна за подобар резултат од третманот. Треба да се воведе некој протокол за третман на посттрауматскиот остеоартрит , со оглед на високиот процент на негово појавување и покрај задоволителната оперативна техника.

Слика бр 1. Остеосинтеза со плочка



Слика бр. 2 Остеосинтеза со шрафови



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Profesional paper

COGNITIVE DEFICIT, POSITIVE AND NEGATIVE SYMPTOMS IN PATIENTS WITH SCHIZOPHRENIA

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ABSTRACT

Objective: The aim of the study was to introduce the relationship between positive and negative symptoms, cognitive deficit and antipsychotic treatment in acute schizophrenic patients.

Methods: The study included 21 acute schizophrenic patients who were selected from the Psychiatric Hospital in Skopje, and were diagnosed according to the ICD-10. All patients were receiving antipsychotic medication treatment at the time of testing and during the time they were clinically stable. At the beginning of the treatment all subjects received higher dose of neuroleptics, and before they left the hospital they were given lower drug doses. The Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of positive and negative symptoms respectively. The Schizophrenia Cognition Rating Scale (SCoRS) was used to assess the cognitive function before and after the neuroleptic treatment. Statistical analysis of the results obtained in the research was conducted with SPSS 20.0 for Windows package program. The results were analyzed by applying Wilcoxon Signed Ranks Test and Pearson correlation coefficient.

Results: The results indicated that the acute schizophrenic patients had higher global rating score in the SCoRS assessment (M=53.667, SD=8.345) in the first weeks after psychosis onset. After 6-8 weeks treatment with antipsychotic medications, they had lower global rating score in the SCoRS assessment (M=41.952, SD=6.951). There was a positive relationship between the total SCoRS score and the dose of neuroleptics (Z=-3.925, sig.=0.000, p<.001). The high degree of positive and negative symptoms was a strong predictor of higher cognitive deficits in schizophrenic patients. The positive relationship was observed between the high dose of therapy, PANSS-Positive and ScoRS level (r=.552, p<.01) and PANSS-Negative and ScoRS level (r=.607, p<.01). In addition, there was a positive relationship between the low dose of therapy, PANSS-Positive and ScoRS level (r=.342, p<.05) and PANSS-Negative and ScoRS level (r=.432, p<.01).

Conclusions: During our work, we found that the regular and continued use of antipsychotic medications in schizophrenic disorders and good co-operation with the patients during the therapy could be important for better cognitive function of the person.

Keyword: cognitive deficit, positive and negative symtoms, schizofrenia, treatment.

INTRODUCTION

Psychotic disorders are a heterogeneous group of diseases that also include schizophrenia which is described in literature as a severe chronic and progressive psychotic disorder. Schizophrenia is an endogenous mental disorder with a chronic course, characterized by dysfunction in many domains, such as: perceptions, thinking, emotions and cognition [1].

The scientific and clinical public is oriented toward early detection, treatment and rehabilitation, with a special focus on treatment in the community, however over the past 20 years with the advancement of science, schizophrenia has been studied in the direction of a neurodevelopmental and a neurodegenerative process. In the acute phase, schizophrenia is manifested by subtle behavioral changes, changes in the neuromotor and the cognitive sphere [2]. Due to the heterogeneity of the symptomatology manifestation in the early phase of schizophrenia, along with the predominance of positive and negative symptoms, cognitive deficit is also monitored, therefore early detection and treatment play a major role in reducing the difficulties of the person's functioning, but already in the chronic phase the disease is dominated by negative symptoms and cognitive dysfunction, which of course leaves sequels from a personal and behavioral aspect of the schizophrenic person.

Modern approaches to schizophrenia focus on symptomatic and functional remission in order to improve the overall functionality and quality of life in patients with schizophrenia. At the same time, the psychopharmacological treatment, the psychotherapeutic and social therapeutic interventions are directed towards this approach, which is an imperative in order to prevent a bad prognosis, i.e. to achieve long remissions, to reduce the positive and negative symptoms, as well as the cognitive impairment, which is a fundamental prerequisite for partial to complete recovery and achievement of a satisfactory quality of life [3].

From a clinical perspective, schizophrenia is usually manifested with a gradual and slow onset, very rarely abruptly within a few days or weeks and mostly in early adolescence or at young age, but may also occur later in life, and is more common in females. The clinical presentation is focused on the subjective and objective syndromes, symptoms or signs of schizophrenia, i.e. the manifestation of the disorder is heterogeneous and is best described by the so-called pentagonal model of symptoms that includes positive, negative, cognitive, affective, and aggressive-hostile symptoms [4, 5]. The positive or psychotic symptoms in schizophrenia refer to painful ideas - delusions, illogical speech and hallucinations, and the negative symptoms include: decreased motivation, lethargy, numbness of emotional expression and poorer speech [6]. From pathophysiological aspects, the positive symptoms originate from the hyperactivity of the dopaminergic neurotransmitter system in the mesolimbic brain structures (hyperdopaminergia), and therefore respond therapeutically well to classical antipsychotics [7]. The negative symptoms arise from the hyperactivity of the serotonergic neurotransmitter system and the hypoactivity of the dopaminergic system in the frontal cortex (hypodopaminergia).

In recent years there has been a growing belief that neurocognitive deficit is a functional component of schizophrenia rather than a result of symptoms or treatment consequences. This deficiency is most commonly associated with dysfunction of the prefrontal cortex, the sensory and associative cortex, the motor cortex, and the basal ganglia [8]. The impairment of the cognitive functions is observed early in patients, initially it acts as an impairment of a milder degree, and the intensity may worsen over the course of the disease. Cognitive dysfunction in schizophrenia is manifested through the speed of information processing, attention, memory, thinking, the learning process, problem solving and social cognition, it is considered an important and basic feature in almost all patients with schizophrenia which appears as early as in the first episode of schizophrenia, but is also found in the premorbid phase, and in the more advanced phase the cognitive deficit is already constant and cannot be reduced to secondary, rather it is inherent to the disease [9. 10]. The influence of psychotic symptoms on cognitive dysfunction shows moderate correlations, with the possibility to reflect on certain domains of cognition such as the ability to solve problems, where the cognitive process has the main role through the poor speech expression [11, 12]. Neurocognitive tests show that only 30% of patients with schizophrenia have satisfactory cognitive functioning [13].

AIM OF STUDY

- To evaluate the level of positive and negative symptoms among patients with schizophrenic disorder.
- To determine the degree of cognitive deficit in patients

in the acute phase of schizophrenia using certain psychological scales.

• To investigate the relationship between cognitive deficit, positive and negative symptoms and treatment with neuroleptics in patients in the acute phase of schizophrenia.

MATERIAL AND METHODS

This average study according to its design included 21 respondents of both genders, from 20 to 40 years of age, who received hospital treatment at the Psychiatric Hospital Skopje-Skopje, diagnosed with schizophrenia according to the diagnostic criteria of the ICD-10 classification in the period from January to June 2020. All patients were monitored in a period of 3 to 5 weeks after hospitalization. The criteria for inclusion of the respondents were as follows: male and female, 18 to 60 years of age, schizophrenia (according to ICD-10), patients in the first episode of schizophrenia without prior antipsychotic therapy, while the criteria for exclusion of the respondents were as follows: younger than 18 years of age, diagnosis of comorbid psychiatric disorder, use of more than one antipsychotic. Initially all patients were treated with high doses of neuroleptics, and before they leave the hospital they received lower doses of each of the mediations indicated above.

The examination was monitored through the following structured test and clinical procedure:

Standardized psychiatric clinical interview.

Non-standardized questionnaire for socio-demographic and clinical data designed for the needs of the research.

Psychiatric rating scales for clinical assessment of the expression of the symptomatology: the Positive and Negative Syndrome Scale – PANSS for schizophrenia assessment and the Schizophrenia Cognition Rating Scale - ScoRS.

The Positive and Negative Syndrome Scale – PANSS for schizophrenia assessment consists of three subscales [14]. The positive scale contains 7 items (madness, cognitive disorganization, hallucinatory behavior, anxiety, grandness, suspicion and hostility), which same as all the other items in this scale, are scored from 1 (absent) to 7 (extreme). The negative scale also contains 7 items (flat affect, emotional withdrawal, impairment of emotional reasoning, social withdrawal, difficulty in abstract thinking, lack of spontaneity, stereotypical thinking). The maximum score on this scale is 49 points. The General Psychopathology Scale contains 16 items and presents the structure of the clinical presentation. Cronbach's Alpha for the 28 of 30 items were .756, which represents a good correlation between items.

The Schizophrenia Cognition Rating Scale - ScoRS is a scale for assessing the cognitive impairment and the extent of its effect on the everyday functioning in patients with schizophrenia [15]. The scale itself consists of 20 items that cover the following cognitive domains: memory (4 items), learning (2 items), attention (3 items), working memory (2 items), reasoning and problem solving (3 items), motor skills (2 items), language (1 item) and social skills (3 items). Each item is ranked from 1 (absent deviation) to 4 (expressed deviation), whereby higher scores reflect a greater degree of disorder. The time frame for the cognitive deficit should not be shorter than two weeks, with retesting performed 3-4 weeks after the commencement of the drug treatment. The statistical validity of the scales expressed with Cronbach is within the range from 0.743 to 0.782.

The statistical analysis was performed with the SPSS software package (Statistical Package for the Social Science, version 20), by applying the Wilcoxon Signed Ranks Tests and the Pearson correlation coefficient. The values of $p<0.01$ and $p<0.05$ were considered statistically significant and important.

RESULTS

In the study was designed as a prospective, we included 21 (M:F=12:9) acute schizophrenic patients with an average age of 31.34 years, within the range from 20 to 40 years of age, and a standard deviation of 6.43. With respect to marital status, most of the participants were unmarried (62.25 percent), while 37.75 percent were married at the time of the study. 14.7 percent had low level of studies, medium educational level was 81.1 percent of the sample, and only 4.2 percent had high educational level.

From Table 1 and Figure 1 we can see that the average value of the total score on the Positive and Negative Syndrome Scale for schizophrenia assessment is M=130.286 with a minimum and maximum value ranging from 77 to 175, of the negative symptoms M=31.143 with minimum and maximum values from 10 to 43, of the positive symptoms M=32.476 with minimum and maximum values from 20 to 40, and on the scale for general psychopathology M=67.143 with minimum and maximum values from 39 to 97.

Table 1. Means and standard deviations of PANSS measures in the study participants

Descriptive Statistic	PANSS-Positive	PANSS-Negative	PANSS-General psychopathology	PANSS-Total score
Mean	31.143	32.476	67.143	130.286
Standard Deviation	9.096	6.022	14.482	25.285
Minimum	10	20	39	77
Maximum	43	40	97	175
Count	21	21	21	21

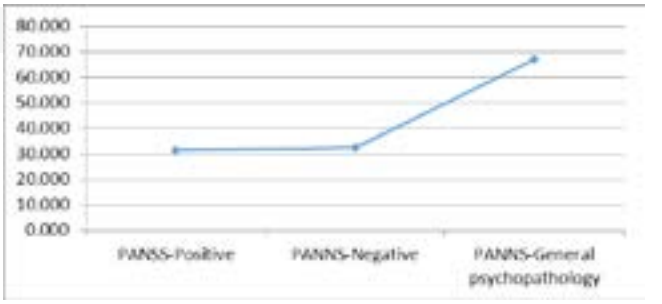

Figure 1. The level of PANSS subscales among participants

Table 2 and Table 3 show the mean values of the Schizophrenia Cognition Rating Scale and its domains in patients when they were receiving high and low doses of neuroleptic therapy. It is evident that at the beginning of the treatment the cognitive deficit is more expressed compared to the end of the hospital treatment, i.e. in the period when the patients left the hospital.

Table 2. Means and standard deviations of cognitive measures in patients with schizophrenia who used high doses of antipsychotic medications

	SCoRS (maximal drug use)	Memory	Learning	Attention	Working memory	Problem solving	Processing speed	Social cognition	Language	Global rating
Mean	53.66	10.52	5.42	8.19	5.66	7.85	4.95	8.23	2.66	3.90
SD	8.34	1.96	1.12	1.69	1.19	2.05	0.92	2.04	0.79	0.62
Minimum	38	7	3	4	4	3	3	4	1	3
Maximum	71	14	7	11	9	11	6	12	4	5
Count	21	21	21	21	21	21	21	21	21	21

Table 3. Means and standard deviations of cognitive measures in patients with schizophrenia who used low doses of antipsychotic medications

	SCoRS (minimal drug use)	Memory	Learning	Attention	Working memory	Problem solving	Processing speed	Social cognition	Language	Global rating
Mean	41.95	8.19	4.57	6.43	4.33	5.95	3.90	6.48	2.05	6.48
SD	6.95	1.50	1.08	1.36	1.39	1.77	0.89	2.16	0.59	0.60
Minimum	29	6	3	3	2	2	2	3	1	5
Maximum	54	10	7	9	7	9	6	12	3	7
Count	21	21	21	21	21	21	21	21	21	21

Figure 2 shows the values of the domains of the Schizophrenia Cognition Rating Scale at the beginning and the end of the treatment. By using the Wilcoxon signed-rank test, we found that a statistically significant correlation is present between the total SCoRS score and the dose of neuroleptic therapy (Z=-3.925, sig.= 0.000, p<.001).

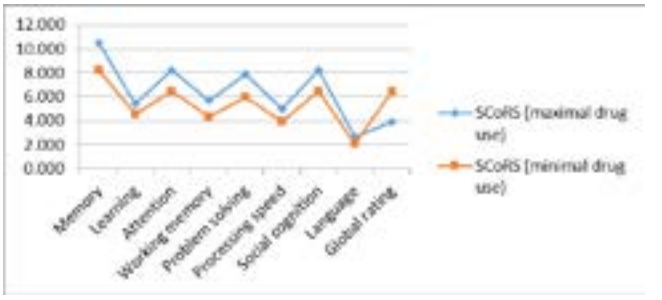

Figure 2. SCoRS global rating measures among schizophrenic patients

In Table 4 we can see that there is a statistically significant correlation between the high dose of therapy, the positive psychopathology of the disease and the total score of the ScoRS (r=.552, p<.01), as well as the negative symptomatology level (r =.607, p<.01). In addition, in Table 5 we can observe a positive correlation between the low dose of therapy, the positive psychopathology of the disease and the total score of the ScoRS (r=.342, p<.05) and the negative symptomatology and the total score of ScoRS (r=.432, p<.01).

Table 4. Correlation between the ScoRS (Maximal drug use) global rating and symptoms scales

Pearson Correlation	ScoRS (Maximal drug use)	PANSS-Positive	PANSS-Negative	PANSS-General psychopathology
ScoRS (Maximal drug use)	1			
PANSS-Positive	.557**	1		
PANSS-Negative	.607**	.666**	1	
PANSS-General psychopathology	.318	.060	.181	1

**. Correlation is significant at the 0.01 level (2-tailed).

Table 5. Correlation between ScoRS (Minimal drug use) global rating and symptoms scale

Pearson Correlation	ScoRS (Minimal drug use)	PANSS-Positive	PANSS-Negative	PANSS-General psychopathology
ScoRS (Minimal drug use)	1			
PANSS-Positive	.342*	1		
PANSS-Negative	. .432**	.324*	1	
PANSS-General	-.204	-.447*	-.325	1

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

DISCUSSION

Research shows that patients with schizophrenia suffer

from a wide range of a cognitive deficits, which usually occur over a certain period of time, before and after the onset of the disorder, and this further determines the outcome of the mental condition. The cognitive deficits include changes in memory, attention, learning, performance function, abstract thinking, and language. It should be noted that 75% of patients with schizophrenia suffer from cognitive symptoms as a result of the disease. Our obtained results confirm that positive and negative symptoms affect the cognitive functioning of the examined group of schizophrenic subjects.

Patients with schizophrenia suffer from a wide range of cognitive deficits, which usually occur within a specific period of time after the onset of the disorder, depending on the severity of the mental condition. Cognitive impairments include deficits in memory, attention, learning, performance function, abstraction, and language. It should be noted that up to 75% of patients with schizophrenia suffer from cognitive symptoms as a result of the disease. The most common cognitive symptom that leads to temporary or permanent damage to mental processes is the reduced ability to concentrate, which has a great impact on the process of acquiring new knowledge, it affects the form of the cognitive process, attention, speech, behavior, etc. The results of our research show that a cognitive deficit was present in the examined subjects at the beginning of the disease, but the application of an appropriate neuroleptic therapy leads to improved cognitive functioning in schizophrenic subjects in the acute phase of the disease.

Therefore, patients with schizophrenia need timely commenced antipsychotic therapy and psychosocial therapeutic interventions, in order to be able to affect the natural course of the disease. Simultaneously, the longer period that is required to achieve a satisfactory improvement of the patient's mental condition results in an extension of each subsequent deterioration from a mental aspect. At the same time, patients who show a poor response to neuroleptic therapy have residual psychotic symptoms that reduce the person's functional capacities [21, 22]. Therefore, it is believed that timely application of therapy (pharmacological, psychosocial and psychotherapeutic interventions) can reduce psychotic symptoms, reduce the regressive course of schizophrenia and prevent the development of therapeutic resistance.

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Disclosure statement

None of the authors report any conflict of interest with this research.

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Profesional paper

MALIGNITY IN PARASAGITTAL MENINGIOMAS

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ABSTRACT

INTRODUCTION: Malignity in parasagittal meningioams become of Gr-III, WHO Clasification 2007.Grade III Rhabdoid Meningioma, Papilar Meningioma, Anaplastic Meningioma. PURPOSE OF THE STUDY: The purpose of this study is to evaluate the results of surgical treatment and analysis of new surgical methods in meningiomas of the parasagittal region. MATERIAL AND METHODS: This is a retrospective study, conducted between January 2012 and December 2019, 47 cases were included, treated in Neurosurgery Service, University Hospital Center "Mother Teresa", Tirana, Clinical Hospital Tetovo and the Hospital "September 8" Skopje. RESULTS: Simpson, I surgery was performed in 38 cases or 100% of small and medium tumors by tumor size, whereas in large tumors, Simpson I surgery was performed in 6 cases or%, Simpson II in 4 cases or (%) of cases, Simpson III in 4 (%) of cases and Simpson IV in 1 of cases or (%). The results are shown in the table below. Simpson I was performed in (100%) of cases in 32 cases with small and medium meningiomas. In the middle third of meningiomas Simpson I surgery was performed in 15 (35%) cases, Simpson II in 22 (51%) cases and Simpson III in 6 (14%) cases. Simpson I surgery was performed in 1 (8%) cases, Simpson II in 8 (62%) cases and Simpson III in 4 (30%) cases in meningiomas of the inner third of the sphenoid. DISCUSSION: The natural progression of parasagittal meningiomas. Following modern technological development and progressive and gradual popularization, as well as improved imaging by CT, RM, and DSA it has become possible to clearly define, qualitatively diagnose meningiomas of all regions. Surgical indications in parasagittal meningiomas The indications for surgical intervention consist of the removal of neurological signs, decreased intracranial pressure, decompression of surrounding tumor structures, histologic gradients, reports of venous and arterial blood vessels.CONCLUSION:Parasagittal meningiomas in our study from 2012 to 2019 were 47 out of 262 meningiomas as a whole or 18% which corresponds to the percentage of parasagittal meningiomas in the world literature as well. A significantly higher incidence is seen between the ages of 51 and 70 years. Women dominate over men 26 F and 21 B. The dominant clinic is a headache and neuromotor deficit. The time from the start of the complaints to the diagnosis varies from a few weeks to 120 months. The median delay in diagnosis was 10 months. At the time of diagnosis, a large proportion of them are very large. The quality of complete tumor removal was 47 cases, 42 cases according to Simpson I and Simpson II.

Key words: Malignity, Brain Tumors, Parasagittal region, Surgery.

INTRODUCTION

Meningioma is in many ways the soul of Neurosurgery, progress in the treatment of meningiomas reflects advances in Neurosurgery. These advances have been put to maximum use to improve the treatment of meningiomas. Meningiomas are female-dominated tumors and mainly affect middle age 90% of whom are benign, 6% are atypical, and only 2% are malignant, in most cases patients with meningioma diagnosis decide to surgically remove, and are advised to do so based on neurological symptoms. In most cases, complete removal of the tumor surgically results in a cure, when the meningioma is undetectable or when all other medications have failed (Surgery-Radiotherapy). Immunochemistry can be successful.

Superior Sagittal Sinus (SSS) –Anatomy

The upper sagittal breast (sinus sagittalis superior) is the breast on which it is placed duplication of the upper convex lip of the falx cerebrum. This sinus extends, sulcus sinus superior sagittalis, from foramen cecum to protuberantia occipitalis interna, where flows into confluent sinuum, or less commonly into sinus transversus.

Meninges

Meninges are complex and highly complex brain and spinal cord covers, essentially consisting of three closely related layers: dura mater, arachnoidea and pia mater. The dura mater is the thick layer, it consists of the periosteal and meningeal site, the subdural spaces also serve as a barrier because the archnoidal cells extend throughout its extension, while the vascular wall system is essential because meningiomas receive vascularization from neighboring dural spaces, whereas the archnoidea is a thin layer but varies depending on the region, its thickness varies, and the pia mater is of varying thickness depending on the region, and its vascular system is virtually non-existent. (1,2,5,6)

Table 1-1 - WHO Grading of meningiomas 2007

Grade III

Rhabdoid Meningioma

Papilar Meningioma

Anaplastic Meningioma

Risk factors

Ionizing radiation

Hormones

Head trauma

Mobile phones

Breast cancer

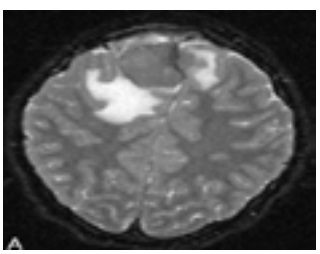
Family connection

Image on CT and RM meningiomas

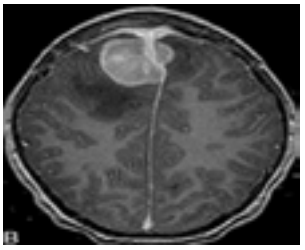
Meningiomas in large numbers display different stereotypes in their imaging features, which you combine with intracranial localization as well as dural adhesions, often becoming easily diagnosed without the need for other diagnostic methods that are often invasive. CT and RM are the most commonly used.(1)

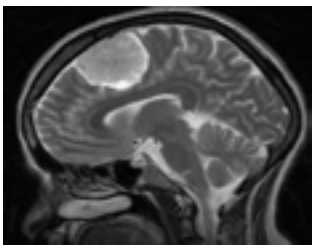
Fig. 1. MRI imaging in parasagittal meningiomas.

a-Axial T2



b-MRI with contrast axial T1 MRI; c- FLAIR MRI and sagital T2.





Diagnostic features during RM and CT

HIPERDENSITY

CALCIFICATION

HIPEROSTOZIS

DURAL BEAST

ANGIOGRAPHICAL VASCULAR TEMPLATE (AVT)(2)

1.6. Surgical classification of parasagital meningiomas according to Bonnal-Brotchi, Sindou-Auvernia and Shinshu Okudera Kobayashi

1) The first type (I) are those that attack only the outer surface of the SSS wall

2) Type II (II) are those that attack SSS side pages.

3) The third type (III) are those that occupy part of the SSS wall.

4) The fourth type (IV) are those who have already invaded two walls of the sinus, but without affecting the passage.

5) The fifth type (V) are those that have crossed the midline, and have invaded all the sinus walls by completely closing the passage (106, 110).(3)

1.7. Sindou and Auvernia have proposed a similar classification that attempts to guide surgical decision making and preoperative planning based on six categories, in this classification we have VI types of tumor invasion by the sinus:

1. The first type (I) -cuts the outer surface of the sinus wall, but without

caused wall breakage or penetration into the SSS.

2. The second type (II) -selection attacks the sinus, but without causing side wall cracks.

3. The third type (III) - ipsilateral sinus wall infiltration.

4. Type IV (IV) -invasion of both side walls and roof of SSS.

5-6. Fifth and sixth type (V-VI) -full sinus inclusion with or without a free wall.(4)

1.8. Kobayashi (Microscopic) Classification:

• I-Complete microscopic resection of the tumor and wall as well as adhesions with the bone that may also be abnormal.

• II- Complete microscopic resection of the tumor by diathermy coagulation of its attachment to the wall.

• IIIA- Complete microscopic resection of intradural and extradural tumor without resection or coagulation of its dural attachment.

• IIIB- Complete microscopic resection of intradural tumor without resection or coagulation of the dural attachment or any extradural extension.

• IVA - Deliberate sub-total removal to preserve cranial nerves or blood vessels as well as complete microscopic removal of the attachment to the wall.

• IVB- Partial removal of TU, leaving <10% by volume tumor mass.

• V - Partial removal of TU, leaving tumor> 10% in tumor mass volume, or decompression with or without biopsy. (130.131)

These types of classifications are still used today. Different schools tend to use the Simpson classification although a bit outdated, but it has been shown to be the most practical in the language of Neurosurgeons.(5,6,7)

2. The Clinic

The presentation of clinical symptoms to parasagittal meningiomas is largely related to the proximity of the lesion to the Rolandic tribe as described by Cushing's case of General Leonard Wood. These patients usually present with sensory or motor neurologic deficits, including lower contralateral extremities, following the above neurological deficits, with more frequent secondary symptoms being paresthesia, papillae, and dementia disorders, described.(1,3,8)

Presentation of symptoms in parasagittal meningiomas

Focal seizures

General convulsions

Headache

Confusion

Monoparesis of the lower extremities

Visual symptomatology

Calvary deformity

Dysphasia

Cerebrovascular Insult

Vertiginous syndrome

Mental symptoms

2.1 Treatment

Treatment of parasagittal meningiomas is surgical as the indispensable method of successful treatment, achieving a total resection of the tumor, as the likelihood of recurrence is lower. The classification and grade of surgical resection was described by Simpson in 1957, who proposed it many years ago but is still widely used in the treatment of meningiomas, as shown in Tab.(5,7,8)

Table 1.2. The Simpson classification

Grade I Total tumor resection along with infiltrated wall or bone

Grade II Total tumor resection and coagulation of infiltrated wall

Grade III Total tumor resection without coagulated infiltrated wall

Grade IV Subtotal tumor resection

Grade V Intracapsular tumor decompression.

Operating techniques with SSS involved

Surgery of the parasagittal miniatures, including SSS, puts the neurosurgeon in a great dilemma and challenge, such as:

- Leaving part of the tumor inside the large sinus with a high risk of recurrence, and

- Radical removal of the tumor and greater exposure to risk for the patient during surgery. These contradictions persist to this day, as to which of these ways is best for the patient, it remains a subject of discussion and debate. (1,9,10,)

2.2. Preoperative Investigations

CT scan and contrast RM are the key to diagnosis. The accumulation of Gadolinium in the wall should be considered because it indicates the site of exposure as well as the proximity of the tumor mass that is the site of tumor invasion or simply peritomal hyperemia.

2.3.Observation of meningiomas

Due to the aging of the population and the increasing use of MRI as a diagnostic tool, the detection of incidental meningiomas in asymptomatic patients is becoming more common. Recent studies have shown that tumor growth occurs from 37% to 63% of patients, with annual growth rates of 1.9 mm, 4 mm, and 0.54 cm3 in those younger than 60 years and 0.83 cm3 in older ones than 60 years.

2.4.General principles in operating techniques

1. Bicoronal incision is preferred due to greater skin vascularization, especially when reintervention is expected.

2. The pericranial flap reflects separately.

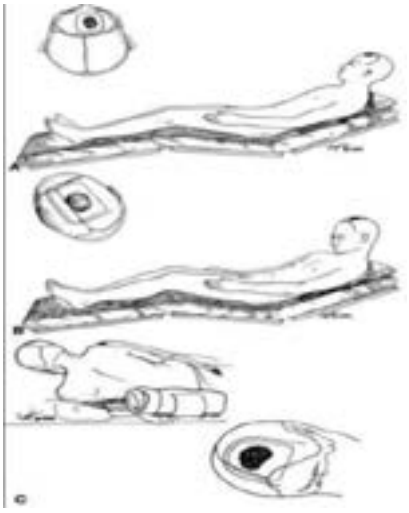
3. Multiple holes should be in close alignment with a hole in the periphery of the tumor.

4. The numerous holes around the SSS allow the bone to be securely separated from the bone

5. Microsurgical preparation of the tumor capsule from the surrounding cortex is performed while maintaining normal vascularization of the cortex.

Patient Positioning - Placing the patient in a lounging position allows for safer venous drainage and without the risk of ICP increase, the risk of air embolism is always present but is rare due to pressure high venous in these patients. For anterior 1/3 tumors, the patient is positioned on the supine spine and a bi-coronary incision is used. In the middle 1/3 tumors, the patient is in a semi lateral position and the 1/3 posterior lesions are the inverted prone position.

Fig.2. Patient positioning with parasagittal meningioma and MPS skin incision.



1. Operational exposure should be as wide as possible. Skin unfolding and craniotomy should extend along the entire midline to allow visualization of both sides of the sinus and approximately 3 cm outside the borders of the occluded sinus. However, such a large approach should be reconsidered if the skin, pericranium, or collateral veins can be damaged during such an opening. A bi-coronary incision is preferred because it allows for maximum vascularization in the skin, especially if subsequent craniotomies are to be performed.

2. Afferent tumor arteries within the wall must be coagulated or clipped before being cut.

3. The dura is cut peripherally around the tumor mass in the convex form to the convex margins, along the border of the superior SSS sagittal sinus. Multiple holes are made close to each other on the periphery of the tumor.

4. Craniotomy (Bur holes) around the tumor and SSS allow bone preparation for the bone.

5. The microscope is installed.

6. Microsurgery separation of the tumor capsule from the surrounding cortex is performed by preserving the vessels that overlap in the normal cortex.

7. Adhesion of the meningioma to the lateral sinus wall and adjoining phalanx structures should be discontinued using the method of incision with a bipolar clamp for coagulation, cutting off the tumor from the meningeal supply.

PURPOSE OF THE STUDY

The purpose of this study is to evaluate the results of surgical treatment and analysis of new surgical methods in meningiomas of the parasagittal region.

2.1. Overall objectives

Presentation of data on patients operated on with parasagittal meningiomas. In the period January 2012 - October 2019, at the Neurosurgery Service Hospital Center

University “Mother Teresa”, Tirana, Tetovo Clinical Hospital and Hospital “8 Septemvri” Skopje.

2.2.Specific objectives

1. Indicate the percentage of parassagital meningiomas in the brain meningiomas.

2. Determination of age by parassagital meningiomas.

3. Clinical signs, patient complaints, touch of the sensory cortex.

4. Imaging of parassagital meningiomas and the possibility of removing them completely.

5. To present the results of the surgical treatment.

6. The likelihood of recidivism and the factors affecting it.

7. Presentation of postoperative and long-term functional outcomes.

8. Compare the presence of parassagital meningiomas in Albania and N.Macedonia.

MATERIALS AND METHODS

This study is a retrospective study, conducted between January 2012 - December 2019, involving 47 cases treated at the Neurosurgery Service, Mother Teresa University Hospital Center, Tirana, Tetovo Clinical Hospital and, 8 Septemvri, City Hospital Skopje. .Our cohort is homogeneous and unselected. For this kind of pathology our center is a reference center for Albania, Albanians in Kosovo, Montenegro, and Macedonia. Patients are operated by the same surgeon Prof. Mentor Petrela PU βH Paris, thereby eliminating the effects of experiential learning on the outcomes of the interventions. The study included patients with a histologic diagnosis of meningioma and localized to the anterior 1/3, middle 1/3, and 1/3 posterior throughout the length of the Sagital Superior Sinus. Their identification was performed by examining the intervention registers and admission cards. Intervention registries indicate the date of intervention, patient's generalities, preoperative diagnosis, intraoperative diagnosis, brief history of illness, operative act. follow-up of patients. Data on age, sex, preoperative diagnosis, anamnesis, objective neurological examination, intraoperative diagnosis, description of operative act as well as details of immediate postoperative progress were obtained from follow-up files. Data on the long-term progression of the disease, including imaging and clinical progress. Radiological data were obtained from the review of distance radiological examination films. Data obtained from the above documentation were entered into the Microsoft ® Office Excel 2010 numeric software. of surgery Time of onset of complaints Clinical data (epilepsy, increased intracranial pressure, motor deficits) preoperative radiological data Tumor size: 1) <2 cm; 2) <4 cm; 3) <6 cm; 4)> 6 cm tumor localization (based on Cushing's classification) tumor ratio to SSS, cortex, aa.cortical, surgical tumor approaches, excision according to Simpson, Sindou Auvernia and Okudera Kobayashi histopathology data from all three centers Hospital, postoperative radiologic data and follow-up postoperative neurological status and follow-up time of relapse and treatment. I processed the statistical analysis by collecting data and transferring it to the computer to perform the statistical analysis which was run in Microsoft® Excel 2010. The statistical analysis was performed with the Statistical Package for Social Sciences, version 17.0. The data shows some cases with a partial lack of data.

RESULTS

Simpson, I surgery was performed in 38 cases or 100% of small and medium tumors by tumor size, whereas in large tumors, Simpson I surgery was performed in 6 cases or%, Simpson II in 4 cases or (%) of cases, Simpson III in 4 (%) of cases and Simpson IV in 1 of cases or (%). The results are shown in the table below. Simpson I was performed in (100%) of cases in 32 cases with small and medium meningiomas. In the middle third of meningiomas Simpson I surgery was performed in 15 (35%) cases, Simpson II in 22 (51%) cases and Simpson III in 6 (14%) cases. Simpson I surgery was performed in 1 (8%) cases, Simpson II in 8 (62%) cases and Simpson III in 4 (30%) cases in meningiomas of the inner third of the sphenoid. Mortality and morbidity. In our study, it was found that early post-operative mortality (within 30 days) was 0%. Late mortality was at a low rate, in a single case of meningiomatosis where he subsequently performed a second reintervention after 7 months, and again relapsed, was treated with radiosurgery, but the condition worsened, a third intervention was attempted, but has resulted in complications, cerebral edema palsy with subarachnoid and intracerebral hemorrhage as well as hydrocephalus, where he has been treated with dysfunctional DVP, where all these factors lead to the cause of death.

Table and graphical representations by age, out of a total of 47 patients, mean age is 57.8 years, with the youngest age ranging from 32 to 77 years. Table 4, graph 1.

Table 2. Distribution of patients by age

Total patients studied by age	47 in total
Minimal	32.0 years old
Average	57.8 years old
Maximal	77.0 years old

Chart 1. Patients distribution by age.

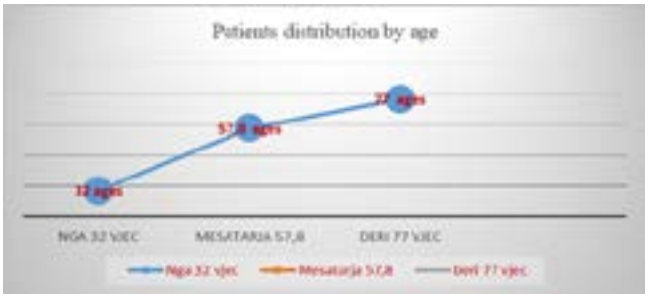
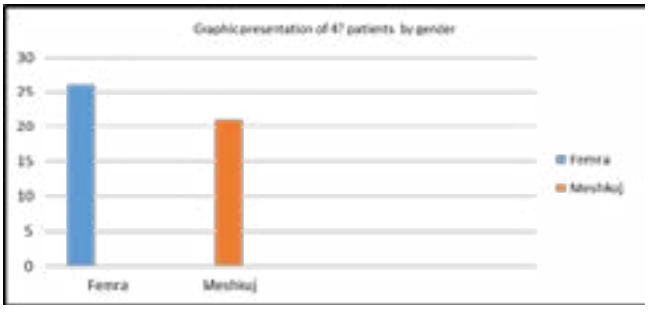


Table 3. and graphic 1. representation by sex, out of a total of 47 patients, 26 are female, and 21 are men.

Table 4 and graph 2.

Total patients studied by sex	Total 47	100 %
Female	26	55,31 %
Male	21	44,68 %

Table 4. Tab. by gender, out of a total of 47 patients, 26 are female and 21 are male,



Graph 2. Graphic representation by gender, out of a total of 47 patients, 26 are female, and 21 are male.

DISCUSSION

After modern technological development and progressive popularization, as well as improved images from CT, RM and DSA it has become possible to clearly define, diagnose, qualitatively, meningiomas of all regions. Regarding the natural progression of meningiomas are not sufficient Among the largest studies conducted with 75 patients, no severe complications were observed such as thrombotic occlusion of the SSS, no mortality, neurological deficits reported in only 5 cases, edema brain in only one case, venous stroke in 1 case, liquid in 2 cases, and systemic complication in 1 case.

Fig: 3.-A Large middle 1/3 parasagittal meningeoma a - T2 axial pre op; b pre operative coronary T2; cβ T2 sagittal pre op.

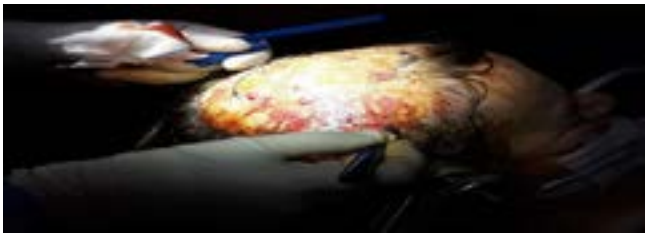
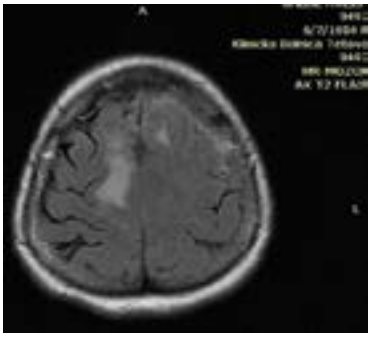
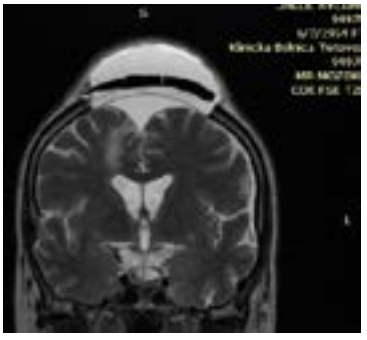


Fig.3.1. Marking of skin incision





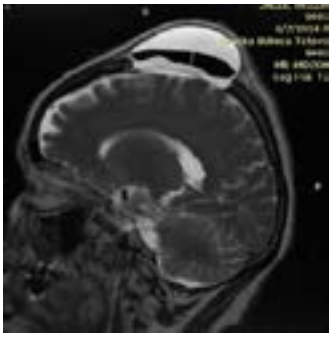
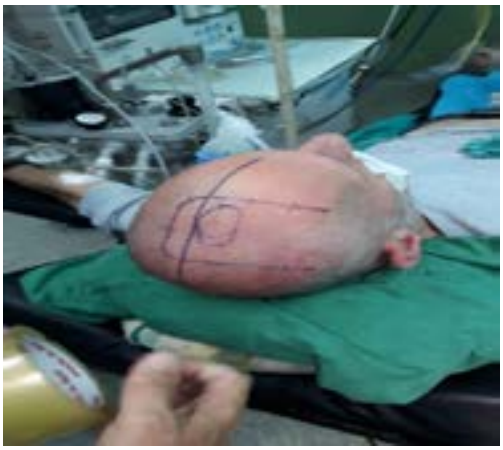


Fig.3.2.-B: Large middle 1/3 parasagittal meningioma a-T1 axial with Gadolinium postop; b1 postop coronary T1; c- T1 sagittal post op.



A

B

Fig.4. Small meningioma A-situation PRE-OP and B-Situation POST-OP

9.1 Surgical Strategy

The surgical strategy and approaches for removing parasagittal meningiomas depends on the location of the tumor, but the preferred approach is the bi-coronary, with extensive flap, for vascularization reasons. This approach offers several advantages, having a good and comfortable approach to attack the dura that may be involved in SSS, safe dissection of tumor mass with regard to vascularization, especially the veins that drain the blood toward SSS- Troland, where SSI should not be overlooked and no cases of surgical intervention in the parasagittal meningiomas have been observed and avoided so far, or minimally invasive or by endoscopy remove the tumor mass especially when it comes to parasagittal meningiomas safety and a challenge to the surgeon, due to the sensitive anatomical structures around the tumor.

CONCLUSIONS

Parasagittal meningiomas in our study from 2012 to 2019 were 47 out of 262 meningiomas in total or 18% which corresponds to the percentage of parasagittal meningiomas in the world literature.

A significantly higher incidence is between 51 years to 70 years

Females predominate in relation to males 26 F and 21 M

The dominant clinic is headache and neuromotor deficit

The time from onset of complaints to diagnosis is several weeks to 120 months. The Medline in diagnosis was 10 months.

At the moment of diagnosis, a large of them are very large tumors.

The quality of complete tumor removal was 47 cases, 38 cases according to Simpson I 4 cases Simpson II, 4 cases Simpson III, 1 Case Simpson IV and 0 Cases Simpson V.

Tumor removal is conditioned by the dimension of the tumor, the relationship with SSS, and the relationship with normal brain structures.

The complete result was 37 patients 80.29 %, significant improvement was at 4 patients or 8.68 %, worsened 2 patients or 4.34 % and the same condition 4 patients or 8.68 %.

Parasagittal meningiomas are the majority of them GR I - 38 cases and rarely recidiv.

Parasagittal meningiomas are localized: 21 cases 1/3 anterior, 20 1/3 middle, 6 cases 1/3 posterior.

Life has increased qualitatively after tumor removal.

Recidiv has been low.

The incidence of parasagittal meningiomas in various literature varies from 16.8% to 25.6%, according to the initial classification based on morphological criteria, whereas the latter classifications are based on tumor location along the SSS. The report is 2.3 cases per 100,000 citizens per year (1.5 for males and 3.1 for females). They make up about 20% of all intracranial tumors.

Almost 50% attack SSS, 50% tend to attack falx and only 25% are bilateral, 25% are associated with skeletal hyperostosis and are a valuable indicator for

diagnosis.

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Profesional paper

EFFECTIVENESS OF VITAMIN K ANTAGONISTS FOR SECONDARY PROPHYLAXIS OF BRAIN STROKE IN PATIENTS WITH ATRIAL FIBRILLATION IN ROUTINE PUBLIC CARE SETTINGS

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ABSTRACT

Intro : Vitamin K antagonists are the mainstay for prevention of strokes in patients with atrial fibrillation (AF) world-wide. Yet estimates on its effectiveness are heterogeneous and reveal stark differences between different health-care systems. The aim of the present study was to assess the laboratory parameters for achieving the goal of the therapy (Time in therapeutic range – TTR) and to describe the effectiveness of the therapy in real-time setting.

Methods : Patients treated in our clinic, with confirmed AF were considered in the study. The study was prospective observational study by design, where the participants were assessed at baseline for known risk factors for stroke, diagnosis for atrial fibrillation, use of anticoagulant medication and presence of identifiable ischemic lesions in the brain with non-contrast computed tomography (NCCT). The drug of choice was acenocoumarol, with planned monthly measurements of INR with the duration of 6 months, and the study was concluded with additional NCCT at the end, in order to assess for differences.

Results : 96 patients finished the observation. The mean age of the patients was 64.5 years (SD = 6.36), and 50 (52%) were male. Regarding the INR measurement, we collected data from 88.2% of the planed measurements; 69.7% of the patients achieved TTR above 60%. Cross-comparison between groups (TTR < 59% and TTR > 60%) revealed that the first group had statistically significant higher proportion of patients with newly registered lesions on NCCT (p-value < 0.05).

Conclusion: Acenocoumarol is the only therapeutic VKA option in our country, despite the availability of other VKA antagonists that show better indices for effectiveness. Our sample confirmed that the proper use of VKA significantly reduces the incidence of new NCCT ischemic lesions in conditions of routine public health care.

Authors keywords: atrial fibrillation, oral anticoagulants, stroke prevention, time in therapeutic range, vitamin-K antagonists, silent stroke, effectiveness;

INTRODUCTION

Vitamin-K antagonists (VKA) represent the most utilized class of drugs in the secondary prophylaxis of thromboembolism and brain stroke in patients with atrial fibrillation on global level. They partake an important role in reducing the associated risks with atrial fibrillation (1,2), mainly regarding thromboembolic events in the brain (3–5). The use of VKA therapy has associated burdens – narrow therapeutic index (6) and sensitive pharmacokinetics (7,8), which necessitate regular laboratory monitoring and risk for complications, such as persistent bleeds from wounds or spontaneous bleeds. Some of these complications are predictable (9) by following a laboratory parameter - the international standardized ratio (INR) (10), a derivate of prothrombin time, which is used to express the targets of the therapy and to properly dose the VKA (11). As recommended, the best treatment effect of VKA therapy in this scenario is achieved when the value of INR is in the range 2-3 (11,12), while values below and above are associated with thromboembolic and hemorrhagic events, respectively (13). Recent studies report on the use of VKA in terms of serial INR measurements, finding out that in setting of regular care, patients achieve the targets of therapy in 30-75% of all measurements (14–16), which is less than in settings of randomized control trials.

The use of VKA at local level has not been subject to a systematic study. Previous study conducted in the Balkans (neighboring countries) revealed that patients achieved TTR of 49.5% (Potpara et al.) In Macedonia there is only one registered VKA, acenocoumarol (tablets, 4 mg), which is used in the secondary prophylaxis of stroke in patients with atrial fibrillation.

The aim of the present study is to analyze the correlation of time in therapeutic range in patients taking VKA and incident ischemic stroke (diagnosed with clinical and imaging modalities).

METHODS AND POPULATION

This was prospective, observational cohort study, conducted at the Neurology Department of the University Clinic – Tetovo, Macedonia. All registered patients in the last six months and patients in the period from January 2019 to April 2019 with findings of atrial fibrillation were considered in the study, based on their informed consent. The patient population is representative of the northwestern part of the country, as the overall majority of the citizens use the public health service. Patients were evaluated for indication for oral anticoagulant therapy use (and previous OAT use). Inclusion criteria were: EGC-evidenced atrial fibrillation (2) and diagnosis set by cardiologist (ICD-10 code I-48), CHA2DS2Vasc-Score above 1 (or above 0 for males) (17), actual use of acenocoumarol or willing to start with prescribed therapy with acenocoumarol (in accordance with treatment guidelines), and consent to attend regular INR monitoring on monthly basis and undergo native computed tomography scan of the brain on two occasions, six months apart. As exclusion criteria we used concurrent use of/or indication for antiplatelet drug, presence of contraindications for acenocoumarol (active bleeding or previous major bleeding due to acenocoumarol, previous major surgery). All patients signed informed consent to participate in the study.

MEASUREMENTS

At study enrollment, patients underwent native non-contrast computed tomography (NCCT) of the brain and measurement of the international standardized ratio (INR). Their previous health records were checked for previous/actual conditions of the vasculature, heart, thromboembolic events, diabetes mellitus, presence of implants and rheumatological conditions and targets for INR other than 2-3. All of the measurements were done at the Clinical hospital – Tetovo. For performing CT of the brain, we used SOMATOFORM SIEMENS CT, with generating 1.6 mm axial slices. All of the CT-scans of the brain were evaluated for the presence of fields of ischemic sequelae in the brain by trained radiologist and neurologist. As findings of interest were CT-hypo-intense signals with Handsfield unit (HU) values approximating the HU values of the cerebrospinal liquor in the same case which were localized in single arterial territory and were not consequence of known trauma or bleeding, including both cortical and lacunar infarctions. At the end of the observation period patients were scanned again, and the second NCCT-scan of the brain was used for comparison, in order to register new lesions. Patients came regularly at three-month visit for follow-up, with monthly check of the INR at the transfuziology unit at our hospital with the use of Hymanclot Analyzer. The time in therapeutic range was determined individually under the assumption that patients performed monthly INR measurements as number of INR measurements in range of 2-3 over number of total INR measurements,

with projected 7 measurements during the 6 months of observation. Patients with less than 4 measurements were not included in the analysis, as their TTR could not be reliably determined.

CHA2DS2Vasc score (18) represents a quantitative tool for determining future stroke risk in patients with diagnosed atrial fibrillation. It takes into account the age (>= 75 years – 2 points, 65-75 years – 1 point), presence of arterial hypertension (1 point), presence of congestive heart failure or left-ventricular systolic dysfunction (1 point), diabetes mellitus (1 point), prior stroke, transient ischemic attack or embolic event (2 points), vascular disease (1 point), female sex (1 point), with 9 points in total, with projected annual risks for incident disease rising significantly above 1 point. It's use has entered the practice as clinical tool for risk assessment (19), making compound measure of risk factors for thromboembolism in patients with AF.

Table 1. Descriptive statistics on patient sample characteristics (n = 96)

Variable	Patient sample
Age (x, SD)	64.5 (6.36)
Gender (% males)	50 (52%)
Previous VKA use (%)	67 (69.7%)
Past/current thromboembolic conditions	56 (55.2%)
Arterial hypertension (%)	70 (72.9%)
Diabetes mellitus (%)	26 (27.1%)
INR measurements (x, SD)	6 (0.6)

INR – International Normalized Ratio

ANALYSIS

In order to describe the patient group, demographic characteristics on age, gender, ethnicity, previous OAT use, CHA2DS2-Vasc score, presence of arterial hypertension and diabetes mellitus are presented in terms of mean (with standard deviation) for continuous and proportions for categorical variables. The values regarding time in therapeutic range, presence of NCCT-identifiable lesions at enrollment and follow-up are derived from individual patient data and were described with mean, SD, median. In order to test for differences in NCCT-incident lesions between patients with TTR above and below 60%, the Fischer's exact test for comparison of proportions was used. The analysis of data employs intention-to-treat analysis. Statistical significance was determined at the level of 0.05.

RESULTS

From the initial 126 patients enrolled at the beginning, 96 (76%) patients finished the observation period. The resulting sample of 96 patients had average age of 64.5 years (SD = 6.36) and 50 (52%) were male. 29 patients were newly prescribed VKA users while the remaining 67 patients had continued VKA use in the last 3 months. The descriptive statistics on the patient sample are available in table 1.

From 96 patients and planned 672 measurements, we collected data from 593 of the measurements (88.2%). The mean time in therapeutic range was 0.65 (SD = 0.15), ranging from 0.28 to 1 (3 cases). The corresponding distribution is presented with histogram in figure 1. Patients that did not show up during the study had an average of 3.1 INR measurements, insufficient for calculating the time in therapeutic range. The resulting sample revealed that 67 patients (69.7%) achieved TTR above 60%, while 29 patients achieved TTR below that threshold.

The results from the first NCCT-scan revealed that 59 patients were free of identifiable lesions while 37 patients had at least one identifiable lesion that could be attributed to ischemic event in the brain. From the 37 patients with CT findings, 2 patients had 2 lesions registered on the NCCT-scan. The results from the second NCCT-scan revealed that 42 patients had NCCT-registered lesions in the brain, out of which 5 patients had 2 lesions, while 54 patients did not have any finding.

Cross-comparison between the patients with TTR above 60% and the other group revealed that 2 patients (3%) of the first group had NCCT-findings consistent with new ischemic lesion, while 5 patients (17.2%) in the second group had NCCT-findings for new lesion.

Differences between the two groups in terms of incident CT-lesions were assessed by the Fisher's exact test, which revealed statistically significant differences in proportions of 0.142, with p-value of 0.025 (figure 2). The odds ratio for incident CT lesion was 5.78 higher in the group that did not maintain TTR above 60% (95%CI 1.189 – 28.067) (Figure 2).

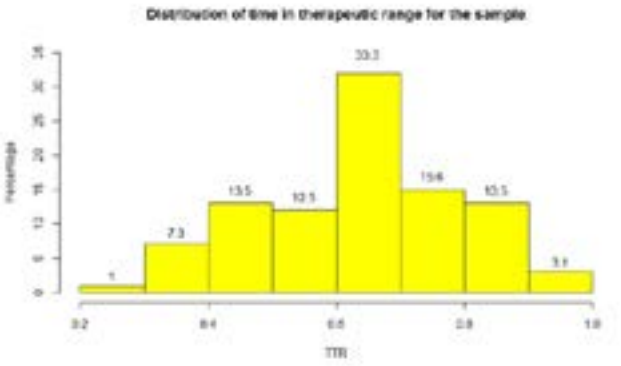

Figure 1. Histogram of individual time in therapeutic range (TTR) of the patient sample (n = 96). Numbers above bars denote percentages.

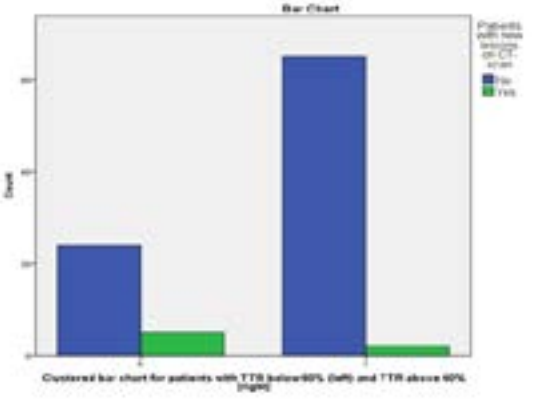

Figure 2. Comparison between proportion of patients with new CT-lesions between patients that achieved TTR above 60% and patients that achieved TTR below 60%.

Legend: TTR- time in therapeutic range

DISCUSSION

The present study is the first study to investigate the importance of maintaining time in therapeutic range for prophylaxis of incident brain strokes in Macedonia. Given the fact that 38% of the patients had identifiable lesion that can be attributed to ischemic event in the brain on the baseline computed tomography reflects the patient base drawn from neurological practice.

From the planned measurements for INR, patients that finished the study managed to attend at the 89% of the monthly regular measurements. In our sample, 67% of the patients maintained TTR of at least 60%, and the mean TTR was 0.65. This finding is slightly different than the results from another regional study, where the measure of TTR was secondary objective, reports that TTR was available for 18.7% of the analyzed patients, with reported mean TTR of 49.5% (95%CI 20-90%), while the most recent measurement of INR was available for 79% of the patients, where 55.2% of the patients were in therapeutic range (20). Of note is that patients treated with VKA's were not exclusively on monotherapy and this was not the primary objective of the study, which could explain the differences in comparing the results for TTR (0.65 vs 0.52) and availability of past INR measurements (89% vs 79%).

One of the earliest meta-analysis on the topic from Walraven (21) revealed differences of achieving good anticoagulation control in the setting of RCT, anticoagulation clinic and community follow-up. For instance, the mean unadjusted mean of TTR followed in clinic or RCT was 65.4% (95%CI 63.7-67.7%) and 66.4% (95%CI - 59.4%-73.3%) respectively, while TTR measured in community practice was estimated at 56.7% (95%CI - 51.5%-62%), giving statistically significant difference, while the conclusions of the study revealed that self-monitoring of INR could increase TTR in selected populations, an option that is still not employed in the health systems in Macedonia. The findings of the study are comparable to our results, taking into account that the INR measurements were conducted at the transfusiology department of Clinical Hospital – Tetovo. Still, of note is one curious finding, albeit statistically insignificant (p = 0.08) – the metanalysis compared TTR in studies conducted before 1998, finding out that studies conducted later reported slightly better anticoagulation control, which might be indicative of the gained experience of the health systems in prescribing therapy with VKA and follow-up. The reported results are in line with the findings of other studies conducted at European level (22)

Another consideration in this study is the choice of the anticoagulant drug. Currently, our market has only one registered drug, acenocoumarol. Recent observational study from PREFER IN AF Registry reports that patients on monotherapy with acenocoumarol achieved the lowest TTR (65.9%), in comparison to warfarin (69.3%), fluindione (72.7%), phenprocoumon (80.4%) (22) Another recent observational study from Spain, where the most utilized drug is acenocoumarol, conducted on older sample than ours (mean age = 73.8 +- 9.4 years), estimated that the mean TTR was 63.77%, while 54% of the patients exhibited poor control (TTR < 65%) ((23). Regarding the long-term stability of this parameter, it has been found that most of the patients show stable trajectory after the first 6 months of measurement (Pokorney et al.; Witt et

al.; McAlister et al.).

Although 37 patients did have previous findings on CT scan, additional 19 patients had either recorded finding in the past for transient ischemic attack, acute myocardial infarction or deep venous thrombosis. Additionally, 67 of the patients had already been put on routine Vitamin-K antagonists, while during the recruitment, 32 patients started treatment with VKA. The results of the study confirm the finding of effectiveness of VKA antagonist with regard to strokes as registered on NCCT.

The variability of the findings in the reported studies are due to factors regarding the patients, the drug used in the study, but also due to the different health care setting among different countries. The last has been investigated in a cost-benefit analysis, comparing the use of NOACs vs the traditional VKAs – for instance, where three NOACs have been calculated as cost-effective alternative of coumarins in Great Britain, while two of them were significantly better in terms of cost-effectiveness in The Netherlands. The findings of the study emphasize the quality of INR control, which is main determinant of effectiveness of this therapy (24). This finding is in line with other studies on cost-effectiveness, where the importance of maintaining INR is highlighted (25).

The limitations of our study might stem from the sample population, which is drawn from population that utilize public health services. Next, the possibility for information bias is present since the outcome is derived from inferior imaging method (CT in comparison to MRI). CT in this scenario has lower sensitivity than advanced imaging techniques, such as the computed-tomography perfusion (CTP), computed tomography angiography (CTA) (26) and magnetic resonance imaging (MRI) (27). Although the analysis was done in intention-to-treat manner, the study assumes that the INR measurements are indicative of real use of the medication by the patients.

CONCLUSIONS

As important finding of this study is the high rate of INR control in our sample. The differences between the patients that achieve TTR > 60% had significantly lower number for new ischemic lesions as registered on CT. One realization of the present study is the unavailability of other drugs from the same class on our market. The use of acenocoumarol provides certain benefits with regard to its short half-life, which is convenient as therapy before anticipated invasive or semi-invasive procedures. The absence of other VKA antagonists in our health-care system should be reconsidered, as it has been found out that acenocoumarol achieves lowest TTR, as provided from the literature, and showed similar TTR to the studies that pointed out this difference. This necessity is emphasized for countries in development, where the health care systems cannot afford to provide the NOACs which are much more expensive and where the use of anticoagulant therapy in the patients with risk is underutilized.

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Profesional paper

EVALUATION OF THE ASSOCIATION BETWEEN PSYCHOSOCIAL FACTORS AND PLAQUE AND BLEEDING INDEX AS INDICATORS OF PERIODONTAL STATUS

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ABSTRACT

The aim of the study is to evaluate the psychosocial factors association with periodontal status indeces such as plaque index and bleeding index.

Material and method: This was a case-control study carried out in 69 patients (33 patients in case group and 36 patients in control group) requiring dental check up and treatment in the University Dental Clinic in Tirana. Socio demographic data were recorded alongside information regarding dental health behavior. Psychosocial factors were evaluated through Beck Depression Inventory (BDI). Clinical data of PDD, CAL, BOP and PI were recorded.

Results: With regards to oral hygiene behavior in the case group the largest part show a poor dental care with 61.5% of the patients brush their teeth ''rarely'', whereas only 33.3% of the control group show this low level of dental care. The evaluation of PI showed that the highest percentage of patients in the case group had compromised and poor oral hygiene. There were no patients with good oral hygiene. In the control group the highest number of patients also showed poor hygiene, but in contrary with the control group there is a percentage of patients showing good oral hygiene in this group.

There is a statistical relationship between PI and depression level $\chi 2=23.716$, $P<0.05$ ($P=.005$);

There is a statistical relationship between bleeding index and depression level $\chi 2=24.061$, $P<0.05$ ($P=.020$)

Conclusions: The results bring evidence in favor of a relation between psychosocial factors and some indecis of psychological status.

Key words: periodontitis, psychosocial factors, behavioral factors, stress, depression, bleeding on probing, plaque index.

INTRODUCTION

New research in periodontology is adding to the boddy of evidence on a putative relationship between psychosocial stress and forms of periodontal disease. This has brought to the recognition of psychosocial stress as a risk indicator for this diseases (1). This evidence can be seen in a broader theoretical perspective of the influence of stress in a range of systemic conditions, justifying the search for other possible relations between mental health and periodontal disease. The scientific evidence of the association of stress to periodontal disease date back in the 1950 when necrotizing ulcerative gingivitis (NUG) was the first disease studied from this aspect. The investigation was based on some unique charachterisitics of NUG etiology as an acute pathology in which the causing bacteria are otherwise non pathogenic under normal conditions. This would suggest for a deeper search into alterations of the patients immunity that could explain the breakout (2).

Some other studies focused on specific psychological

factors showed that individuals with the highest work related stress, also show signs of gingival inflammation and gingival recession (3).

Another study from Mengel et al. (4) investigating on the interactions between periodontitis and psychological stress, using measures of hormone levels and inflammation mediators, found a significant correlation between family stress and gingival inflammation.

Mechanisms explaining the relation- Hipotalamus pituitary adrenal axis (HPA)

The evidence emerging from interdisciplinary psychoneuroimmunology studies offers a deeper view into the mechanisms aiming at explaining the relation between stress and periodontal disease. The immune response modulation under the effects of psychological stress forms the basis of these mechanisms as showed in a range of studies (5), (6). One of the best accepted models is the one proposed by Genco et al. 1998 (7). Stressful stimuli illicit a complex response with the involvement of neurological, immune and endocrine pathways. HPA axis receives a signal to release corticotropine releasing hormone (CRH), which in response induces the release of adenocorticotropic hormone (ACTH), the last one leading to release of glucocorticoids. The latest can impede the immune response and promote tissue destruction phenomena.

Behavioral changes

Another mechanism explaining the effects of psychosocial stress on periodontal conditions focuses on the behavioral changes like smoking, oral hygiene neglecting and fewer dental visits (8)4,25]]},"issued":{"date-parts":[["1999",7]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . A considerable amount of studies provide evidence on the relation between the modification of oral hygiene behaviors under stressful conditions and a worsening of periodontal health. Deinzer et al. 2001 conducted a study on a group of students under academic stress and proved that their oral hygiene evaluated through dental plaque was poorer in comparison to control group (9). It is now a well accepted fact that a poor oral hygiene with accumulation of plaque leads to gingival inflammation (10).

Based on the above evidence and arguments, this study evaluated the relation between depression and dental plaque index and bleeding index as indicators of gingival inflammation.

MATERIAL AND METHOD

This is a case-control study conducted in 69 patients (33 patients were signed up in the case group and 36 patients in the control group) who presented themselves for dental treatment and check up at the University Dental Clinic, Tirana, their age ranging from 19-63-year-old. The groups had an even number of patients at the beginning of the study, but during the analysis of the psychological questionnaire, it was noticed that three patients assigned to the case group had invalidated the form, therefore had to be excluded from the study. Exclusion criteria were having received periodontal therapy in the past 3 months, uncontrolled diabetes, cardiovascular disease, immunosuppressive drug therapy or calcium blocking agents, pregnancy, diagnosed mental disease and use of psychotropic drugs. The patients qualified for the study were introduced with the scope and the procedures of the study and were invited to sign a consent form based on free will. Sociodemographic information and health behavior related data were recorded, including age, gender, marrtial status, education, employment status, tooth brushing frequency, dental visiting frequency and smoking. Afterwards they were introduced to a psychological evaluation questionnaire Beck Depression Inventory (BDI) applied in many international studies of this type. This instrument evaluates the level of depression categorizing it in clinical terms after simple scoring of the patients multiple choice responses. Cases or ''periodontitis patients'' were defined after the new classification of 2017 World Workshop where '' a patient is considered periodontitis in a clinical context when there is an interproximal attachment loss in two or more non adjecent sites or when there is an attachment loss of more than 3mm with a periodontal pocket equal or deeper than 3mm in oral and buccal site in two or more theeth.

Clinical attachment level and periodontal pockets were measured in 6 sites per tooth, respectively in the mesiobucal, bucal, distobucal, mesiolingual, lingual and distolingual site in all fully erupted teeth, using a manual probe Hu-Friedy, Chicago, IL, USA. Bleeding on probing BOP and Plaque Index PI (Sillnes & Loe 1964). All parameters were measured by a single clinicist and an assistant recorded the data during the procedure. Statistical analysis consisted in extracting the frequencies for all the variables included in the study, 2x2 tables to control for the existence of a relationship between two variables. Chi-Square test was used for this purpose,

which is applied in case of nominal and ordinal data. Our variables were of nominal and ordinal type.

RESULTS

Results are presented in tables and figures as essential findings of a first study of this kinf in our country.

	Case	Control
Gender	n = 33	n = 36
Male	11 (33.3%)	17 (47.2%)
Female	22 (66.7%)	19 (52.8%)
Age	n = 33	n = 36
20-40	14 (42.4%)	22 (61.1%)
40-60	18 (54.5%)	12 (33.3%)
Over 60	1 (3.0%)	2 (5.6%)
Employment	n = 33	n = 36
Unemployed	0 (0.0%)	1 (2.8%)
Retired	12 (36.4%)	7 (19.4)
Student	14 (42.4%)	18 (50.0%)
Employed	7 (21.2%)	10 (27.8%)
Education	n = 33	n = 36
Low	0 (0.0%)	1 (2.8%)
Elementary	12 (36.4%)	7 (19.4)
High school	14 (42.4%)	18 (50.0%)
University degree	7 21.2%)	10 (27.8%)

Tab1. Distribution of demographic data of case and control groups.

The distribution according to gender in the case and control group shows that females are the highest represented gender in both groups. Shpërndarja sipas gjinisë në grup–popullatën rast si dhe në grup-popullatën kontroll tregon se në përqindjen më të lartë janë përfshirë gjinia femër.

Në grupin e kontrollit janë përfshirë 36 individë shpërndarja e të cilëve sipas gjinisë tregon se numrin dhe përqindjen më të lartë e ka gjinia femër, even though with a small difference. The results of age distribution in the case group showed that 40-60 year old group was the highest represented age group with (54.5%). In the control group the age group with the highest representation was 20-40 year olds with 61.1%, followed by 40-60-year-old with 33.3%.

In the case group the education status analysis showed that most individuals had a high school degree, followed by elementary education and university degree. In the case group most individuals had a high school degree with 50%, followed by a university degree with 27.8%.

	Case	Control
Toothbrushing frequency	n =33	n = 36
Never	2 (6.1%)	3 (8.3%)
Rarely	17 (51.5%)	12 (33.3%)
Once a day	11 (33.3)	12 (33.3%)
Twice a day	3 (9.1%)	9 (25.1 %)
Doing a dental checkup despite of lack of symptoms	n =33	n = 36
Never	22 (66.7%)	21 (58.3%)
Rarely	3 (9.1%)	2 (5.6%)
Once a year	8 (24.2%)	13 (36.1%)
Smoker	n =33	n = 36
Po	10 (30.3%)	5 (13.9%)
Jo	23 (69.7%)	31 (86.1%)

Tab.2 Distribution of oral hygiene behavior

The results of the toothbrushing frequency in the case group showed that 51.5% of individuals were brushing ''rarely'', followed by those who were brushing ''once a day'' and only 9.1% were brushing twice a day, while 6.1% were ''never'' brushing their teeth. In the control group the data showed that individuals who were brushing ''rarely'' and ''once a day'' were in the same percentage and 8% ''never'' brush. Regarding 11 individuals who admit to visit the dentist for a checkup despite of lack of symptoms, the results show that 24.2% do the checkup once a year and only 9.1% do it rarely. In the control group 41.7% admit to do dental checkup despite a lack of sypmtoms, with 36.1% doing it ''once a year'' and only 5.6% do te checkup ''rarely''.

Only 30.3% of the individuals in the case group are smokers. A low percentage of smokers is noticed in the control group as well. Smoking habit results in the control group show that only 13.9% of them are smokers.

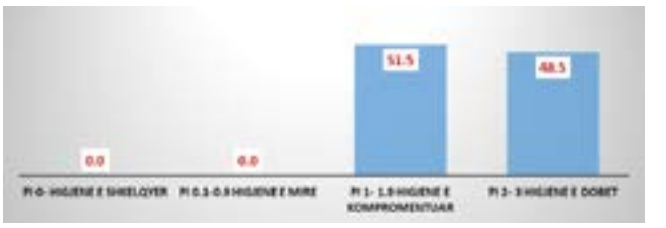

Fig.1 Plaque Index levels in the case group

The evaluation of PI results showed that none of the individuals included in this study showed excellent or

good oral hygiene. Their oral hygiene levels were mostly compromised and poor. Different from the case group, oral hygiene levels were good for a part of the individuals in the control group, but poor hygiene was noticed in the highest percentage of individuals here too.

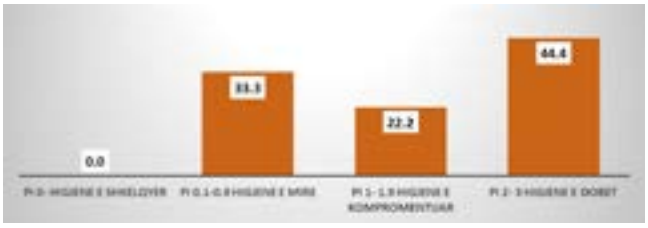

Fig.2 Plaque Index levels in control group

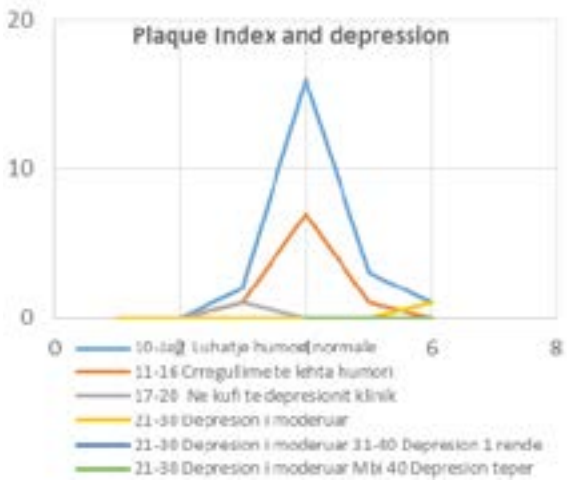

Fig. 3 Plaque index and depression level (case group)

With regards to the evaluation of depression levels, we noticed that most of the individuals in the case group have normal mood swings 66.7%, followed by mild mood disturbances in 27.3% of the individuals and borderline clinical depression and moderate depression in equal values of 3%. In the control group most of the individuals showed normal mood swings in 80.6% of the cases, followed by 8.3% of the individuals with moderate depression and 5.6% of individuals with mild mood disturbances and borderline clinical depression in equal values of 5.6%.

A strong statistical relation was founf between plaque index and level of depression in the case group, $\beta 2=23.716$, $P<0.05$ ($P=.005$).

No relation between these variables was found in the control group.

Statistical relation between bleeding index and depression

Chi-Square test results showed the existence of an important statistical relation treguan se ekziston një marrëdhenie e rëndësishme statistikore between bleeding index and depression in the case group, $\beta 2=24.061$, $P<0.05$ ($P=.020$). No relation between these variables was found in the control group.

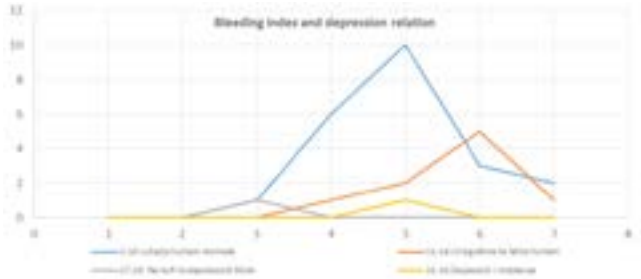

Fig.4. Bleeding index and depression levels in case group.

Discussion

In this case-control study the relation between depression as a psychological factor and some periodontal parameters like plaque index and bleeding on probing was evaluated. A descriptive analysis of the data related to oral health behavior and smoking between two groups was conducted (Tabel 2). Similar studies were conducted by other authors presenting similar findings (11), (12), (13). Different studies have used a range of psychometric instruments such as Life Event Questionnaires'', ''Beck Anxiety Inventory'', ''SCL 90-R'' Studime të ndryshme kanë përdorur edhe instrumenta psikometrike të ndryshëm si ''Life Even Questionnaires'', ''Beck Anxiety Inventory'' etc and this might pose difficulties in comparing the results among those. In our study the patients were selected through random selection from the pool of patients showing up for dental checkup and treatment at our University Clinic. After analyzing the demographic data of age, gender, education, marital status and employment, a similar distribution was noticed between both groups although with regards to gender, a higher percentage of female patients was seen in the case group (Tab.1).

In this study the psychological factor was evaluated through B.D.I, which consists of 21 questions related to mental health and through simple scoring the level of depression is defined which varies from normal mood disturbances to severe depression. The results of this study provided evidence on the existence of a statisrical relation between depression as a psychological factor evaluated by B.D.I and plaque and bleeding in the case group of individuals with periodontal pathology (Fig. 3 & 4). Similar results were reported in other studies like that of Moss et al. 1996 (14). Meanwhile this putative relation

was not proved in some studies of this nature like that of Vettore et al. 2005 (15). A lack of correlation between PI and depression was reported in the study conducted by Monteiro da Silva et al. 1998 (16). The differences in results could be explained with the different methodology approaches in these studies, the criteria of defining periodontitis cases in the case-control studies and with the different psychoinstruments used to evaluate the psychological factor. We have to keep in mind that the depression level in this study, like in several other studies is measured by a self reporting instrument. These type of instruments carry the risk of subjectivity and a lack of accurate professional evaluation of the patient mental status. In order to understand if this relation between depression and gingival inflammation is a result of a compromised dental hygiene due to a modification of health behavior under stress, or the impairment of the immune system under the effects of stress, other studies and research is needed. Nevertheless, it is worth mentioning that there were differences in levels of oral hygiene between case and control groups and that there was no statistical relation found between periodontal parameters and depression in the control group. fakti që nuk u gjet ndonjë lidhje statistikore midis parametrave periodontalë dhe depresionit në grupin e kontrollit.

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ACUTE PANCREATITIS: CURRENT PERSPECTIVES ON DIAGNOSIS AND TREATMENT

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ABSTRACT

The last two decades have seen the emergence of significant evidence that has altered certain aspects of the management of acute pancreatitis. While most cases of acute pancreatitis are mild, the challenge remains in managing the severe cases and the complications associated with acute pancreatitis. Gallstones are still the most common cause with epidemiological trends indicating a rising incidence. The surgical management of acute gallstone pancreatitis has evolved. In this article, we revisit and review the methods in diagnosing acute pancreatitis. We present the evidence for the supportive management of the condition, and then discuss the management of acute gallstone pancreatitis. Management of acute pancreatitis is largely supportive. There is still no consensus on the ideal type and regimen of fluid for resuscitation, but goal-directed fluid therapy is associated with better outcomes. Early enteral nutrition modulates the inflammatory response and improves outcomes by decreasing infective complications of acute pancreatitis.

Keywords: acute pancreatitis, diagnostic imaging, management of gallstone pancreatitis

INTRODUCTION

A patient complaining of sudden onset of epigastric pain radiating to the back, associated with nausea and vomiting, requires rapid exclusion of a wide range of life-threatening conditions involving the cardiovascular (myocardial infarction, ruptured, and/or dissecting aortic aneurysm) and gastrointestinal (peptic ulcer disease with perforation or bleeding, acute pancreatitis) systems. The clinician's history and examination findings are augmented by relevant investigations in narrowing the differential diagnoses to eventually guide the management and treatment of a certain condition and its associated complications.

The incidence of acute pancreatitis in the UK is ~56 cases per 100,000 persons per year,1 while in the US over 220,000 hospital admissions annually are attributed to acute pancreatitis.2 An epidemiologic study that utilized UK and European data demonstrated an increasing incidence in all-cause acute pancreatitis.3 The incidence of acute pancreatitis was also noted to increase with age.3,4 The male population had an incidence that was 10%–30% higher than females.4 Despite a reduction in the case fatality being observed over time, the population mortality has remained largely unchanged.3 Of all hospital admissions with acute pancreatitis, ~20%–30% of patients have a severe course,1 while severe life-threatening complications will develop in ~25% of these patients.4 The mortality in severe acute pancreatitis can be as high as 30%,2 but the overall mortality in acute pancreatitis is estimated to be 5%.1

Gallstones remain the most common cause for acute pancreatitis. Gallstone-related acute pancreatitis accounts for approximately half of all UK cases, while up to 25% of acute pancreatitis cases can be attributed to alcohol.1 Epidemiologic data have shown a linear increase in the incidence of gallstone pancreatitis across the UK and European countries studied. However, the UK has a much lower incidence of alcohol-induced pancreatitis compared with European studies.3 Alcohol-induced acute pancreatitis is more common in middle-aged men. Idiopathic acute pancreatitis accounts for 20%–34%

of cases and its incidence is similar in both men and women.3 The incidence of idiopathic acute pancreatitis depends on the extent to which a clinician investigates a patient's episode of acute pancreatitis for its causative etiology. Recent advances in laboratory pathology tests and radiologic imaging techniques have contributed to a reduction in the number of acute pancreatitis cases being labeled as idiopathic.

The incidence of gallstone-related acute pancreatitis in both men and women increases with age, with women over the age of 60 years at higher risk.2,3 Patients with gallstones smaller than 5 mm, microlithiasis, or biliary sludge are thought to be at higher risk of gallstone pancreatitis. Microlithiasis causes a functional obstruction at the sphincter of Oddi, which subsequently results in bile and/or biliary-pancreatic secretion reflux that injures the pancreatic duct.5 The common channel theory in the pathogenesis of acute gallstone pancreatitis has been refuted by some.6 Instead, it has been postulated that acute gallstone pancreatitis is the result of pancreatic acinar hyperstimulation secondary to ductal obstruction that triggers trypsin release, which induces a cascade of enzyme-led pancreatic and peripancreatic inflammation.6 Others speculate that duodenal content reflux is more causative of pancreatic ductal injury than bile reflux.7 There are multiple theories implicated in the pathogenesis of acute pancreatitis, and all remain controversial.

Inappropriate release and activation of pancreatic enzymes induce acute pancreatitis. The key enzyme in the activation of pancreatic zymogens has been thought to be trypsin. The inappropriate activation of trypsinogen to trypsin and the lack of prompt pancreatic clearance of active trypsin result in pancreatic inflammation and subsequent triggering of the inflammatory cascade.2 Cytokines including interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor a, and platelet-activating factor are released.7 These in turn induce the hepatic synthesis of acute phase reaction proteins such as C-reactive protein (CRP). Leukocyte migration and activation may represent the major determining factor for both local and systemic complications.4

CLINICAL PRESENTATION

The hallmark symptom of acute pancreatitis is the acute onset of persistent upper abdominal pain, usually with nausea and vomiting. The usual locations of the pain are the epigastric and periumbilical regions. The pain may radiate to the back, chest, flanks, and lower abdomen. Patients are usually restless and bend forward (the knee-chest position) in an effort to relieve the pain because the supine position may exacerbate the intensity of symptoms.8 Physical examination findings are variable but may include fever, hypotension, severe abdominal tenderness, guarding, respiratory distress, and abdominal distention.9,10

DIAGNOSIS AND SEVERITY ASSESSMENT OF ACUTE PANCREATITIS

Clinical diagnosis of acute pancreatitis is based on patient symptoms, physical examination, laboratory analysis, and radiological data. Diagnosis of acute pancreatitis requires two out of three main features: (1) abdominal pain typical for acute pancreatitis, (2) serum amylase and/or lipase greater than or equal to three times the upper normal limit; and (3) evidence of acute pancreatitis on computed tomography (CT) scans.11

Almost all patients with acute pancreatitis have acute upper abdominal pain at onset. The pain is usually severe and constant. The pain may be confined to the mid-epigastrium or may be diffuse throughout the abdomen. Approximately half of patients report pain that radiates to the back that may be relieved by sitting or leaning forward. Patients frequently experience nausea and vomiting as well. However, the differential diagnosis for patients presenting with these symptoms is broad and includes diagnoses ranging from biliary colic, gastric or duodenal ulcer perforation and bowel obstruction, to mesenteric ischemia, aortic aneurysm or dissection, and even inferior wall myocardial infarction.11

Physical signs and symptoms often depend on the severity of the attack. Systemic features include fever and tachycardia, and in severe cases patients may be in shock. In mild disease, the epigastrium may be minimally tender on physical examination, whereas patients with severe pancreatitis may have abdominal distention, tenderness, and guarding. Jaundice can occur due to obstruction of the common bile duct secondary to choledocholithiasis or due to extrinsic compression of the common bile duct due to edema within the pancreas head.

Laboratory analysis for work-up of patients with signs and symptoms of acute pancreatitis includes serum amylase and lipase levels, as well as a complete blood count, electrolytes, blood urea nitrogen (BUN), creatinine, liver function tests, and inflammatory

markers, such as C reactive protein (CRP). In a recent retrospective analysis, the sensitivity and specificity for lipase levels in the diagnosis of acute pancreatitis were 96.6% and 99.4%, respectively. The sensitivity and specificity of amylase levels in diagnosing acute pancreatitis were 78.6% and 99.1%, respectively.12 An elevated serum amylase level is less specific as it can also occur in a number of other conditions aside from acute pancreatitis, including diseases of the salivary glands, cholecystitis, bowel obstruction or ischemia, and peptic ulcer disease. In addition, the longer half-life of lipase in comparison to amylase makes it a useful diagnostic measure in patients with delayed presentation in whom amylase levels may have already returned to normal. The level of pancreatic enzyme elevation does not correlate with the severity of the disease, and serial measurements should not be used as a tool to assess the prognosis or progress of acute pancreatitis. However, it has been noted that CRP levels >150 mg/dL at 48 hours help to differentiate between severe and mild disease.12 Severity is classified as mild, moderate, or severe. Mild acute pancreatitis, the most common form, has no organ failure or local or systemic complications and usually resolves in the first week. Moderately severe acute pancreatitis is defined by the presence of transient organ failure, local complications, or exacerbation of co-morbid disease. Severe acute pancreatitis is defined by persistent organ failure lasting longer than 48 hours.13 Contrast-enhanced multi-detector CT (CECT) is the primary imaging modality used for further evaluation when acute pancreatitis is suspected or diagnosed clinically. Its speed and reproducibility, as well as its ability to accurately demonstrate morphologic changes in acute pancreatitis, make it an ideal first step in imaging of patients with acute pancreatitis. The main drawback of CT is its use of ionizing radiation, especially for younger patients who may require several repeat scans over the course of their illness. What remains somewhat unclear is the best time frame in which to perform CT after the patient's initial presentation. It is generally accepted that early in the course of the disease, the clinical severity and morphologic characteristics seen on CT may not directly correlate with each other. Imaging too early, before 48 hours, may significantly underestimate disease severity on the basis of imaging characteristics.14 In general, CT is not indicated in patients who are clinically classified as having mild pancreatitis (no clinical signs of severe pancreatitis) and show rapid improvement with appropriate medical management. CT should be used in patients who are classified as having severe pancreatitis or are at risk of developing severe pancreatitis, ideally after 72 hours, to best assess the full extent of the disease. In addition, while generally not used for evaluation of the pancreas itself, ultrasound (US) is often performed early in the course of the disease, regardless of the severity, to help establish an etiology for the pancreatitis (i.e. the presence of cholelithiasis or choledocholithiasis) and direct the need for further endoscopic or surgical management [endoscopic retrograde cholangiopancreatography (ERCP) or cholecystectomy].14

TREATMENT

Many patients with severe acute pancreatitis (SAP) develop complications and require prolonged intensive care. To guarantee optimum management, most guidelines recommend the close co-operation of an experienced multidisciplinary team consisting of intensivists, (interventional) radiologists, surgeons and gastroenterologists. Implementation of a specialised treatment protocol can reduce complications and improve outcome. Unfortunately, only few patients with acute pancreatitis are amenable to causative treatments. Nonetheless, each patient, particularly those with SAP, must be evaluated to determine if the underlying cause can be eliminated.

Fluid menagment

Management of AP revolves around supportive care, adequate nutrition, and intravenous hydration. The rationale for hydration is based on the need to resolve the hypovolemia that occurs secondary to vomiting, reduced oral intake, third space extravasation, respiratory losses and diaphoresis. In addition, early hydration provides macrocirculatory and microcirculatory support to prevent the cascade of events leading to pancreatic necrosis.15

Correction of hypovolemia, as assessed by changes in hematocrit and serum creatinine, has been documented to limit necrosis and improve outcome. Hemoconcentration, as a marker of hypovolemia and severity of pancreatitis, has been studied since the 1960s.16 A hematocrit of ≥ 44%-47% on admission combined with failure of a decrease in the hematocrit at 24 h was reported as the best risk factor for development of necrosis.17 Wu et al,18 showed that early hemoconcentration was associated with increased mortality only among hospital transferred cases, and not among non-transferred cases. This difference could

be due to variations in the early management of the studied cases, further emphasizing the fact that fluid resuscitation should be instituted early. Similarly, changes in creatinine from baseline are indicative of intravascular volume depletion these marker is used to predict outcome. Monitoring of these parameters can gauge the effectiveness of initial resuscitative measures.19-24 These parameters can, therefore, be used to optimize goal-directed resuscitation.

Microcirculatory disturbances in AP are different from simple hypovolemia of trauma or bleeding, as they are caused by SIRS with overexpression of inflammatory mediators which injure the endothelium and increase capillary permeability, leading to fluid sequestration and capillary leak syndrome.25 Thus, the purpose of effective fluid resuscitation in severe AP is not only to replenish the blood volume but also to stabilize the capillary permeability, modulate the inflammatory reaction, and sustain intestinal barrier function.25

A number of animal studies have shown the benefit of fluid resuscitation in AP, using both colloids and crystalloids. Juvonen et al.25 used a pig model of AP to show that signs of splanchnic hypoperfusion could be prevented with fluid resuscitation. In that study, the authors measured splanchnic perfusion by local pC02 gap, oxygen delivery and consumption, lactate production, and blood flow. On the other hand, Niederau et al. 26 used a mouse model of AP to show that subcutaneous administration of fluid could normalize hemoconcentration and improve survival. High volume crystalloid infusion with Ringer's lactate has also been shown to improve pancreatic microcirculation in a canine model 27 and with balanced salt solution in a rat model.28

Fluid resuscitation has emerged as a key therapeutic strategy in patients with acute pancreatitis. It has to be acknowledged that fluid resuscitation in AP is a complex process, with need to take into account the dynamics of fluid sequestration during different stages of the disease. Current knowledge suggests that controlled fluid resuscitation (3.0-4.0 L/24 h) should be started after a bolus infusion of 20 mL/kg (1000 mL over one hour). Among the different fluids, lactated Ringers' is the one recommended by most guidelines. There is a need to carry out fluid resuscitation with a goal-directed strategy, with urine output > 0.5 mL/kg and a drop in BUN as simple goals.

Antibiotics

Aminoglycoside antibiotics (e.g., gentamicin and tobramycin) in standard intravenous dosages fail to penetrate into the pancreas in sufficient tissue concentrations to cover the minimal inhibitory concentration (MIC) of the bacteria that are commonly found in secondary pancreatic infections.29 Acylureidopenicillins and third-generation cephalosporins have an intermediate penetration into pancreas tissue and are effective against gram-negative microorganisms and can cover the MIC for most gram-negative organisms found in pancreatic infections.30 Among these antibiotics, only piperacillin/tazobactam is effective against gram-positive bacteria and anaerobes. Quinolones (ciprofloxacin and moxifloxacin) and carbapenems both show good tissue penetration into the pancreas the additional benefit of excellent anaerobic coverage.31-34 However, because of quinolones high rate of resistance worldwide, quinolones should be discouraged and used only in patients with allergy to beta-lactam agents. Carbapenems due to the spread of carbapenem resistant Klebsiella pneumoniae should be always optimized and should be used only in very critically ill patients.Metronidazole, with its bactericidal spectrum focused almost exclusively against anaerobes, also shows good penetration into the pancreas. Pathogenesis of secondary bacterial pancreatic infection is still debated. Pathogens can reach the pancreas through the hematogenous pathway, via the biliary system, ascending from the duodenum via the main pancreatic duct, or through transmural colonic migration via translocation of the colonic bacteria.35 Most pathogens in pancreatic infection are gastrointestinal Gram-negative bacteria (Escherichia coli, Proteus, Klebsiella pneumonia), which occur via disruption of the intestinal flora and damage to the bowel mucosa. Impaired body defenses predispose to translocation of the gastrointestinal organisms and toxins with subsequent secondary pancreatic infection. However, Gram-positive bacteria (Staphylococcus aureus, Streptococcus faecalis, Enterococcus), anaerobes, and, occasionally, fungi have also been found. 36 Fungal infection is a serious complication of acute pancreatitis with an associated increase in morbidity and mortality.37 Candida albicans is the most frequent organism encountered, followed by Candida tropicalis and Candida krusei. Although fungal infections complicating acute pancreatitis generally arise proportionately to the extent of pancreatic necrosis, there is not enough data to support the prevention of

fungal infections and therefore is not recommended. Carbapenems and metronidazole together should be performed for SAP in intensive care units.

Nutrition

Nutrition and nutritional supplements have demonstrated necessity and importance not only in restoring energy balance but also in maintaining gut barrier function and providing important immunomodulatory and antioxidant effects. The gut is an important secondary organ and also a site of starting severe systemic complications during AP. Intestinal barrier dysfunction is associated with translocation of bacteria and their inflammatory and toxic products, responsible for infection of the necrotic pancreas and systemic inflammatory responses. Therefore, maintaining the integrity of the gut barrier in the small intestine is one of the main goals in early-phase treatment of severe AP.38 Optimal nutritional support in AP has been under debate for decades. Bowl at rest (nothing by mouth) strategy has been implemented conventionally to treat AP. 39,40 However, dietary restrictions exacerbate patient's malnutrition due to imbalance between reduced food intake and higher nutritional requirements, leading to further catabolism, bacterial translocation,41 and ultimate mortality.42 Evidence of clinical trials has demonstrated parenteral nutrition (PN) in preventing pancreatic stimulation and many benefits of enteral nutrition (EN). However, in daily practice, it remains challenging to predict whether EN will be tolerated in patients with AP.43 Strategic approaches to include nutritional supplements have also been attempted to provide additional immune regulatory and antioxidative effects. Probiotics and prebiotics have been shown to stabilize the disturbed intestinal barrier homeostasis and be beneficial in reducing the infection rate in primary clinical trials.44-47 Due to the immunosuppressive and inflammatory nature of the disease, immunonutrients like glutamine and omega-3 fatty acids (β-3 FAs) have been added to parenteral or enteral formulas to modulate immune functions, suppress the hyper inflammatory responses, and reestablish tissue and organ homeostasis in clinical practice.48,49 Supplements with antioxidative properties like glutamine and vitamin C have also been suggested to provide additional beneficial effects.50

EN versus PN

Traditionally, AP patients were maintained on nil per os or nothing per mouth treatment until resolution of pain or normalization of pancreatic enzymes to allow the pancreas to rest.51 Currently, it is widely accepted that early EN may be critical to improve AP-associated malnutrition and the overall outcomes, as bowel rest is associated with intestinal mucosal atrophy and increased infectious complications.52 Gut barrier dysfunction is found in approximately 60% of patients with AP.43,53 Importantly, EN exerts immunomodulatory effects to preserve gut mucosa integrity, stimulate intestinal motility, and reduce bacterial overgrowth.43,54 A randomized clinical study demonstrated that immediate oral feeding in patients with mild AP was feasible and safe and accelerated recovery without adverse gastrointestinal events.55 Another randomized controlled trial supported early-stage introduction of initial oral nutrition with either a clear liquid diet or a low-fat solid diet for patients who developed mild AP.56 In these patients, if oral intake is not tolerated, enteral feeding is recommended.52 In patients with severe AP or predicted severe AP, EN with oral or tube feeding thought to preserve the gut barrier function to prevent bacterial translocation is preferred over PN. A multicenter randomized study in the New England Journal of Medicine demonstrated that early tube feeding and oral diet after 72 h are equivalent in reducing infection rates or death in AP patients at high risk for complications.57 A Cochrane meta-analysis of eight randomized controlled studies found that EN reduced mortality, systemic infections, and multiorgan failure among patients with AP as compared to PN.58 Another meta-analysis of 381 patients confirmed the benefit of EN versus PN support in patients with severe AP with lower mortality, fewer infectious complications, decreased organ failure and surgical intervention rate.59 Over the optimal route of EN, several trials have suggested the nasogastric route as an alternative to nasoduodenal or nasojejunal routes.60 Multiple randomized controlled trials involving 157 patients with predicted severe AP demonstrated that nasogastric feeding was safe and well tolerated compared with nasojejunal feeding.61 Given its demonstrated beneficial outcomes, it remains challenging to predict whether EN will be tolerated in patients with AP.43 However, as shown by multiple randomized trials that have associated total PN (TPN) with risks of infection and other complications59, PN should still be minimized unless the enteral route is not available, not tolerated, or not meeting caloric requirements.

Other supportive measures

Analgesia: Although analgesics are important to relieve pain and attenuate neuroendocrine stress, their use in SAP

has traditionally been debated because of experimental findings that morphine (i.v) can induce spasm of the sphincter of Oddi and may precipitate pancreatitis. A consistent review of the literature revealed that all opiates increase sphincter of Oddi persistalsis and biliary pressure. No evidence exists to support the preference for any one opiate (i.v) in pancreatitis patients.62

Epidural analgesia is performed for patients with acute pancreatitis in critical care units.

Strict glycaemic control: In a multicentre trial, strict glycaemic control (target blood sugar levels 80 to 110 mg/dl) improved morbidity and mortality in surgical critically ill patients.63Advantageous effects of normoglycaemia were first attributed to the improvement of immunologic function and reduction of free radical production.64 Recent evidence shows that insulin itself exerts potent anti-inflammatory effects, mostly by decreasing free fatty acids levels. Furthermore, insulin has antithrombotic effects and stimulates the endothelial nitric oxide synthase.65 Since endothelial nitric oxide plays an important role in maintaining myocardial function, insulin may have cardioprotective properties also.66

Stress ulcer prophylaxis: In patients with severe sepsis or septic shock, stress ulcer prophylaxis using H2 blockers or proton pump inhibitors is recommended to prevent upper gastrointestinal haemorrhage. In acute pancreatitis, this would mean that patients with signs of systemic inflammation and one or more organ dysfunctions should receive stress ulcer prophylaxis. In all cases, particularly in patients with mild acute pancreatitis, the benefit of preventing stress ulceration must be critically weighed against the potential risk of nosocomial pneumonia.67

Antithrombotic prophylaxis: Antithrombotic prophylaxis should be instituted in critically ill patients with acute pancreatitis.68 Unfractionated or low molecular weight heparins reduce the incidence of deep vein thrombosis with pulmonary embolism and may prevent portal vein thrombosis. In patients with coagulopathy or a high risk of bleeding (e.g. into pancreatic necrosis), mechanical techniques (e.g. antithrombotic stockings, intermittent pneumatic compression) can be used to avert deep vein thrombosis.69

Therapies targeting the inflammatory response: Since it is widely accepted that MODS associated with SAP originates from an uncontrolled inflammatory response, several experimental and clinical studies evaluated the role of therapies targeting pro-inflammatory mediators. Although most strategies were associated with beneficial effects in animal experiments, none could improve outcome in a major clinical trial. Therefore, most guidelines recommend against the use of immunemodulating therapies in SAP, such as anti-TNFβ therapy70, gabexate mesilate71, lexipafant72 or activated protein C.73 Although high-dose selenium therapy showed promising results in critically ill patients with sepsis and systemic inflammation74, a small prospective study found that the combination of N-acetylcysteine, selenium and vitamin C had no beneficial influence on the course of SAP.75

Surgery: Early surgical intervention has almost vanished from the management of SAP because of increased mortality rates.76 Consequently, only few indications for surgery (e.g. abdominal compartment syndrome, intestinal ischaemia) remain during early acute pancreatitis. The aim of surgery in patients with infected pancreatic necrosis is to remove necrotic tissue and preserve as much vital tissue as possible.77 Partial or total pancreatectomy should be avoided rigorously in order to reduce mortality and the risk of postoperative endocrine and exocrine pancreatic insufficiency. No consensus exists on the best surgical technique to debride pancreas necrosis. Most guidelines suggest three techniques which share comparable success and mortality rates: 1) open necrosectomy with closed continuous lavage of the retroperitoneum; 2) open necrosectomy combined either with planned re-laparotomies followed by delayed primary closure and drainage or with multiple drainage and re-laparotomy on demand; 3) open necrosectomy with open packing and planned re-laparotomies.

CONCLUSIONS

Acute pancreatitis is frequently encountered on the emergency surgical take. Once the diagnosis is made, clinical efforts should simultaneously concentrate on investigating for the underlying etiology and managing the condition by anticipating its complications, which can be aided by using any of the severity scoring systems described. Management of acute pancreatitis is largely supportive. There is still no consensus on the ideal type and regimen of fluid for resuscitation, but goal-directed fluid therapy is associated with better outcomes. Early enteral nutrition modulates the inflammatory response and improves outcomes by decreasing infective complications of acute pancreatitis. Antibiotics should be used judiciously as prophylactic antibiotics have not

shown any benefit in preventing infective complications of acute pancreatitis. Carbapenems and metronidazole are preferred in patients with severe acute pancreatitis. Patients with mild acute gallstone pancreatitis should be recommended to undergo a laparoscopic cholecystectomy at the index admission, while those with severe gallstone pancreatitis and evidence of cholangitis and/or choledocholithiasis benefit from early ERCP. Early fluid resuscitation and nutrition are essencial for patients with AP. Analgesia, glycaemic control, stress ulcer and antithrombotic prophilaxis should be performed in patients with severe acute pancreatitis.

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Review

MBETJET E ANTIBIOTIKËVE NË QUMËSHT: RREZIK I MUNDSHËM PËR SHËNDETIN E NJEIRUT

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ABSTRAKT

Antibiotikët janë produkte farmaceutike të cilat përdoren kryesisht për qëllime terapeutike, profilaktike dhe si nxitës të rritjes për të përmisuar efikasitetin e ushqimit. Përdorimi i paligjshëm i antibiotikëve dhe sulfonamideve mund të çojë deri në shfaqjen e mbetjeve të tyre në qumësht, të cilat shkaktojnë rrezik të mundshëm për shëndetin e njeriut dhe efekte të padëshirueshme te konsumatorët.

Efektet patologjike nga mbetjet e antibiotikëve janë reaksionet alergjike te individët e mbindjeshëm (penicilinat), rrezistenca bakteriale (fluorokinolonet), efekte kancerogjene (sulfametazina, oksitetraciklina, furazolidoni), efekte mutagjene, nefropati (gentamicinaa) dhe dhe efekte toksike. Prania e mbetjeje të antibiotikëve në qumësht gjithashtu kaanë ndikim negative edhe në ekonomin e industrisë së qumështit. Prandaj, për të mbrojtur shëndetin e njeriut, Bashkimi Evropian ka vendosur nivelet maksimale të mbetjeve (MRL) për shumicën e antibiotikëve dhe sulfonamideve në qumësht dhe produktet tjera ushqimore. Monitorimi i mbetjeve të antibiotikëve është i nevojshëm për të garantuar sigurinë e ushqimit dhe për të parandaluar ekspozimin e konsumatorëve.

Fjalët kyçe: Mbetjet e Antibiotikëve, Qumështi, Shëndetit Publik, Metodat e Zbulimit

HYRJE

Antibiotikët janë lëndë kimike me preardhje natyrore ose produkte sintetike me strukturë të ngjashme me lëndët natyrore, të cilat në përqëndrime të vogla, janë të afta të antagonizojnë rritjen ose zhvillimin e një apo më shumë lloj mikroorganizmash [1].

Ne bazë të mekanizmit të veprimit farmakologjik antibiotikët klasifikohen në :

Frenues të biosintezës së murit qelizor të baktereve (penicilinat, cefalosporinat),

Frenues të sintezës së proteinave të baktereve (aminoglikozidet, kloramfenikoli, tetraciklinet, makrolidet),

Frenues të sintezës së acideve nukleike të bakterieve (kinolonet, rifampicina)

Frenues të sintezës së folateve (sulfonamidet)

Veprues mbi membranen citoplazmike (antibiotikët polipeptidikë e antibiotikët polienikë) (figura, 1)

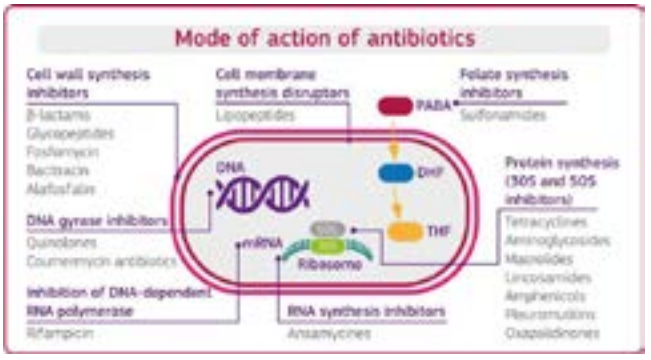

Figura 1. Mekanizmi i veprimit farmakologjik të antibiotikëve

Kriterin e bazuar në mënyren si antibiotikët antagonizojnë jetën e mikroorganizmave antibiotikët ndahen në: baktericid-antibiotikë vrasës të mikroorganizmave (beta-laktamikët, aminozidikët etj) dhe bakterostatik-antibiotikë që ndalojnë rritjen dhe shumëzimin e mikroorganizmave (tetraciklinat, kloramfenikoli etj) [2].

Mjekësia moderne mbështet në masë të madhe përdorimin e këtyre agjentëve kimiko-farmaceutike për mjekimin dhe parandalimin e infeksioneve bakteriale në njerëz dhe në kafshë. Shumica e antibiotikëve përveç që përdoren për qëllime terapeutike për të trajtuar sëmundjet e ndryshme dhe profilaktike për të parandaluar nxitësit e infeksioneve, në disa raste në mjekësin veterinare janë përdorur si nxitës të rritjes për të përmirësuar efikasitetin dhe prodhimin e ushqimit [3].

Antibiotikët më të përdorur janë: betalaktamet, tetraciklinet, sulfonamidet, kinolonet, linkosamidet dhe makrolidët. Përdorimi i paligjshëm i antibiotikëve shfaq mbetjet ose metabolitët e tyre në ushqim, të cilët paraqesin një kërcënim të mundshëm për shëndetin e njeriut dhe efekte të padëshirueshme për konsumatorët dhe industrin ushqimore [4,5]. Prania e mbetjeve të antibiotikëve në qumësht paraqesin rrezik për shëndetin e njeriut sepse shkaktojnë reaksione te ndryshme alergjike, efekte toksike, rezistencë bakteriale, efekte kancerogjene, poashtu pengojnë fermentimin e kulturave bakteriale dhe ndikojnë negativisht në cilësin e produktit përfundimtar të qumshtit [6,7]. Për garantuar sigurinë ushqimore dhe për të mbrojtur shëndetin e njeriut duhet vazhdimish të bëhet monitorimi dhe kontrrolimi i mbetjeve të barnave në produktet ushqimore veçenarisht në qumësht duke u bazuar në rregulloret e Bashkimit Evropian dhe metodat e ndryshme analitike per zbulimin dhe analizën e tyre [8].

Në këtë punim të rishikuar është bërë përmbledhje e literaturës dhe shqyrtimi i metodave analitike për identifikimin e mbetjeve të antibiotikëve dhe sulfonamideve në qumësht dhe rreziqet që shkatojnë keta mbetje të barnave në shëndetin e njeriut.

Kufijtë maksimalë të mbetjeve të barnave (MRL)

Me mbetje nënkupton përqendrimin maksimal të mbetjes së barnave në produktin ushqimor që rezulton nga përdorimi i medikamentit të shprehur në µg kg-1, që është ligjërisht i lejuar si i pranueshëm në një ushqim. Prania e mbetjeve të antibiotikëve në qumësht paraqet rrezik për shëndetin e njeriut sepse shkaktojnë reaksione te ndryshme patologjike në organizmin e njeriut [4,5].

MRL-të antibitikëve dhe sulfonamideve në qumësht (Tabela 1) bazohen në llojin dhe sasinë e mbetjeve që konsiderohen të jenë pa ndonjë rrezik toksikologjik për shëndetin e njeriut siç shprehet nga marrja e pranueshme ditore dhe një faktor shtesë sigurie. [9].

Tabela1. MRL e antibiotikëve dhe sulfonamideve në qumësht

Nr.	Antibiotiku	MRL ng/ml
1	Amoxicillin	4
2	Ampicillin	4
3	Benzylpenicillin	4
4	Cloxacillin	30
5	Oxcillin	30
6	Trimethoprim	50
7	Tylosin	50
8	Cephapirin	60
9	Cefalexin	100
10	Ceftiofur	100
11	Enrofloxacin	100
12	Ciprofloxacin	100
13	Tetracyclin	100
14	Oxytetracyclin	100
15	Chloroteracyclin	100
16	Doxycyclin	100
17	Lincomycin	100
18	Sulfachloropyridazine	100
19	Sulfafurazol	100
20	Sulfadiazine	100
21	Sulfadimidin	100
22	Sulfamethoxazole	100
23	Sulfadimetoxin	100

PËRDORIMI I ANTIBIOTIKËVE

Qumështi është një nga ushqimet më të përdorura sepse përmban të gjitha lëndet e nevojshme si: ujë, yndyrë, karbohidrate, proteina, lëndët minerale si dhe vitaminat. Nga kjo përbërje specifike shihet qartë që ka vlera të larta ushqyese dhe konsiderohet si ushqim bazë në jetën e njeriut. Qumështi poashtu është një ambient ideal për rritjen e mikroorganizmave dhe përmban të gjitha elementet e nevojshme për zhvillimin e tyre [10].

Mastiti është një sëmundje që prek gjëndrrën e qumështit tek kafshët. Kjo sëmundje shoqërohet me inflamacion të indit të gjirit, ku bakteriet futen nëpërmjet kanalit të thithjes së gjirit nga burime të ndryshme bakteriale. Trajtimi intramamare e mastitit me barnat antibakterial ka shkaktuar shqetësim të madh për shkak të shfaqjs së mbetjeve të barnave në qumësht. Shkaku i mundshëm i mbetjeve të tyre ishte mosrespektimi i kohës së eliminit apo karencës, mbidoza dhe barnat me veprim të gjatë [11].

Sundlof dhe bashkëpuntorët e tij (1995) në punimin shkencor raportuan për shfaqjen e mbetjeve të antibiotikëve penicilin, tetraciklin, sulfonamid dhe aminoglikozidet në qymësht pas trajtimit të sëmundjes mastitis [12].

Përdorimi terapeutik - Antibiotikët për qëllime terapeutikë përdoren për të trajtuar infeksionin e shkaktuar nga bakteriet patogjene. Penicilinat janë përdorur për trajtimin e mastitit të gjedhi. Sulfonamidet dhe tetraciklinat janë përdorur për të trajtuar enteritin bakterial dhe pneumonitin bakteriale [11]. Lincosamidet, makrolidët për trajtimin të infeksioneve të lehta stafilokoke dhe kinolonet kundër sëmundjeve të ndryshme te akuakulturat [13].

Përdorimi profilaktik - Antibiotikët për qëllime profilaktike përdoruren për të parandaluar nxitësit e infeksionit. Në raste të caktuara, pra operimetkirurgjikale kanë pasur nevojë për preventivë antibiotikësh [4].

Përdorimi si nxitës të rritjes- Antibiotikët përdoren si nxitës të rritjes për të ndihmuar rritjen dhe shëndetit e kafshëve sepse kanë rritur imunitetin dhe kanë zvogëluar sasinë e toksinave duke krijuar kushte të favorshme për mikrobet e dobishme në zorrët e kafshëve, në anë tjetër duke shkatëruar bakteret patogjene. Mirëpo, duhet theksuar se kjo mënyrë e dhënies së antibiotikëve shkakton dëme të mëdha shëndetësore, të shoqëruara me çrregullime funksionale te njeriu pas marrjes së produktit ushqimor dhe dëme ekonomike për industrit ushqimore [13].

Moore dhe bashkëpuntorët e tij në vitin 1946 si dhe Phillips me bashkëpuntorët e tij në vitin 2004 në studimet e tyre kanë treguar efektet e dobishme të përdorimit të barnave si nxites të rritjes dhe perfitimet nga prodhimet ushqimeve [14,15]. Ndërsa në stdudimin e bërë nga Nisha ne vitin 2008, Priyanka në 2017 treguan efektet patologjike në organizmin e njeriut që shkaktojne mbetjet e antibiotikëve të perdorur si nxitës të rritjes [5,6]

Efektet patologjike të përftuara nga mbetjet e antibiotikëve në qumësht

Mbetjet e barnave kanë rol të rëndësishëm në aspektin e sigurisë ushqimore dhe shëndetin e njeriut. Kimikatet dhe produktet farmaceutike sic janë antibiotikët dhe sulfonamidet të përdorur për kimioterapi, profilaktikë dhe si aditivë të ushqimit mund të çojnë deri në shfaqjen e mbetjeve e tyre. Prania e mbetjeve të tilla në qumësht paraqesin efekte patologjike për shëndetin e njeriut siç janë: reaksionet alergjike, efekte toksike, rezistencë bakteriale dhe efekte kancerogjene [1].

Reaksionet alergjike: Mbetjet e antibiotikëve në qumësht shkaktojnë reaksione alergjike, sidomos te personat që janë të ndjeshëm ndaj mbetjeve të penicilinës në qumësht. Kjo është një nga arsyet pse MRL në rregulloret e BE dhe Codex-it (JECFA) është 4 ng / mL dhe në SHBA toleranca është zero për mbetjet e penicilinës në qumësht. Reaksionet alergjike të shkaktuara nga penicilinat dhe derivatet e saj janë konsideruar nga komiteti JECFA si faktorë përcaktues për vlerësimin dhe vendosjen e niveleve të sigurta të mbetjeve në ushqim. Simptomat e shumëta janë: urtikaria, angioedema, skuqje deri te në raste anafilaktike [16]. Mbetjet e barnave të sulfonamideve shkaktojnë nekrozë epidermale, anemi hemolitike, hepatit, ndërsa mbetjet e makrolidëve shkaktojnë dëmtime në mëlçi [9,17].

Rezistenca bakteriale ndaj antibiotikëve: Kur një mikroorganizëm është në gjendje t'i mbijetojë ekspozimit të një antibiotiku atëherë paraqitet rezistenca e saj ndaj antibiotikëve. Përdorimi pa kriter i antibiotikëve mund të rritë presionin selektiv te bakteret, duke lejuar kështu rezistencën bakterore ndërsa bakteret e ndjeshme të vdesin [1]. Përhapja e baktereve rezistente përmes zinxhirit ushqimor u vu re që në vitin 1969 nga Swan, i cili raportoi zhvillimin e baktereve rezistente ndaj avoparcinës [18]. Zhvillimi dhe përhapja e rezistencës antibakteriale përfaqëson një kërcënim serioz me implikime të mundshme në shëndetit e njeriut sepse mund të kolonizojë florën endogjene te njeriu dhe

ngarkesën shtesë të gjeneve të rezistencës tashmë të pranishme tek njeriu pas konsumit të ushqimit të marrur nga kafshët e trajtur me këto barna [10].

Escherichiacoli, stafilokoku janë rrezistent ndajë fluorokinoloneve, penicilinave, tetraciklinave dhe sulfonamideve [17].

Shqetësimet në lidhje me rezistencën bakteriale dhe efektet toksikologjike tek njerëzit kanë bërë që shumë vende të BE të tërheqin autorizimet për të përdorur antibiotikë dhe sulfonamide si nxitës të rritjes që nga janari i vitit 2006 [5].

Efektet kancerogjene: Termi kancerogjen i referohet efektit të prodhuar nga një substancë me aktivitet kancerogjen dhe lidhja e saj kovalente me përbërës të ndryshëm brendaqelizorë siç janë proteinat, acidi deoksiribonukleik (ADN) dhe acidi ribonukleik (ARN). Sulfonamidet janë grupi I barnave që shkaktojnë kancerin e tiroides. Një studim kronik i bërë nga Qendra Kombëtare për Kërkime Toksikologjike (NCTR) zbuloi se sulfametazina shkaktoj kancerin e qelizave folikulare të gjëndrës tiroide në minj [1,10,17,18,29].

Efektet mutagjene: Termi mutagen përdoret për të përshkruar agjentë kimikë ose fizikë që shkaktojnë një mutacion në molekulën e ADN-së ose të dëmtojnë përbërësin gjenetik të një qelize ose organizmi. Disa kimikate duke përfshirë antibiotikët e alkilimit (antibiotik antikanceror p.sh. Doxorubicin) është treguar se shkaktojnë aktivitete mutagjene duke prodhuar mutacione gjenesh ose devijime të kromozomeve [1,5,6,17].

Efekti teratogjenik: Metabolitët toksikë të barnave shkaktojnë keqformime kongjenitale të fetusit, ndryshojnë integritetin strukturor dhe funksional të embrionit/fetusit në zhvillim gjatë fazës kritike të shtatzënisë [19].

LEGJISLACIONI

Ndodhja e mbetjeve të medikamenteve farmaceutike në produktet e qumështit paraqet një problem serioz në mbar botën. Me qëllim për të mbrojtur konsumatorin dhe për të garantuar sigurinë ushqimore duhet vazhdimish të bëhet monitorimi dhe vëzhgimi i mbetjeve të barnave në produktet e qumështit. Në Bashkimin Evropian dhe në shtetet tjera ekzistojnë rregullore që përshkruajnë procedurë për vendosjen e MRLs të barnave në produktet ushqimore dhe në qumështit, të bazuara në vlerësimin shkencor të sigurisë së këtyre substancave. Keta rregullore identifikojnë përdorimin ilegal të produkteve farmaceutike dhe garantojnë implementimin e procedurave të duhura për të minimizuar rishfaqjen e këtyre mbetjeve në qumësht [8].

Kontrolli dhe monitorimi i mbetjeve të medikamenteve në produktet me origjinë shtazore janë rregulluar nga Direktiva e Këshillit Europian 96/23/EC dhe Rregulloret e Këshillit Europian 37/2010/EU, të cilët pasqyrojn kërkesat që duhet të plotësohen në lidhje me planifikimin dhe ekzekutimin e planeve kombëtare [20,21]. Shtetet anëtare të Bashkimit Europian në Vendimit e Komisionit 2002/657/EC paraqesin performansat e metodave analitike për identifikimin e mbetjeve të barnave dhe interpretimin e rezultateve [22].

Komisioni i Kodit të Ushqimit (CCF) / Codex Alimentarius Commission (CAC) është një nga organizatat që merret me problemet e ushqimit në përgjithësi dhe qumështit në veçanti. Kjo organizatë vepron si një organ ndërqeveritar i vendeve të ndryshme të botës në koordinimin e nivelit të standardeve ushqimore [16].

Ligjërisht kontrolli dhe monitorimi i mbetjeve të antibiotikëve në produktet me origjinë shtazore është e rregulluar edhe nga rregulloret e R. V. e Maqedonisë me rregullore të vecantë (rregullore për kryerjen e monitorimit dhe kontrollit të pranisë së mbetjeve dhe metabolitëve në ushqime me origjinë shtazore) poashtu kontrolli bëhet edhe nga ana e agjencionit për ushqim dhe veterinari [23].

Metodat për zbulimi e mbetjeve të antibiotikëve dhe sulfonamideve në qumësht

Metoda për zbulimin e mbetjeve të antibiotikëve dhe sulfonamide në produktet e qumështit është një fushë kërkimore në zhvillim. Metodat e përdorura për analizën e mbetjes së barnave do të shërbejë për të vlerësuar cilësinë e produktit të qumështit në përputhshëmirinë me rekomandimet e autorizuara te markentingut, si dhe për të zbuluar barnat e falsifikuara.

Metodat që analizojnë mbetjet janë: metodat ekzaminuese dhe konfirmatore.

Në metodat ekzaminuese bëjnë pjesë: testet enzimatike, receptore dhe imunologjike. Metodat ekzaminuese janë të shpejta, të lira, të lehta për analizë, por ofrojnë slektivitet dhe specifitet të ulët për zbulimin e mbetjeve të antibiotikëve në qumësht [24].

Dimitrieska-Stojković me bashkpunëtorët e saj (2011) në R.V. të Maqedoni, nga 915 mostra të analizuara

të qumështit të papërpunuar me anë të metodës ekzaminuese, 1.42% përmbanin mbetje të sulfonamideve.

Metodat konfirmuese ofrojnë identifikimi/konfirmimi e qartë dhe sasiorë të mbetjeve të antibiotikëve në qumësht. Një ndër metodat më të përdorura konfirmatore është kromatografia e lëngt- së bashku me spektroskopin e masës (LC-MS/MS) e cila ka ndjeshmërin dhe selektivitetin të lartë për analizë multiklasore të barnave në matriksat komplekse [25,26,29].

Amatya (2010) në Spanjë për të analizuar njëkohësisht 19 barna të 3 klasave (penicillin, cefalosporin dhe kinolon) në 49 mostra qumështi përdori metodën konfirmatore. Nga të gjithë mostrat e analizuara, 14% e mostrave përmbanin amoksicilinë me një përqendrim të lartë 42.3 µg / kg dhe 16% e mostrave përmbanin benzilpenicilinë me një përqendrim prej 12.7 µg / kg [27].

Martins dhe bashkëpuntorët e tij (2014) në Brazil me anë të metodave konfirmatore zbuluan ciprofloxacin në 4 mostra qumështi, në 6 mostra oksitetracycline dhe në 1 mostër tetraciklin. Një mostër tregoi një përqendrim të oksitetraciklinës me nivel të lartë se 10xMRL (981 ngL-1) [28].

Një studim ynë i bërë (2020) Alija bashk me bashkpunëtorë në R.V.Maqedonisë ku u perdoror metoda konfirmuese LC–MS/MS për përcaktimin e njëkohshëm të mbetjeve të 23 antibiotikëve dhe sulfonamideve nga shtatë klasa të ndryshme (penicillin, cephalosporin, tetraciklni, sulfonamide, makrolid, kinolon dhe linkosamid) në qumështin e papërponuar. Për të vlerësuar zbatueshmërinë e metodës, nga 189 mostrat të qumështit të analizuara, 14 (7.41%) mostra përmbanin mbetje të antibiotikëve dhe sulfonamideve. Përqendrimet e mbetjeve ishin nën nivelet maksimale MRL të vendosura nga BE [26].

PËRFUNDIM

Përdorimi illegal I antibiotikëve dhë sulfonamideve për qëllime terapeutike, profilaktike dhe nxitës të rritjes ndikojnë në paraqitjen e mbetje të këtyre barnave në produktet ushqimore me prejardhje shtazore. Mbetjet e tilla paraqesin një rrezik për shëndetin e njeriut dhe industrin ushqimore. Prandaj është e nevojshme të monitorohen dhe vëzhgohen mbetjet e tyre në ushqim me anë të metodave analitike, të cilët jepin një pasqyrë të plot për rreziqet dhe fatin e njeriut.Disponueshmëria e metodologjive me ndjeshmëri të lartë vë në praktikë legjislacionin, lehtësojn kontrollin e barnave për të siguruar sigurinë e ushqimit dhe për të parandaluar efektet negative te mbetjeve të tyre ndaj shendetit të njeriut.

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RËNDËSIA E INDIVIDUALIZIMI I TERAPISË TE PACIENTËT SPECIFIK

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ABSTRAKT

Terapia racionale e medikamenteve kërkon individualizimin e regjimit të dozimit për t'iu përshtatur nevojave të një pacienti të veçantë.

Individualizimi i terapisë bëhet me qëllim të uljes së efekteve anësore,uljes së toksicitetit dhe dhënies së efektit maximal terapeutik..

Regjimi i dozimit përcaktohet në bazë të disa parametrave klinik për ta vlersuar efikasitetin dhe efektet anësore. Pas fillimit të terapisë bëhet monitorimi terapeutik i barit, pas administrimit matet sasia e barit në organizëm, koha e arritjes së barrit në gjendje të qëndrueshme në organizëm dhe koha që duhet të pastrohet organizmi pas ndërprerjes së administrimit që të kemi efekt terapeutik të pritur. Nëse nuk arrihet efekti terapeutik përsëritet disa here ose shtohet një bar tjetër.

Tek pacentët me çrregullime të funksionit të veshkëve bëhet përshtatja e terapisë sepse çrregullimet e veshkave gjithashtu mund të ndikojnë në proceset farmakokinetike dhe lidhshmërinë me proteinat Individualizimi i terapise bëhet duke matur nivelin e klirensit të kreatininës.Te pacientët e moshuar për shkakt ë rënies progresive të funksionit të mëlçisë veshkëve dhe motilitetit të zvogëluar.

Tek fëmijët për shkak se distribuimi i barit në SNQ është më i lartë tek të porsalindurit për shkak të permeabilitetit të shtuar të barierës së gjakut në tru që mund të zmadhoj efektet terapeutike të SNQ dhe të padëshirueshme të barnave. Tek shtatëzanat si pasojë e ndryshimit hormonal vjen deri te aktivizimi i disa sistemeve të enzimeve CYP dhe inhibimi i të tjereve.

Individualizimi i terapisë është i rëndësishëm për barnat me indeks të ngushtë terapeutik

HYRJE

Terapia racionale e medikamenteve kërkon individualizimin e regjimit të dozimit për t'iu përshtatur nevojave të një pacienti të veçantë.

Qëllimi i individualizimit është të optimizojë efikasitetin e një bari, të minimizojë toksicitetin e tij, ose të dyja. Lehtëson uljen e Toksicitetit dhe efekteve anësore dhe rritjen e efikasitetit farmakologjik të barit.

Lehtëson uljen e reaksioneve alergjike të pacientit për barin nëse ka,rritja e kompliances së pacientëve etj Regjimi i dozimit të barnave zgjidhet në bazë të karakteristikave demografike të pacientit dhe zgjidhen përmbledhje parametrash të cilët janë të vëzhguar në mënyrë klinike për vlerësimin e efektit terapeutik dhe atë të pavolitshëm të barit. Mbas fillimit të terapisë me barin dhe duke mundësuar kohë të mjaftueshme që bari të arrijë gjendjen e baraspeshës, pacienti zakonisht vëzhgohet për të vlerësuar se a thua arrihet efekti terapeutik i dëshiruar. Kujdes të veçantë duhet tu kushtohet pacientëve obez pasi që përmbajtja e yndyrave në organizëm shpesh rritet tek pacientët e trashë, Vd/kg i barnave relativisht lipofil më shpesh rritet tek këta pacientë [1]. Distribuimi i barnave të tjerë është nën ndikimin e limitimeve të ndryshme.Tek pacientët geriatrik për shkak të ndryshimeve fiziologjike dhe patologjike që paraqiten me moshë që mund të ndryshojnë farmakokinetikën dhe farmakodinamikën e barit.Tek pacentët me çrregullime të funksionit të

veshkëve sepse çrregullimet e veshkave gjithashtu mund të ndikojnë në absorbimin e barit, metabolizmin, lidhshmërinë me proteinat dhe në distribuimin. Njehsimi i dozës fillestare të barnave të cilat sekretohen në rrugë renale tek pacientët me çrregullime renale më shpesh është në bazë të klirensit të kreatininës të tyre.Tek pacientët me çrreg të funksionit të mëlçisë për shkak se çrregullimi i mëlçisë mund të ndikojë gjithashtu në lidhjen e proteinave në plazmë që mund të ndikojë në distribuimin e barit dhe eliminimin e tij .Zvogëlimi i proteinave të plazmës së barit gjatë sëmundjes së mëlçisë mund të jetë për shkak të zvogëlimit të albumeve dhe sintezës të β1-acidit glukoproteinik, akumulimit të komponentëve endogjen si bilirubini i cili mund të bëjë garë me barin për vendet e lidhjes dhe ndryshimet cilësore në proteinat e plazmës që mund të ndikojë në lidhshmërinë e barit [2,3]. Tek fëmijët për shkak se distribuimi i barit në sistemin nervor qendror (SNQ) është më i lartë tek të porsalindurit për shkak të permeabilitetit të shtuar të barierës së gjakut në tru) që mund të zmadhoj efektet terapeutike të SNQ dhe të padëshirueshme të barnave. Pjekuria e enzimave është me rëndësi tek fëmijët që thithin për caktimin e dozës adekuate të barit. Tek shtatëzanat për shkak të zvoglimit të koncentrimit të albuminave që shkakton zvoglim të lidhsmërisë së barit me proteinat, si dhe aktiviteti i enzimave metabolike ndryshon gjatë shtatzënisë për shkak të estrogjenit dhe progesteronit të cilët aktivizojnë disa sisteme enzimash CYP dhe inhibojnë të tjerë [4]. Barnat që shfrytëzohen nga lehonat mund të sekretohen në qumështin e saj në vëllim të ndryshëm. Pra, foshnjat që ushqehen me qumësht nëne, nënat e të cilëve marrin barna mund të vëzhgohen se a tregojnë ndonjë farë shenje të efekteve farmakologjike dhe të padëshirueshme.

Karakteristikat specifike të pacientit si mosha, pesha, gjinia, funksioni renal, funksioni hepatal, sëmundja, gjendja hidrike , përdorimi i barnave shoqëruese, dhe çfarëdo faktorë tjetër që mund të ndikoj në farmakokinetikën e medikamentit shfrytëzohen për të parashikuar sjelljen farmakokinetike të medikamentit në atë pacient specifik. [4].

Monitorimi terapeutik i barit (MTB) shfrytëzon koncentrimin e matur të barit në lëngjet biologjike si vegël për individualizim të terapisë së barit dhe përshtatjen e dozimit. Bazohet në korrelacionin e fuqishëm të vëzhguar mes koncentrimit të barit në qarkullimin sistemor të gjakut si dhe efektin terapeutik dhe atë toksik për shumë barna. Ky korrelacion i fuqishëm sugjeron se shumë barna shfaqin efektin e tyre terapeutik me efekt anësor minimal te shumica e pacientëve kur koncentrimet e tyre në gjak ose plazmë qëndrojnë brenda kufijve terapeutik të caktuar.Koncentrimi i barit i arritur në gjendje ekuilibri tek një pacient në veçanti është e varur prej shpejtësisë (shkallës) së dozimit të barit dhe klirensit total (pastrimit të përgjithshëm) te pacienti përkatës. Kur dozimi i njëjtë i pacientit aplikohet te një grup pacientësh, arrihen koncentrime të ndryshme të barit te pacientët e ndryshëm si rezultat të faktorëve të shumtë që kanë të bëjnë me produktin e barit si dhe karakteristikat e veçanta të pacientëve.

MTB paraqet aktivitet multidisciplinor ecila përdor njohuri farmaceutike, farmakokinetike dhe farmakodinamike për optimalizimin e terapisë së barit në situata të ndryshme klinike [5]. Aplikimi i MTB nuk rekomandohet për të gjitha barnat por për barnat me indeks të ngusht terapeutik. Përdorimi i matjes të koncentrimit të barit në gjak për optimizim të dozimeve është përdorur për antibiotik si aminoglikozide dhe vankomicin; barna antiepileptik si fenitoin, karbamazepin, acid valproik, fenobarbital dhe etosukcimid; barna kardiovaskulare si digoksin, lidokain dhe prokainamid; imunosepresivë si ciklosporin, takrolimus , barna citotoksike si metotreksat; bronkodilator si teofilin; dhe barna psikiatrike si litium, benzodiazepine dhe antidepresivët treciklik si shtesë e shumë barnave të ndryshme.[6].

BARNA ME INDEKS TË ULËT TERAPEUTIK

Barnat me indeks terapeutik të ulët prezantojnë raport të koncentrimit minimal toksik me koncentrimin minimal efektiv , kërkon përcaktim të saktë të regjimit të dozimit të barit që të mënjanohet toksiciteti i barit ose efekteve subterapeutike. Kjo është për shkak se gjërësia terapeutike për këto barna është e ngushtë dhe çfarëdo dalje prej regjimit përkatës të dozimit mund të siguroj koncentrime të barit jashtë gjërësisë terapeutike gjatë kohës së intervalit të dozimit.Nga ana tjetër, barnat me indeks të lartë terapeutik, ku raporti i koncentrimit minimal terapeutik dhe koncentrimit minimal efektiv është i lartë, konsiderohen si barna të sigurta. Kështu është për shkak se regjime të ndryshme të dozimit të këtyre barnave mund të arrijnë koncentrime të barit në gjërësine terapeutike për shkak të gjerësisë së tyre të kufirit terapeutik.Kufi i gjerë i regjimit të dozimit duhet të siguroj efektin e duhur terapeutik me toksicitet minimal. Kështu zbatimi i MTB mund të mos jet i domosdoshëm për këta barna me indeks të lartë terapeutik.

BARNA TË CILËT RËNDOM APLIKOHEN TE PACIENT ME RREZIK TË LART OSE ME MË SHUMË PROBLEME SHËNDETËSORE

Pacientët me më tepër probleme shëndetësore mund të ballafaqohen me pasoja serioze shëndetësore nëse ato zhvillojnë toksicitet ndaj barit ose kur kemi anulim në pranimin e dozimeve terapeutike të barnave të shkruar. Domethënë është shumë e rëndësishme zgjedhja e kujdesshme e regjimit të dozimit adekuat te këta pacient.

Individualizimi i regjimit të dozimit ndihmon në zhvillimin e regjimit të dozimit që është specifike për pacientin.

Lehtëson uljen e Toksicitetit dhe efekteve anësore dhe rritjen e efikasitetit farmakologjik të drogës. Lehtëson uljen e reaksioneve alergjike të pacientit për drogës nëse ka. Rritja e kompliances së pacientëve etj

Procesi i fillimit të terapisë me bar zakonisht fillon me diagnozë të gjendjes së pacientit në bazë të të gjitha informacioneve në dispozicion subjektive dhe objektive të pacientit. Regjimi i dozimit të barnave zgjidhet në bazë të karakteristikave demografike të pacientit dhe zgjidhen përmbledhje parametrash të cilët janë të vëzhguar në mënyrë klinike për vlerësimin e efektit terapeutik dhe atë të pavolitshëm të barit.

Mbas fillimit të terapisë me barin dhe duke mundësuar kohë të mjaftueshme që bari të arrijë gjendjen e baraspeshës, pacienti zakonisht vëzhgohet për të vlerësuar se a thua arrihet efekti terapeutik i dëshiruar. Nëse arrihet, bari i zgjedhur dhe regjimi i dozimit duhet të vazhdojnë aq gjatë sa është e domosdoshme përdorimi i vazhduar i barit dhe të ruhen qëllimet e efektit të dëshiruar. Megjithatë, nëse nuk arrihet rezultati terapeutik, regjimi i dozimit të barit duhet të ndryshohet dhe pacienti të monitorohet mbas kalimit të kohës së mjaftueshme që të arrihet koncentrim i ri i barit gjatë gjendjes së baraspeshës. [7,8].

PACIENTËT ME ÇRREGULLIM TË FUNKSIONIT TË VESHKAVE

Humbja funksionale e nefroneve tek sëmundjet e veshkave rezulton me zvogëlimin e sekretimit nëpërmjet veshkave të barit varësisht nga shkalla e çrregullimeve në veshka.

Ndikimi kryesor i çrregullimit të veshkave ndaj farmakokinetikës të barit është si rezultat i zvogëlimit të sekretimit në rrugë renale të barit dhe të metaboliteve të tyre. Çrregullimet e veshkave gjithashtu mund të ndikojnë në absorbimin e barit, metabolizmin, lidhshmërinë me proteinat dhe në distribuimin. Këto efekte janë shprehur më shumë tek pacienetët me çrregullime të renda të veshkave dhe observohen edhe kur rruga e eliminimit nëpërmjet veshkave nuk është rruga kryesore e eliminimit të barit. Zvogëlimi i metabolizmit të mëlçisë tek këta pacientë i përshkruhet çrregullimeve të veshkave të lidhura me ndryshimet fiziologjike dhe patologjike tek çdo sistem i organeve në organizëm, përfshirë këtu edhe mëlçinë. Provat tjera vënë në dukje faktin se akumulimi i disa inhibitorëve të caktuar të endogjen të njohura si toksine uremike tek pacientët me çrregullime të veshkave mund të zvogëlojë aktivitetin të enzimave të heparit si dhe ekspozimin e tyre [9]. Si shtesë për efikasitetin e tyre tek enzimat e metaboliteve, toksine uremike janë përfshirë në ndryshimin e sistemit të transportit ose në aktivitetin e transportit në veshka, mëlçi dhe në zorrën e hollë tek pacientët me funksion normal dhe gjatë insuficiencës së veshkave. Kjo mund të kotribuojë në ndryshimin e distribuimit dhe në eliminimin jo linear të barnave tek pacientët me çrregullime të veshkave [10]. Të gjitha metodat e përdorura më shpesh për njehsimin e regjimit të dozimit tek pacientët me çrregullime të veshkave supozojnë se zvogëlimi i funksionit të veshkave ndikon vetëm në eliminimin e barnave nëpërmjet veshkave.

REGJIMI I DOZIMIT TEK PACIENTËT ME ÇRREGULLIME TË VESHKAVE

Njehsimi i dozës fillestare të barnave të cilat sekretohen në rrugë renale tek pacientët me çrregullime renale më shpesh është në bazë të klirensit të kreatininës të tyre. Kjo ndodh sepse zvogëlimi i funksionit të veshkave që shprehet me zvogëlimin e klirensit të kreatininës rezulton me zvogëlimin në klirensin e veshkave të barit.Metoda të ndryshme empirike shftyrëzohen që të njehsohet klirensi i kreatininës nga parametra të ndryshëm te cilët mund të ndikojnë në klirensin e kreatininës siç janë mosha, pesha dhe kreatinini i serumit. Metoda e Kokoroft dhe Gaultit (Cockoroft dhe Gault) janë shfrytëzuar për të njehsuar klirensin e kreatininës tek të moshuarit prej 18 vjet e më të vjetër me kreatinin stabil të serumit. Janë të kapshme edhe metoda të tjera në njehsimin e klirensit të kreatininës tek pacientët me kreatinin jo stabil të serumit tek fëmijët dhe popullsia më e moshuar e pacientëve. Pershtatja dozimit dhe intervalit te dozimit për barnat të cilët eliminohen me anë të veshkëve në rastet eçrregullimeve funksionale te veshkëve bëhet nedisa mënyra

a)duke ulur dozen pa ndryshuar intervalin dozimit

b)duke zgjatur intervalin dozimit pa ndryshuar dozen

c)duke ndryshuar edhe dozen edhe intervalin dozimit

PACIENTËT ME INSUFICIENCË TË MËLÇISË

Mëlçia ka rrolin qendror në veprimin farmakokinetik të shumë barnave. Zvogëlimi i funksionit të mëlçisë rezulton në zvoglimin e shpejtësisë të metabolizmit të barit nëpërmjet mëlçisë dhe sektretimit nëpërmjet tëmthit.

Çrregullimi i mëlçisë mund të ndikojë gjithashtu në lidhjen e proteinave në plazmë që mund të ndikojë në distribuimin e barit dhe eliminimin e tij. Metabolizmi parasistematik i barnave që merren me rrugë orale mund të jenë nën ndikimin gjithashtu të çrregullimit të funksionit të mëlçisë duke çuar në rritje të tepërt të biodisponibilitetit veçanërisht tek barnat me koeficient të lartë të sekretimit. Disfunksioni i mëlçisë më shpesh lidhet me zvogëlimin jo të barabartë të enzimave metabolike në hepar me citohrome P450 (CYP450) të ndryshëm të enzimave të cilët ndikojnë në shkallë të ndryshme.Pacientët me cirozë të përparuar të mëlçisë kanë edhe çrregullim të funksionimit të veshkave dhe shpejtësi të eliminimit të barnave që eliminohen në rrugë renale që gjithashtu është nën këtë ndikim.

Gjithashtu, zvogëlimi i sintezës së albuminës shkakton ndryshimin e lidhjes së barit me proteinat tek këto pacientë, që mund të ketë pasoja farmakokinetike dhe faramkodinamike. Funksioni i organeve sikurse zorrët, mushkëritë dhe veshkat mund të jenë nën ndikimin e cirrozës së mëlçisë dhe mund të zhvillohet në sindromë hepatorenale që shkakton dëmtimin e rëndë të veshkave.

Ndryshimi i farmakokinetikës së barit gjatë sëmundjeve të mëlçisë mund të shkaktojë ndryshimin e përgjigjes së barit [11]. Gjithashtu, ndryshimi i efektit terapeutik të barit që nuk lidhet me ndryshimin farmakokinetik të barit haset edhe tek cirroza e mëlçisë. Ëfekti i zvogëluar të beta-blokatorëve dhe diuretikëve, efekti i shtuar i analgjetikëve narkotik dhe sedativëve, dhe shtimi i efekteve të padëshirueshme i barnave antiinflamatore josteroide janë paraqitur (dokumentuar) tek pacientët me cirozë [12,13].

PËRSHTATJA E DOZËS GJATË DISFUNKSIONIT TË MËLÇISË

Përshtatja e dozës tek pacientët me disfunksion të mëlçisë nuk është detyre e lehtë. Sepse nuk ekziston test i vetëm klinik që mund të shfrytëzohet në vlerësimin e disfunksionit të mëlçisë. Gjithashtu, sistemet e ndryshme të enzimave metabolike janë nën ndikimin e shkallëve të ndryshme të zvogëlimit të funksionit të mëlçisë. Klasifikimi i Çajld Pugit (Child-Pugh) shfrytëzohet në praktikën klinike për kategorizimin e pacientëve sipas serozitetit të dëmtimit të funksionit të mëlçisë së tyre [13]. Ky klasifikim shfrytëzon pesë teste të ndryshme laboratorike dhe gjendje klinike në vlerësimin e seriozitetit të sëmundjes së mëlçisë: albuminet e serumit, bilirubini i përgjithshëm, koha e protrombinit, asciti dhe encefalopatia.

Rekomandimi i përgjithshëm për përshtatje të dozës në bazë të rezultateve të Çajd Pugit është se pacientët me rezultat 8-9 kërkojnë 25% zvogëlim të dozës së tyre fillestare të barnave të cilat kryesisht eliminohen nga organizmi nëpërmjet metabolizmit të heparit (>60% të metabolizuar), ndërsa pacientët me rezultat 10 ose më shumë kërkojnë zvogëlim prej 50% të dozës së tyre fillestare të barit i cili eliminohet kryesisht nëpërmjet metabolizmit të heparit. Me rëndësi është të theksohet se kjo paraqet rekomandim për fillimin e dozave të barnave. Pas fillimit të terapisë me barnat, efekti terapeutik dhe i padëshirueshëm i barnave duhet të vëzhgohet dhe përshtatja e dozës duhet të bëhet nëse është e nevojshme.

Megjithatë rezultati i Çajld-Pugit shfrytëzohet më shumë në praktikën klinike për ndjekjen e përshtatjes së dozës tek pacientët me sëmundje të mëlçisë sepse informacioni i nevojshëm që të zbatohet kjo qasje tanimë është e kapshme. [14].

PACIENTËT PEDIATRIK

Pacientët pediatrik dallohen nga pacientët e moshuar në shumë aspekte zhvillimore fiziologjike dhe psikologjike. Këto dallime e bëjnë që farmakokinetika e barit dhe farmakokinetika tek fëmijët të dallohet nga të moshuarit. Pra, kur përpunohet regjimi i dozimit të fëmijëve duhet të vëzhgohet si të moshuar në “miniaturë”. Ekzistojnë udhëzues të ndryshëm për regjim të dozimit në bazë të moshës tek pacientët pediatrik. Kjo përfshinë zgjedhjen e metodës së regjimit të dozimit në bazë të moshës që i karakterizon pacientët sipas moshës së tyre tek foshnjat e porsalindur (moshë prej <37 javësh gjestativ) të porsalindur (<1 muaj) infant (<1-24 muaj), fëmijë (2-12 vjet) dhe adoleshentë 12-16 deri 18 vjet) me ç’rast rekomandohet regjim për çdo grup. Megjithatë, kjo qasje nuk njehsohet në përputhshmërinë ndërmjet grupmoshave dhe ndryshimeve të çdo grupi.

Gjithashtu, zbatohet regjimi i dozimit në bazë të peshës trupore ose në bazë të parametrave farmakokinetik të peshës normale, ndërsa limitimi i dozave më të ulëta dhe më të larta duhet të merren parasysh që të mënjanohet dozimi i tepërt dhe mjekimi jo i drejtë. Gjithashtu, dozimi njehsohet në bazë të hapësirës të sipërfaqes trupore (BSA, body surface area) tek pacientët pediatrik. Udhëzuesi i dozimit mund të jetë i dobishëm, por, ekzistojnë dallime në zhvillim dhe ndryshime fiziologjike që manifestohen tek fëmijët që mund të ndikojnë në veprimin farmakokinetik të barnave. Këto ndryshime duhet të shqyrtohen kur zgjidhet regjimi i dozimit për barna të caktuar tek pacientët pediatrik [15].

PACIENTËT E MOSHUAR

Pacientët me të vjetër më shpesh kanë nevojë për ndryshimin e regjimit standard të dozimit për shkak të ndryshimeve fiziologjike dhe patologjike që paraqiten me moshë që mund të ndryshojnë farmakokinetikën dhe farmakodinamikën e barit. Kjo është me rëndësi sidomos tek pacientët me ushqim të dobët, sëmundje kronike, me qëndrim të shpeshtë në spital dhe aktivitet të kufizuar. Edhe pse këto pacientë shpesh marrin më shumë barna që e rrisin mundësinë e interaksionit bar-bar, që paraqet problem kryesor tek kjo popullsi e pacientëve. Megjithatë, shpejtësia e zbrazjes së lukthit është më e ngadalshme dhe koha e transportit nëpërmjet TGI është më e gjatë që shkakton absorbimin më të ngadalshëm të barit

Funksioni i veshkave shpesh zvogëlohet tek popullsia më e vjetër për shkak të zvogëlimit të qarkullimit të gjakut nëpër veshka. Filtrimi glomerular dhe sekretimi tubular zvogëlohen tek popullsia më e vjetër duke shkaktuar edhe zvogëlimin e eliminimit të barit nëpërmjet rrugës renale. Klirensii kretininës mund të shfrytëzohet si masë për funksionin renal tek kjo popullsi e pacientëve.Doza e barnave të cilat eliminohen në rrugë renale duhet të zvogëlohet tek pacientët më të vjetër duke marrë parasysh funksionin e njehsuar të veshkave dhe pjesa e dozës së barit që sekretohet e pandryshuar nëpërmjet urinës.

SHTATËZËNAT DHE LEHONAT

Ndryshimet fiziologjike të cilat paraqiten gjatë periudhës së shtatzënisë mund të ndikojnë në veprimin farmakokinetik të shumë barnave. Shumica e këtyre ndryshimeve fillojn që në tre muajt e para dhe bëhen më intensive deri në fund të shtatzënisë. Këto ndryshime fiziologjike kthehen në nivelin e tyre të para shtatzënisë me shpejtësi të ndryshme pas lindjes [16]. Gjithashtu, krijimi i placentës dhe zhvillimi i fetusit mund të ndikojnë në distribuimin dhe klirensin e barnave.Sasia e përgjithshme e barit që e merr bebja varet nga volumeni i qumështit që konsumohet dhe koncentrimi mesatar i barit në plazmë tek nëna [17]. Barin që e merr bebja në të shumtën e rasteve nuk akumulohet në koncentrime të cilat mund të shkaktojnë efekte të padëshirueshme. Por, foshnjat e porsalindur veçanërisht ata të lindur para kohe janë me rrezik të lartë që të zhvillojnë toksicitet serioz të shkaktuar nga bari që është marrë nëpërmjet qumështit për shkak të funksionit jo adekuat të organeve të tyre të cilët bëjnë eliminimin. Pra, foshnjat që ushqehen me qumësht nëne, nënat e të cilëve marrin barna mund të vëzhgohen se a tregojnë ndonjë farë shenje të efekteve farmakologjike dhe të padëshirueshme. [16,17].

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RETROPERITONEAL FIBROSIS ''ENRICHED" CLINICAL PICTURE WITHE EMPHYSEMATOUS PYELONEPHRITIS ON LEFT KIDNEY

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ABSTRACT

Retroperitoneal fibrosis (RPF) is a relatively uncommon disease. The estimated annual incidence varies from 1 per 200,000-500,000 population . Because of the nonspecific nature of the symptoms, the diagnosis of retroperitoneal fibrosis is often delayed. This may lead to progressive loss of renal function. Retroperitoneal fibrosis has no reported racial predilection. The condition occurs twice as commonly in males as in females. The peak incidence of retroperitoneal fibrosis is in adults aged 40-60 years.Childhood presentation is extremely rare.

Case report - 9 year old child with a few liquid stools, pain and discomfort in lower abdomen. Anamnestic data for surgery, and complications of perforated appendix with abscess in the small pelvis which occurred a month ago. At the time of ultrasonographic investigation left kidney was noticed to be increased in size with enlarged calluses and hyperechogenic zones which can be seen at the level of lower and middle group of calluses, without visible attenuation of the beam behind them and with present reverberation of the ultrasound beam (typical ultrasonographic sign of emphysematous pyelonephritis). This is also supported by laboratory analysis and intravenous anterograde pyelouretrography.

Conclusion – Retroperitoneal fibrosis "enriched" clinical picture of emphysematous pyelonephritis.

Key words: retroperitoneal fibrosis, complications of perforated appendix, echotomography.

INTRODUCTION

Retroperitoneal fibrosis (RPF) is characterized by the development of extensive fibrosis throughout the retroperitoneum, typically centered over the anterior surface of the fourth and fifth lumbar vertebrae. This fibrosis leads to entrapment and obstruction of retroperitoneal structures, notably the ureters. In most cases, the etiology is unknown. However, its occasional association with autoimmune diseases and its response to corticosteroids and immunosuppressive therapy suggest it is probably immunologically mediated. Approximately -8% of cases are associated with metastatic malignancy. Idiopathic retroperitoneal fibrosis carries a good prognosis, with little effect on long-term morbidity or mortality. The symptoms and signs associated with retroperitoneal fibrosis are nonspecific, and diagnosis requires a high degree of suspicion. Although a definitive diagnosis can only be made based on biopsy findings, intravenous urography may provide further support for the diagnosis of retroperitoneal fibrosis, particularly if the classic features are present. CT scanning or MRI is essential for evaluating the extent of the disease process. Because of the nonspecific nature of the symptoms, the diagnosis of retroperitoneal fibrosis is often delayed. This may lead to progressive loss of renal function. Retroperitoneal fibrosis has no reported racial predilection. The condition occurs twice as commonly in males as in females. The peak incidence

of retroperitoneal fibrosis is in adults aged 40-60 years. Childhood presentation is extremely rare. To date, approximately 33 cases in children younger than 18 years have been reported.

CASE REPORT

9 year old child with a few liquid stools, pain and discomfort in lower abdomen. Anamnestic data for surgery, and complications of perforated appendix with abscess in the small pelvis which occurred a month ago. At the time of the ultrasonographic investigation the left kidney was increased in size with enlarged calluses with hyperechogenic zones visible at the level of lower and middle group of calluses, without visible attenuation of the beam behind them and with present reverberation of the ultrasound beam (typical direct ultrasonographic sign of air in calluses).

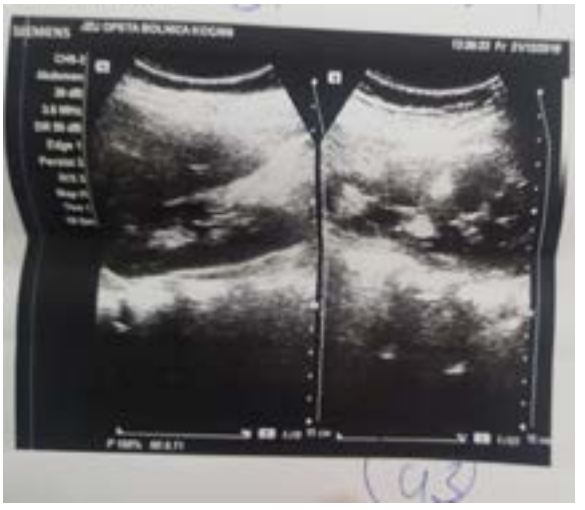
Additional investigation was made such as: intravenous pyeloureterography as well as routine laboratory check ups (CRP-215,0 mg/l; urea-12,5 mmol/l; kreatinin-95,3 mmol/l; glikemia-6,4 mmol/l; total protein-78 g/l and albumin-41 g/l ; Hb-147 gr/l; Er-5,60 x 10; Le-11,0 x 10; control laboratory: SE-15/30 ; urea-4,6 mmol/l; kreatinin-51,4mmol/l; total protein-80 g/l and albumin-44 g/l; Hb-136 gr/l; Er-5,2 x 10; Le-6,3 x 10) .

Control ultrasonographi demonstreated the same size of left kidney with visibly enlarged calluses, moderate hypotony of the pyelon and no visible presence of the hyperechogenic areas at calluses (see picture 1, 2) .

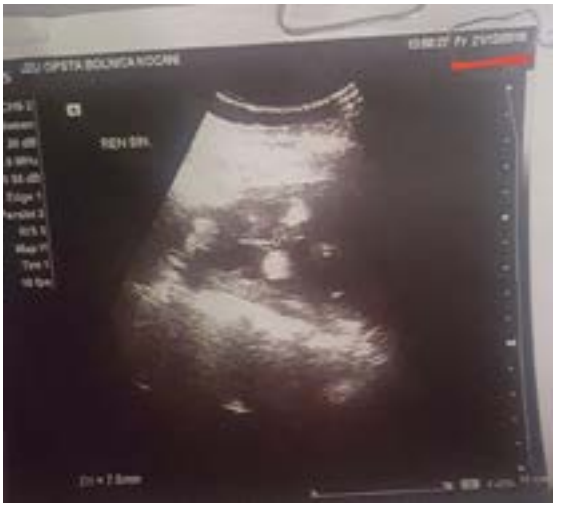
Picture :

1. emphysematous pyelonephritis (a-comparativ ultrasound,b-longitudinal ultrasonography of the left kidney) ;

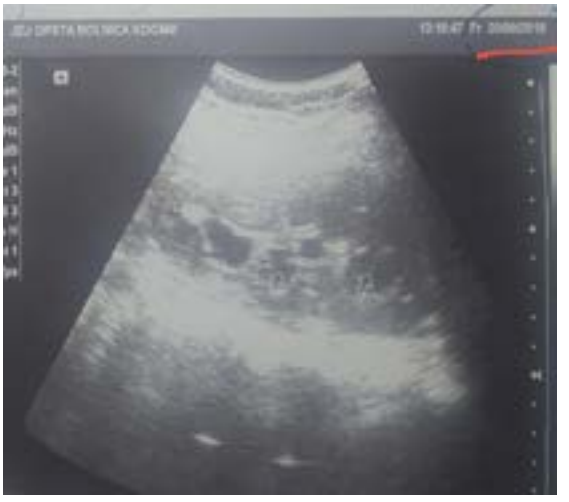
2. control ultrasonographies (a– longitudinal ; b-transversal ultrasound with doppler of the left kidney ; c - comparativ ultrasound of both kidneys, longitudinal ultrasonography) .



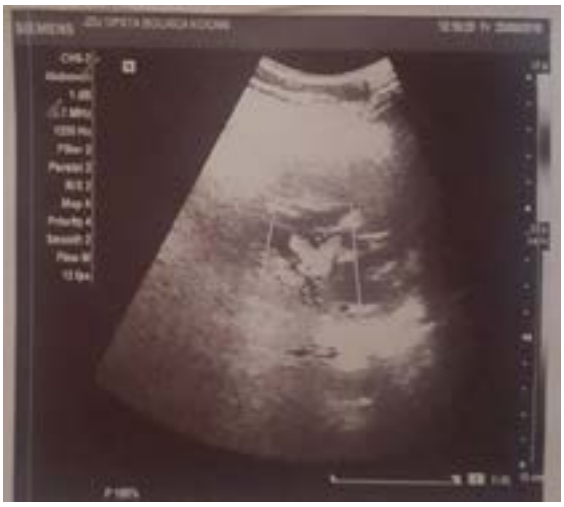
1 a)



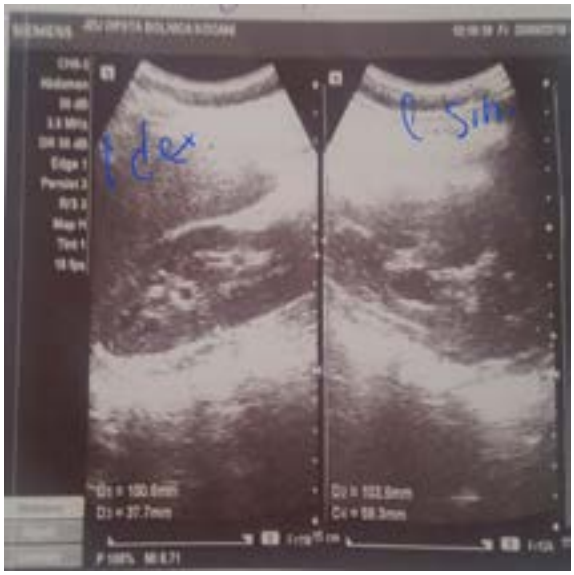
b



2a



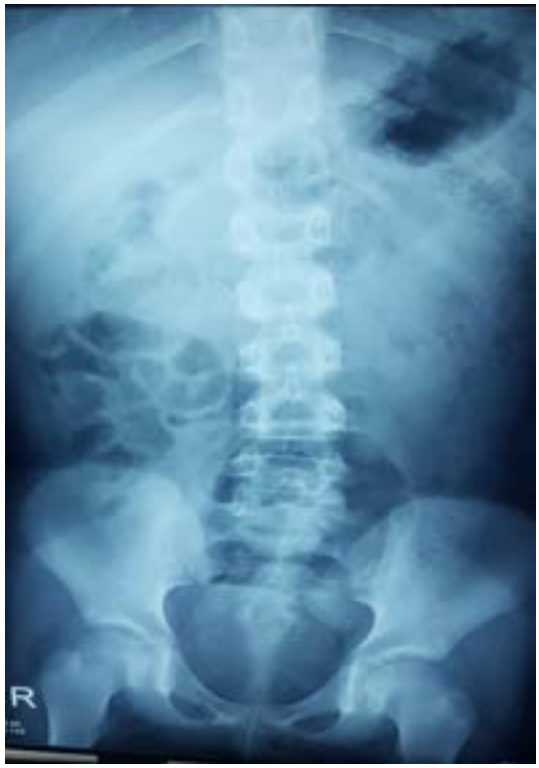
b



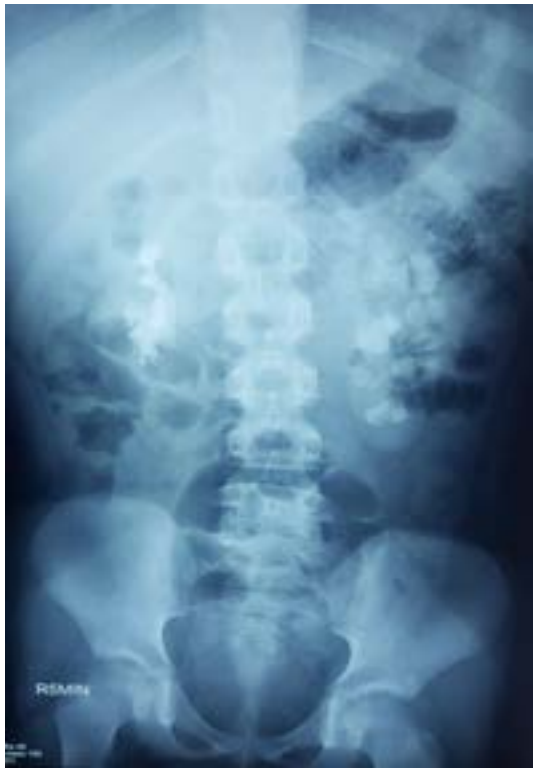
c

Intravenous urographic image demonstrates medial deplacement (deviation) of the left ureter at the L5 vertebral level with stenosis in that segment and visible ureter hypothony above that same segment, which is differentiated retroperitonael fibrosis (see picture 3d). Note the delayed excretion of the hydronephrotic left kidney (picture 3c).

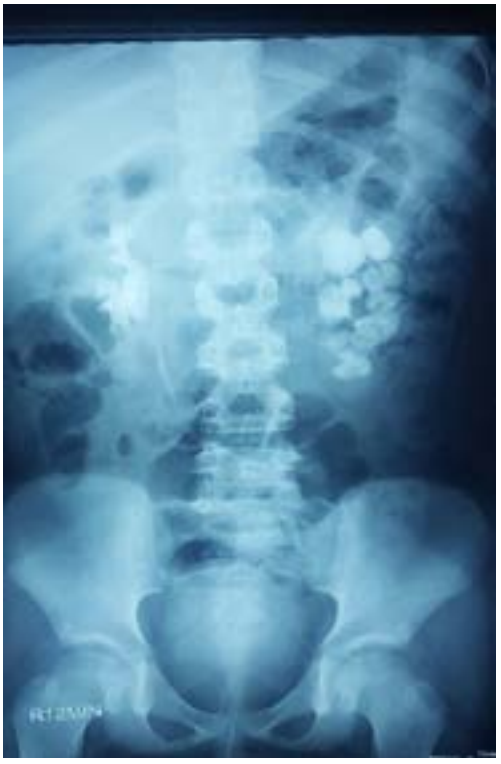
Picture 3 (a-native urinary ; b-5 min. imbibicion phase ; c-12 min. excretory phase ; d- late phase withe magnification) :



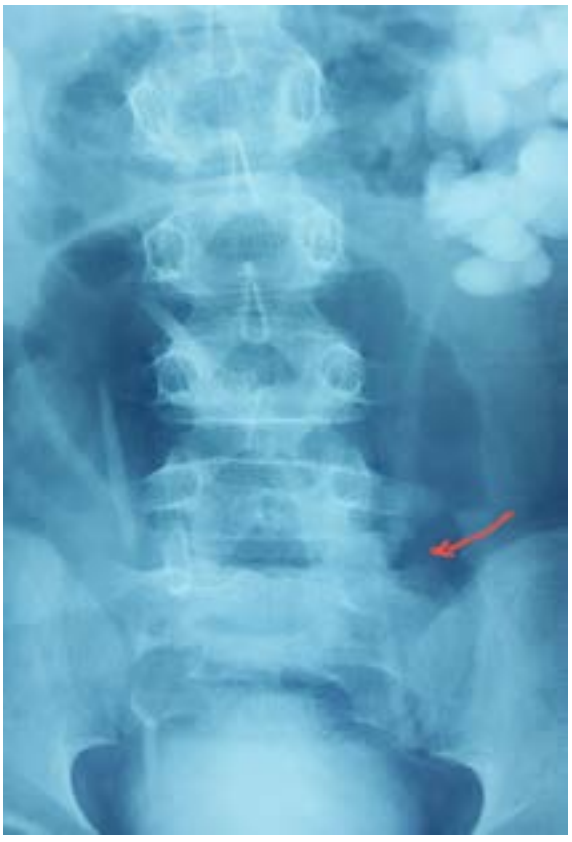
a



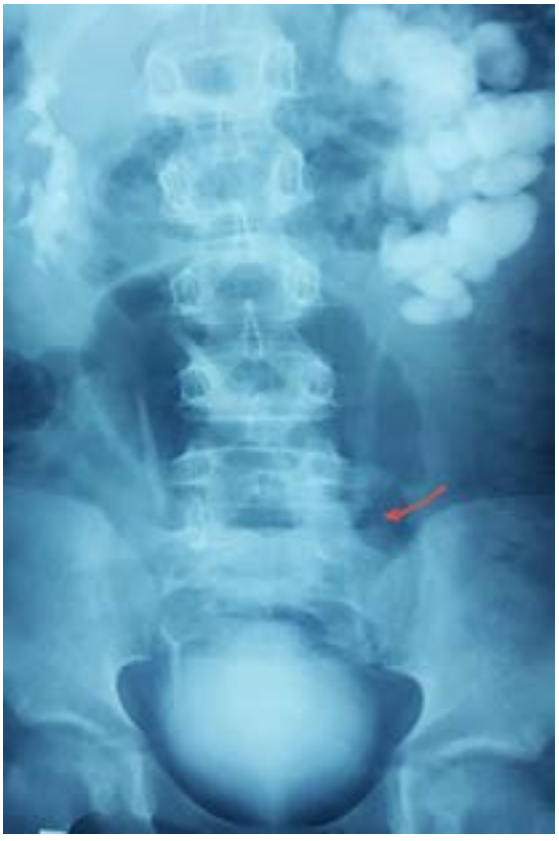
b

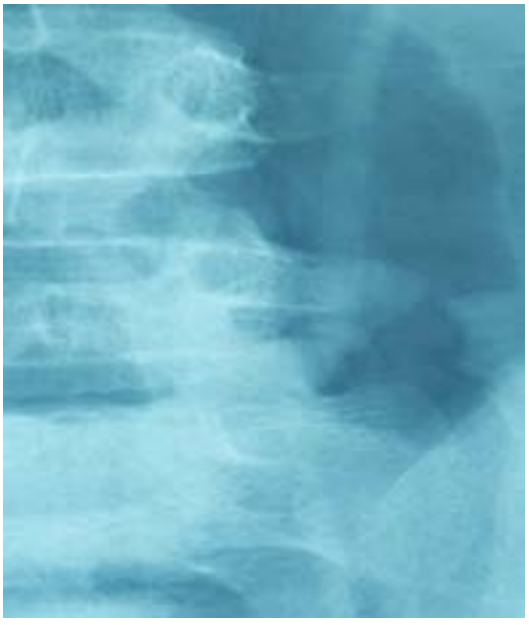


c



d





DISCUSSION

If you now the anatomy of the retroperitoneum, we understand the patogenesis of this case: -The retroperitoneal space is bordered anteriorly by the posterior parietal peritoneum, posteriorly by the transversalis fascia, and superiorly by the diaphragm.

Inferiorly, it extends to the level of pelvic brim. The anterior and posterior layers of renal fascia (Gerota fascia) subdivide the retroperitoneal space on either side of the spine into 3 compartments. The posterior space contains the pararenal fat. The intermediate space contains the kidney, the adrenal gland, and the perirenal fat. The anterior space is more extensive.The anterior pararenal space is bordered anteriorly by the posterior parietal peritoneum, posteriorly by the anterior layer of renal fascia, and laterally by the lateral conal fascia. The anterior pararenal space contains the extraperitoneal portions of the ascending and descending colon, the duodenum, and the pancreas. The anterior pararenal space is continuous across the midline; however, collections of fluid tend to remain ipsilateral to the site of origin. Medially, the anterior layer of renal fascia blends with the connective tissue around the aorta and inferior vena cava. The posterior layer fuses with the psoas fascia. Laterally, both layers merge to form lateral conal fascia .Further recommendation for CT to differentiate primary-(idiopathic) or secondary RPF.

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МИНЕРАЛОКОРТИКОИДНИ ИНХИБИТОРИ ВО ТРЕТМАН НА РЕЦИДИВАНТНА ЦЕНТРАЛНА СЕРОЗНА ХОРИОРЕТИНОПАТИЈА

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ИЗВАДОК

Вовед: Централна серозна хориоретинопатија (CSH) е хориоретинално заболување со серозно одлепување на неуросензорната ретина и/или ретиналниот пигментен епител. Патогенезата на заболувањето се уште не е целосно разјаснета, односно е мултифакториелна, со вклучени бројни егзогени и ендогени фактори кои влијаат на хориоидеата и ретиналниот пигментен епител (RPE). Покачената минералокортикоидна активност е исто така предложена како најверодостојна причина за рецидивантната и хронична CSH, што е причина минералокортикоидните инхибитори да се потенцијална терапија за избор.

Цел на трудот: Да се прикаже ефектот од третманот со минералокортикоидниот антагонист, Еплеренон, во серија случаи со дијагностицирана рецидивантна серозна централна хориоретинопатија, евалуирани со ОСТ на заден очен сегмент.

Приказ на серија случаи: Прикажуваме пациенти со дијагностицирана рецидивантна централна серозна хориоретинопатија, третирани со орален минералокотикоиден антагонист, Еплеренон, последователо (CSH) во период од 3 месеци. Пациентите беа проспективно следени, во период од 6 месеци, со месечни евалуации зависно од клиничкиот наод. Кај пациентите се мереше најдобро корегирана видна острина (BCVA), беше вршен комплетен офталмолошки преглед и снимање со оптичка кохерентна томографија на заден сегмент (ОСТ), со мерење на централната дебелина на макулата (CMT) и на субретиналната течност (SRF).

Резултати: По примениот третман во период од 3 месеци, кај сите следени пациенти дојде до подобрување на клничкиот наод, подобрување на видната острина, комплетна ресорпција на субретиналната течност и намалување на централната макуларна дебелина (CMT), како и стабилизација на состојбата во период од 6 месеци потоа.

Заклучок: Примената на оралниот минералокортикоид Еплеренон во третманот на рецидивантните форми на CSH, претставува интригирачки пристап, а патофизиолошките механизми се основа за примена кај оваа група пациенти. Подобрувањето на клиничкиот наод, со намалување на SRF и CMT несомнено го оправдува третманот, но мултифакториелната патогенеза е причина за понатамошни поголеми рандомизирани клинички иследувања.

Клучни зборови: Централна серозна хориоретинопатија (CSH), Еплеренон, Оптичка кохерентна томографија (ОСТ), видна острина (BCVA)

ВОВЕД

Централна серозна хориоретинопатија (CSH) е хориоретинално заболување, што се карактеризира со серозно одлепување на неуросензорната ретина и/или ретиналниот пигментен епител (RPE), што има за последица акумулација на течност. [1-3] Согласно локацијата и количината на течност, се манифестира и симптоматологијата кај пациентите со CSH. Доколку течноста е локализирана надвор од макулата, може и да нема изразена симптоматологија, што е ретко, додека кај одлепувањето со афекција на макулата, симптомите може да вклучуваат нагло намалување на видот, метаморфопсија, промени во големината на сликата, перцепција на слепи точки или комбинација на овие симптоми. [1]

CSH афектира 1 на 10000 луѓе [2] и претставува најчеста причина за оштетување на видот кај работоспособната популација. Проценета е како четврто најчесто заболување во клиничка пракса на ретиналните заболувања, после сенилната макуларна дегенерација (ARMD), дијабетичната ретинопатија и тромбоза на ретиналната вена. [1-3]

Најчесто се афектирани млади, до средновечни мажи (30-50 год.) и во корелација со стрес.

Оптичката кохерентна томографија на задниот очен сегмент (OCT) како метода се користи за дијагностика на CSH, за мониторирање и квантифицирање на ретиналната дебелина и мерење на количеството на субретинална течност. [4]

Заболувањето е обично идиопатско, често поминува спонтано, со регресија на видот, иако некогаш неуросензорното одлепување може да перзистира или повторно се јавува и води до трајно оштетување на RPE и фоторецепторите со последично оштетување на видот. [1-3] Покажано е дека во акутната фаза, субретиналната течност често се ресорбира спонтано и тоа за 6-12 недели или 12-24 недели. [5] Додека, хронична CSH е доколку субретиналната течност, односно флуид перзистира повеќе од 3 месеци, или постои рекурентност на болеста во тек на 1 година. [6]

Патогенезата на заболувањето иако се уште не е целосно разбрана, се претпоставува дека е мултифакториелна, со вклучени бројни егзогени и ендогени фактори кои влијаат на хороидеата, односно ретиналниот пигментен епител. [1] Примената на инхибиторите на ангиогенезата (анти ВЕГФ препарати) кај хроничните форми, рецидивантни форми и кај присутна неоваскуларизација, се покажа како неопходно, а примената на минералокортикоидите е во тек на иследување.

Еплеренон е селективен алдостерон-рецептор антагонист, примарно одобрен од FDA во 2002 година за третман на хипертензија.

Повеќе автори истакнуваат дека активирањето на минералокортикоидните рецептори во хороидеата, односно ретиналното ткаење е во корелација со појавата на CSH.

Минералокортикоидните рецептор (MP) антагонисти се насочени кон RPE/хороидеа и се покажало дека делуваат како лекови за модификација на заболувањето исто како што доведуваат до промени и во останатите ткива (срце, бубрег, мозок). Студии ги сумираат предклиничките и клиничките докази за примената на оралниот минералокортикоид, еплеренон во третманот за CSH.

Цел на трудот е да се прикаже ефектот од третманот со минералокортикоидниот антагонист, еплеренон во серија случаи со дијагностицирана рецидивантна серозна централна хориоретинопатија, евалуирани со OCT, на месечни интервали.

ПРИКАЗ НА СЛУЧАИ

Прикажуваме серија случаи со хронична централна серозна хориоретинопатија кои се третираа со орален минералокортикоид, Еплеренон и беа евалуирани проспективно.

На пациентите примарно им беше извршен комплетен офталмолошки преглед кој вклучуваше видна острина, тонометрија, биомикроскопија на предниот сегмент и на задниот сегмент, со примена на неконтактна лупа 78 Д. Кај истите пациенти се направи и снимање оптичка кохерентна томографија на задниот сегмент на окото (OCT), како супериорна метода за детекција и евалуација на пациентите со оваа семиологија. Евалуацијата се правеше на 4-та недела, по примена на третманот и на 3-от месец во зависност од клиничкиот наод.

Оралната доза на Еплеренон во првиот месец беше 50мг, потоа во следните два месеци 25мг, еднаш дневно.

Приказ на случај 1:

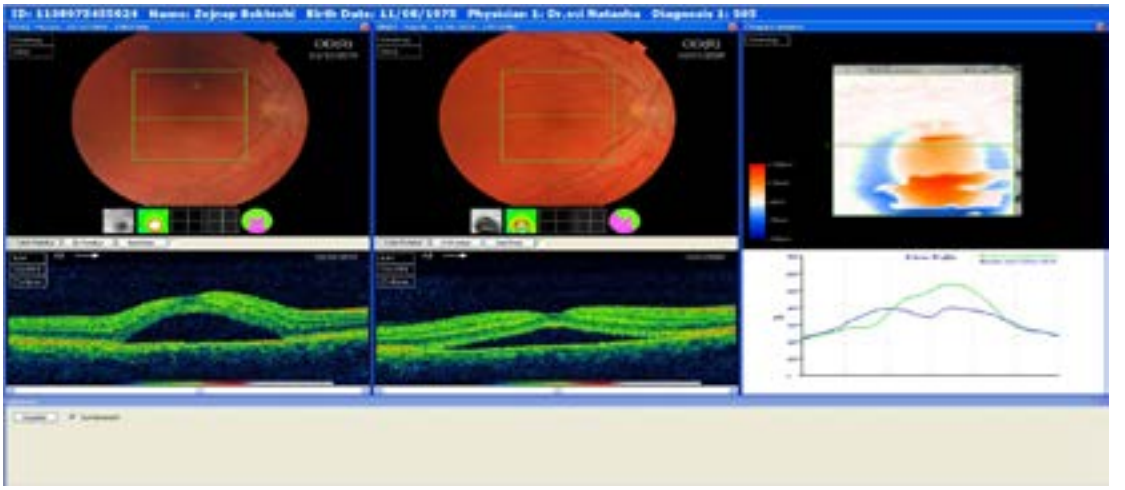
Жена, на 40 год. возраст, која пред 6 месеци имаше

акутна форма на CSH.

Видната острина на десното око 0,9 s.c., на левото 1,0 s.c. Интраокуларниот притисок (ИОП) обострано уреден. Биомикроскопијата на предниот сегмент обострано уреден наод, а фундоскопијата на десното око: во макула булозно надигнување на ретина, семитранспарентно. (сл.1 лево). Фундоскопијата на левото око покажа уреден наод.

ОСТ наодот на десно прикажа серозно ретинално одлепување со субретинална течност во фовеа CMT 465μ и SRF 270μ пред третманот. (сл.1а)

На првиот контролен преглед за 4 недели по употребата на Еплеренон, покажа регресија на клиничкиот наод со намалување на CMT 363μ SRF 171μ (сл.1б), додека на 8-та недела веќе имаше комплетна регресија на клиничкиот наод, со ресорпција на субретиналната течност. (сл.2)



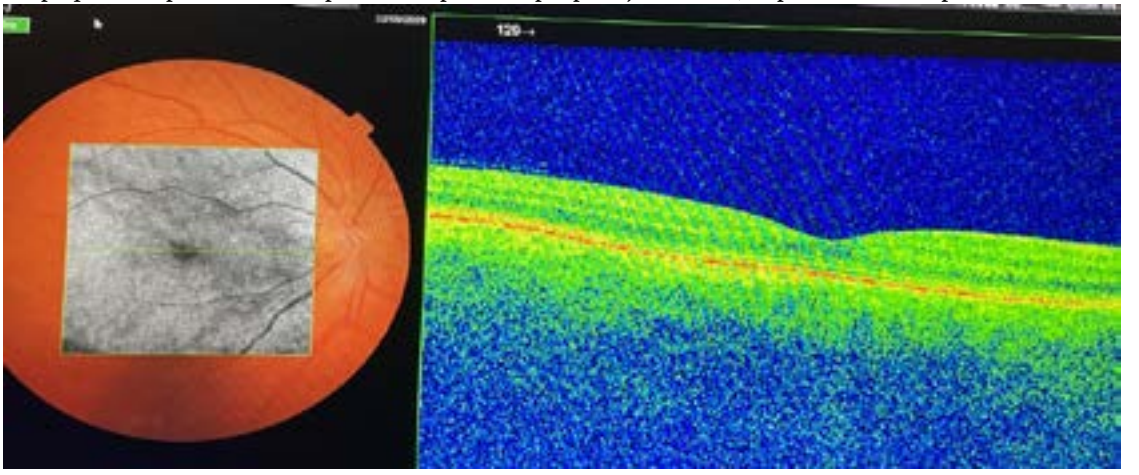
а б в

Сл.1 Комппаративен ОСТ наод: случај 1,

а. приказ на фунус на десното око и ОСТ пред започнување на третман, CMT 465μ, SRF 270μ

б. приказ на фундус на десното око 4 недела од третманот, CMT 363μ, SRF 171μ;

в. графички приказ - компаративна крива на регресија на CMT, изразена во микрони.



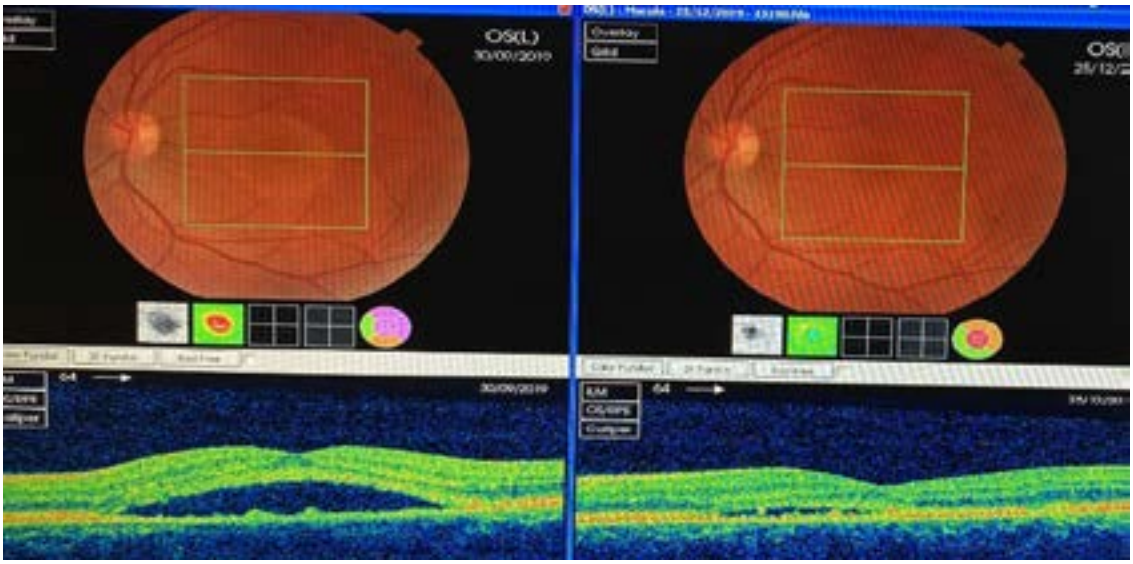
Сл.2 Приказ на случај 1, на 2 месец по примената терапија

Приказ на случај 2:

Маж 47 години, примарно во 2018 год. имал акутна CSH, и за 6 месеци рецидив кој своевремено е третиран со една сеанса микропулсен ласер, по што состојбата се подобрува, со регресија на клиничкиот наод и подобрување на видот. Декември 2019 год. пациентот повторно се јавува со метаморфопсии на десното око и видна острина VOD: 0,8 sc. при што се дијагностицира хронична CSH.

Иследувањата го потврдија клиничкиот наод, булозно надигнување на ретиналните слоеви, со промер 3-4 DD, и на OCT - серозно ретинално одлепување со CMT 449μ и SRF 230μ. пред третманот, односно CMT 172 μ и SRF 50μ на првиот контролен преглед по 5 недели (сл.3а, 3б).

По 3 месечниот третман со Еплеренон, дојде до комплетно налегнување на ретиналните структури и видна острина VOD: 1.0 del sc.

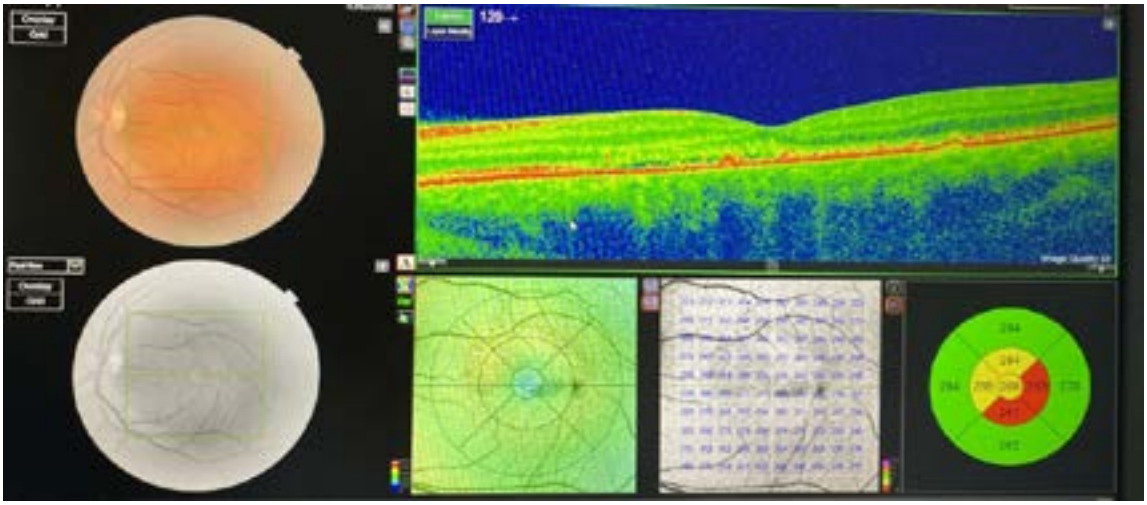


а. б.

Сл. 3 Комппаративен OCT наод: случај 2

а. фунус и OCT приказ пред третман, CMT 449μ, SRF 230μ,

б. приказ на фундус и OCT на 5-та недела, од третманот CMT 172μ, SRF 50μ.

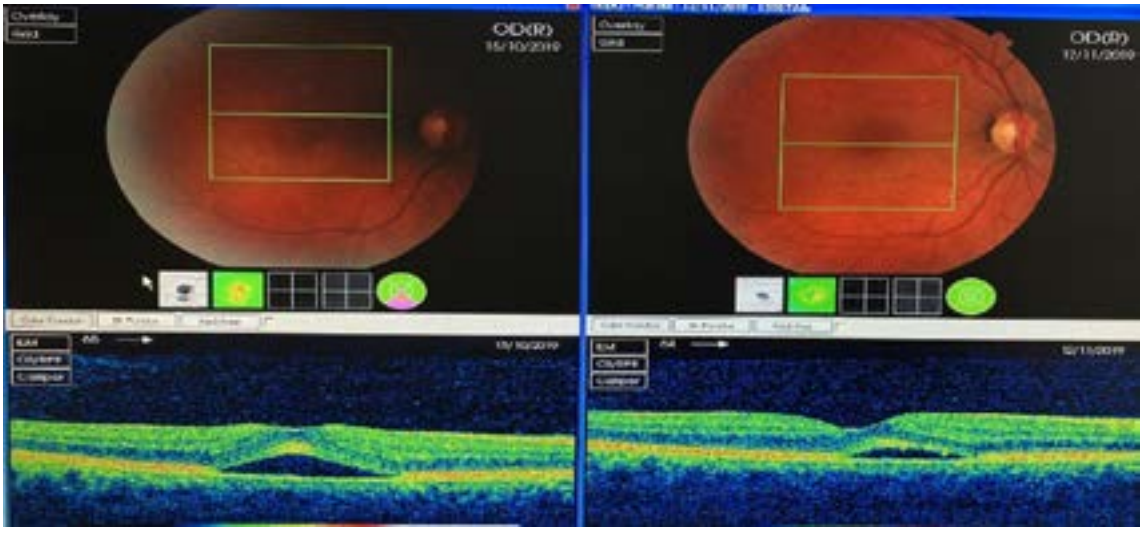


Сл. 4 Приказ OCT наод по примена терапија, 3 месец по третман, случај 2

Приказ на случај 3:

Маж, 42 год. возраст, прв пат се јави на Клиниката за очни болести во јуни 2019год., со дијагностицирана акутна форма на CSH. Во месец октомври, 2019 год. има рецидив. Направена е OCT со измерена CMT 354μ и SRF 152μ. (сл.5а)

Пациентот беше ставен на терапија со Еплеренон првиот месец 50 мг, потоа 25 мг во следните два месеци. На контролниот преглед направен во месец декември 2019 година, имаше CMT 254μ и SRF 80μ. (сл.5б)

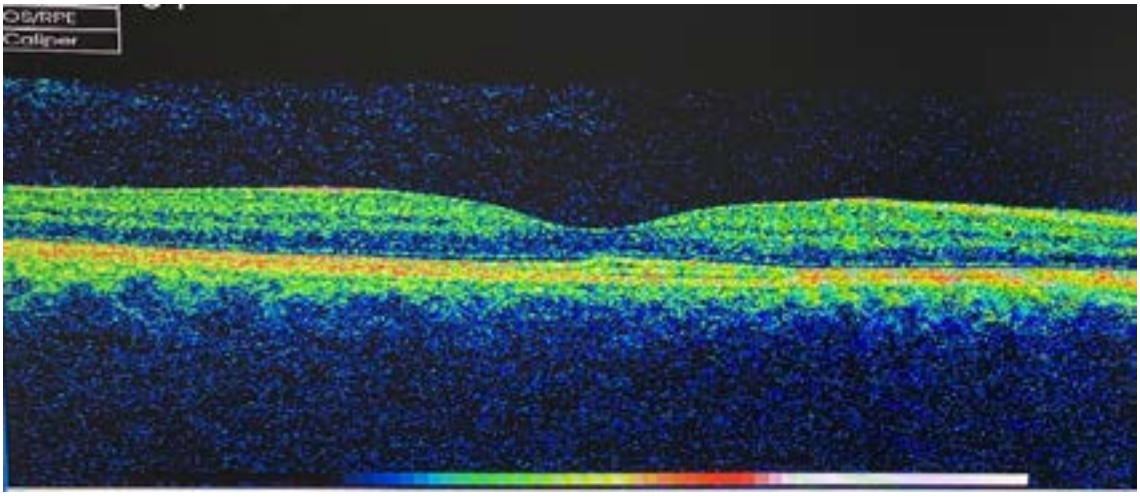


а. б.

Сл. 5 Комппаративен OCT наод на случај 3,

а.приказ на фундус и OCT приказ пред третман, CMT 354μ, SRF 152μ,

б. прикаџ на 4-та недела, од третманот CMT 254μ, SRF 80μ.



Сл. 6 Приказ на ОЦТ наод на 3 месец по третманот

Пациентите проспективно беа следени во текот на 6, односно 9 месеци. Состојбата кај сите е стабилна, нема регресија, ниту влошување на клиничкиот наод. Ниту еден од пациентите не пројави негативни несакани дејства во тек на терапискиот третман.

ДИСКУСИЈА

Патогенезата на CSH е мултифакториелна. Според бројни студии се истакнува дека вишокот на едногени кај Кушинг синдромот или во тек на бременост, или пак присуството на егзогени (како интраартикуларни инекции, интраназално, локално или системски) кортикостероиди, обструктивна sleep apnea, абнормална коагулација, инфекција со Helicobacter pylori, машки пол, бременост, пушење, хипертензија, користење на антибиотици, консумација на алкохол и оксидативен стрес, се најчестите ризик фактори за развивање на CSH. [7-10]

Истовремено, повеќе автори потенцираат дека генетската подложност игра значајна улога во патофизиологијата на CSH, односно генетскиот полиморфизам е асоциран со CSH. [11-13] Додека студијата на Van Dijk и сораб. (Van Dijk, 2017), го прикажува rs2070951 во генот NR3C2, кој го кодира рецепторот на минералокортикоидите, како значителен за корелација со хроничната CSH. Истовремено, хаплотиповите на NR3C2, кои претходно биле поврзани со стрес, исто така, биле поврзани со CSH, што може да е откритие за премостување на клинички фактори до основните генетски асоцијации. [14]

Впрочем и покрај разликите во клиничката презентација, акутната и хронична CSH може да имаат слична генетска предиспозиција. [14]

Еплеренонот спаѓа во класа на лекови наречени антагонисти на минералокортикоидни рецептори. Функционира со блокирање на дејството на алдостеронот, природна супстанца во организмот која го зголемува крвниот притисок. Класифициран како селективен антагонист на рецептор алдостерон (CAPA), сличен на диуретичниот спиронолактон, иако е многу селективен за минералокортикоидниот рецептор (MP), со примарна индикација за пациентите со висок кардиоваскуларен ризик, како миокарден инфаркт. (FDA, 2015). [15]

Имено, Еплеренон потекнува од спиронолактон и најзабележлива разлика помеѓу двата лека е во нивниот афинитет за андрогени и прогестеронски рецептори. Еплеренонот има поголема минералокортикоидна селективност и поголем афинитет споредено со спиронолактонот. Исто така, има 10-20 преклопувања помалку со прогестеронски и андрогени рецептори и не ги вклучува хормоналните ефекти, лимитирајќи ги полово-хормонските несакани ефекти. [15] Прикажани се и потенцијално несакани ефекти на еплеренон како хиперкалемија, ренална инсуфициенција, дијабетес мелитус, напреднато срцево оштетување, повеќе кај постари пациенти и во интеракција со други лекови, како диуретици, инхибитори на ангиотензин конвертирачки ензим и ангиотензин рецептор блокатори, замор, седативни ефекти, дијареа или констипација, гинекомастија, намалување на тежината, иритација на дебелото црево, миотонија и сл. [16, 17, 18, 19]

Несаканите ефекти зависат од дозата и се реверзибилни по прекинување на третманот, но во нашата серија случаи немаше пријавено несакани дејства од третманот кај пациентите. [18, 19]

CSH е дел од нарушувањата на пахихороидниот спектар, и со серозно одвојување на мрежницата, промени на ретиналниот пигментен епител, проширување на хороидалните садови. [20] Нема јасно дефиниран став во однос на клиничката класификација и физиопатогените механизми на заболувањето, што го одложува разбирањето на најоптималните опции за третман.

Уште многу одамна Gass (Gass, 1977), смета дека постои фокална хороидална хиперпропустливост, што ќе резултира со акумулација на течност во субретиналниот простор. [21] Но, студиите спроведени од Marmor (Marmor, 1988) и Prunte (Prunte, 1996) тврдат дека фокалното нарушување на RPE не може да предизвика серозно одвојување, поради способноста на RPE да компензира, истакнувајќи дека CSH е резултат на дифузно метаболно нарушување на RPE, каде хороидалната исхемија е вклучена во хороидна хиперпропустливост и дисфункција на RPE. [22, 23]

Оваа форма на механичка алтерација на интегритетот на RPE се нарекува “blowout” `или т.н.“micro rip” што ќе доведе до серозно одлепување. Впрочем се смета дека зафаќањето на ретиналното ткиво е секундарно, додека внатрешните хороидални промени се примарна патогенеза на заболувањето, што е причина за нарекување на заболувањето како централна серозна хориоретиноапатија. Нарушувањето на внатрешната хороидеа што резултира со макуларно серозно одлепување е аваскуларно, односно примарно не е асоцирано со пролиферација на крвни садови. [8]

Целта на третманот е да се подобри способноста на RPE да ја отстрани суберетиналната течност, да се

намали истекувањето од хориоидалните крвни садови, или да се намали течноста што поминува преку RPE бариера. [7] Третманот најчесто вклучува чекање на спонтана резолуција, фокална ласерфотокоагулација (LFC) кај некои пациенти со акутна CSH, анти-VEGF терапија во случај на хориодална неоваскуларизација и фотодинамска терапија. [24, 25]

Од неодамна прикажаните сознанија за покачена минералокортикоидна активност е предложена како најверодостојна причина за CSH. Поради тоа, минералокортикоидните инхибитори се испитувани како потенцијална терапија за CSH.[15]

McCurley со сораб. (McCurley, 2012) потенцираат дека васкуларно, покачените алдостерон (минералокортикоидни) нивоа може да доведат во зголемена инфламација, покачени васкуларни реактивни кислородни партикли и намалена продукција на азотен оксид. Наведените промени имаат ефект на ендотелот и мазната мускулатура во крвните садови, афектирајќи ги контрактилните делови на артериите, артерискиот тонус и крвниот притисок. Во ретината, минералокортикоидите можат да ја афектираат и хориоидалната и ретиналната циркулација. [26] [27] Се смета дека CSH е резултат на прекумерно активирање на минералокортикоидните рецептори во хориоидеата.

Zhao и сораб. (Zhao, 2012) први прикажале третман на два пациенти со хронична CSH со орален еплеренон, при тоа презентирајќи брза регресија на субретиналната течност и подобрување на видната острина, што се оддржало и во периодот на евалуација во следните 6 месеци. [25] Оттогаш, неколку студии ја испитале и прикажале ефикасноста и безбедноста на еплереноното за третман на CSH.

Sampo и сораб. (Sampo, 2016) прикажале бројна ретроспективна студија од повеќе од 27 пациенти каде по третманот со оралниот еплеренон, настанало значително подобрување на клиничкиот анатомски и функционален наод, со подобрување на видната острина за период од 3 месеци. [28]

Друга рандомизирана студија, вршела споредување на третманот со еплеренон со плацебо ефект, при што дошло до статистички значително подобрување на острината на видот и намалување на субретинална течност и централната макуларна дебелина, но во обете групи. [29] Во главно ефектот со еплеренон е помал кај пациенти со дифузни промени на RPE. [30]

Автори истакнале дека преку активирање на MP рецептори во хороидалните ендотелни клетки се предизвикува регулирање на вазодилататорниот калиумови канали, кои ја модулираат релаксацијата на мазните мускулни клетки, односно до вазодиталација во хороидалната васкулатура. [31]

OCT, како и OCT- ангиографијата обезбедуваат комплетни морфолошки информации кај пациентите со CSH. Присуството на повеќе дифузни промени на RPE само го потврдува концептот дека промените се дифузни, притоа детектирајќи ги и најсуптилните промени на ретиналното ткиво со хороидалните крвни садови, односно евентуалното присуство на неоваскуларизацијата. [32] Впрочем присуството на хороидалната неоваскуларизацијата (CNV) најчесто се јавува кај пациенти со долго перзистирачка форма, рецидиви, хронична дифузна епителиопатија или кај повозрасни индивидуи. Авторите ја истакнуваат хипотезата дека хроничната декомпензација или нарушување на комплексот Bruch – RPE со исхемичните промени на хориокапиларната мрежа може да бидат важен фактор за CNV. [32]

ЗАКЛУЧОК

Мултимодалното снимање со имицинг техники доведе до опис на широк спектар на манифестации на заболувањето и истовремено ја истакна инволвираноста на хородеата и RPE во патогенезата на CSH. Иако, точните молекуларни механизми на CSH се уште се неизвесни, оралниот еплеренон се покажува како безбеден и ефикасен третман кај рецидивантните форми на CSH.

Регресијата на функционалниот и клиничкиот наод, во однос на намалување на SRF кај случаи на рецидивантна серозна централна хориоретинопатија, и намалување на макуларната централна дебелина и следствено подобрување на видната острина, се причина повеќе за примената на препаратот во секојдневната пракса. Но, повеќето студии како и нашата серија кои го испитуваат еплереноното како третман кај CSH се со краткорочно следење и на помала група третирани пациенти, па неопходно е во иднина да следат поголеми, рандомизирани студии со цел да се утврди улогата на MP антагонистите во третманот на CSH.

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INTRADUCTAL PAPILLOMA IN LACTATING WOMEN, CASE REPORT

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ABSTRACT

Intraductal papilloma is a benign tumor in female breast, found in the breast duct .It can be located centrally ,near the nipple, like solitary lesion or it can be located in the periphery of the breast, multiple ductal papillomas. Depending of the localization can be presented with nipple discharge(centrally located) and like palpable mass(located in the periphery ducts) although small papilomas can be asymptomatic. They can occur in women of all ages, commonly in premenopausal women, also in pregnancy and lactating, as it was presented in our case.

Material and methods: This presentation is case report, of a breast papilloma in 32years lactating women.

Aim of this study: description of clinical and radiological findings of intraductal papillomas using different diagnostic methods

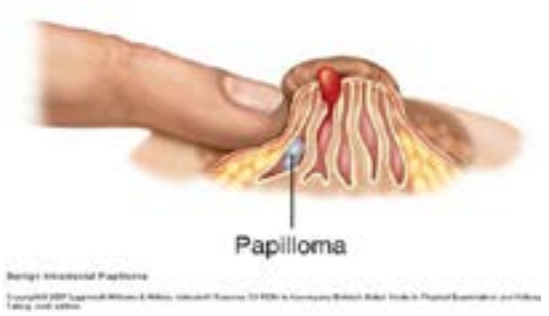
Keywords: intraductal breast papilloma, ultrasound, breast duct

INTRODUCTION

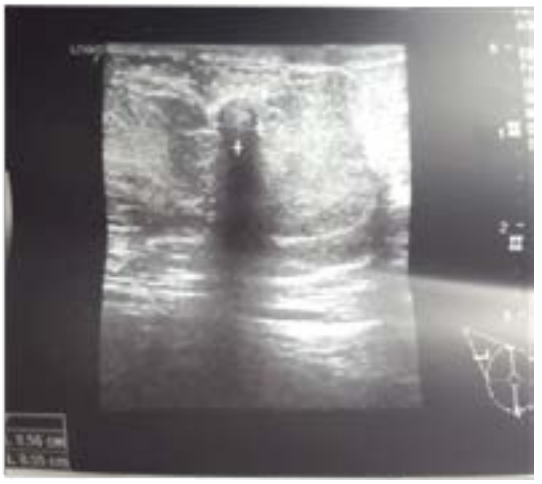
Breast papillomas are usually benign lesion arising from the lining of the ducts, although a small percentage can be malignant.. Solitary papilomas are located in the central ducts, clinically manifested with clear or bloody nipple discharge while multiple paplilomas has peripherally ducts location with palpable lump presentation. Multiple papilomas are less common then solitary papilomas but they show an increased risk of breast cancer, as high as 10-30%.1 Booth benign and malignant papilomas have same symptoms: breast enlargement, pain, nipple discharge ,palpable lump or they can be asymptomatic.3 Can occur in women of all ages, usually in premenopausal women(35-55)2,rarly in pregnant and lactating women. Breast tumor factor include family history, long period of estrogen exposure, contraceptive pills. Detection of this lesion is difficult, but very important for their diagnosis and treatment. Radiological imaging methods: mammography ,ultrasound and ductography are used to identify papilomas while magnetic resonance for evaluation of known papilomas. Ultrasound, with varies sonographic techniques has crucial role in detecting intraductal papilomas.

Case report

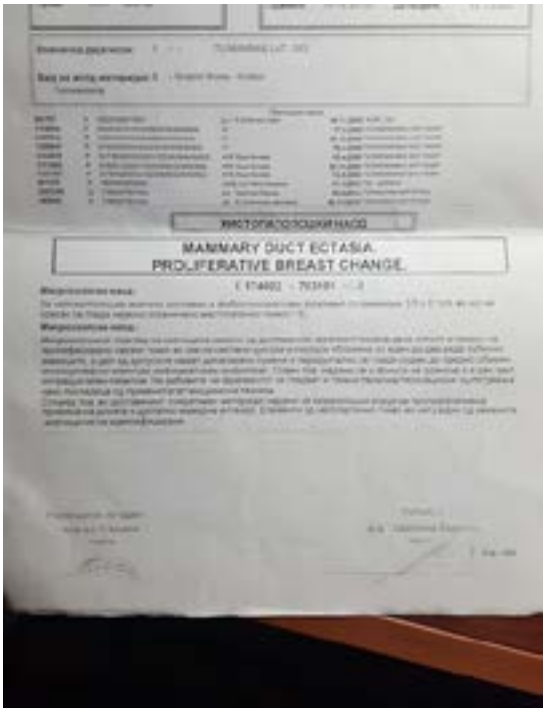
We presented a rare case of intraductal papilloma in lactating women, age 32. She came in our institution, with palpable lump in the upper lateral quadrant in her right breast, in 5th mounts of breastfeeding period. She didn't has any other symptom, but she has positive family history, her mother has nipple discharge, diagnosed and surgically treated from intraductal tumor. Ultrasound was preformed, and we reveled a dilated duct in the periphery of the breast, with solid intraductal component. pic.1 Mammography finding were normal, so we referred her to the breast surgeon. Based on our suspicion of intraductal papilloma, and our ultrasound exam, surgical excision of the affected area of the breast was preformed, and histopathologic analysis of the tissue was made. Patohistology report confirmed our initial diagnosis of intraductal papilloma. Pic 2. On ultrasonography exam after period of one year of surgical treatment, results were normal, without recurrence.



Pic1.ultasonographic image of papilloma



Pic2.patohistology report



DISSCUSION

Although intraductal papillomas are benign lesion, they are classified as high precursor lesion. This classification is due to its association with atypia, DCIS, and carcinoma.4 The most distinguishing feature between benign and atypical papillomas is the epithelium. In benign papillomas the epithelial layer is supported by myoepithelial cells, whereas papillary carcinoma show disrupted or completely absent myoepithelial layer. A variety of changes can accompany intraductal papilloma which include sclerosis, epithelial or myoepithelial hyperplasia, atypical proliferation, and squamous or apocrine metaplasia.6 Intraductal papillomas are usually found in women between 30-55 years, also in pregnant and lactating women as it was in our case. During this two periods, women breast face several physiological changes, attributed to various hormones, which may cause vascular hyperplasia and hyperplastic lobules. Most of breast lesion in pregnancy and lactation are benign, but differential diagnose with breast cancer is challenging in this two period.5

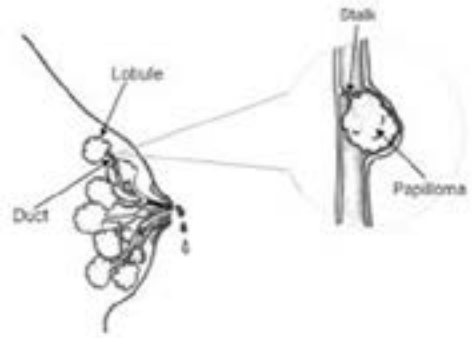


Figure 1: Breast papilloma

Clinical symptoms are present for about 5% of all women, and include nipple discharge, palpable lump, breast pain but they can be asymptomatic, discovered on routine check up, so regular exams of the breast are recommended for every women in reproductive and postmenopausal period. Diagnosis of this tumors, is made with radiological imaging methods, but differentiation of benign from malignant papillary tumors on imaging is often difficult because of the wide spectrum of appearances of these lesions on MRI, ultrasound, and mammography.4In most cases mammography is occult, still ultrasonography remands a mandatory method, with intraductal soft tissue component. On galactography, intraductal papilloma appears as an intraluminal filling defect with ductal dilation leading up to the mass with an abrupt ductal cutoff. MRI findings include an enhancing round or ovoid intraductal mass with likely either washout or plateau kinetics. Treatment of this lesion is surgical excision and complete removal of the tumor, due to possibility of upgrading to atypical ductal hyperplasia or DCIS.6

CONCLUSION

Intraductal papilloma are benign tumor but still tissue sampling with radiologic-pathologic correlation is usually warranted for diagnosis.

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EPILEPSY WITH HETEROZYGOUS ALDH7A1 AND SLC6A1 MUTATIONS

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ABSTRACT

Epilepsy is one of the most common neurologic disorders, 75% of which begins during childhood. With the development of genetic technology, an increasing number of genes associated with epilepsy are identified. These discoveries will improve diagnosis and treatment of epilepsy and provide the basis for including genetic tests in clinical practice. We report cases of epilepsy in two sisters with heterozygous mutations in ALDH7A1 and SLC6A1 gene. Including genetic tests in the clinical practice and evaluating the results of genetic tests with the goal to better characterize the association between genes and epilepsies and to further understand the mechanisms of underlying epilepsy. The variant c.-17C>G, in 5-UTR of ALDH7A1 and c.1436G>A (p.Arg479Gln) in exon 14 of SLC6A1 gene are mutations classified as a mutations with unknown clinical meaning. The presence of variants with unknown clinical meaning should not be neglected and should not affect the clinical course and treatment.

Key words: epilepsy, genes, ALDH7A1, SLC6A1mutation

INTRODUCTION

Epilepsy is one of the most common neurologic disorders, affecting 1% of the population of which about one-third of patients have refractory epilepsy (i.e., seizures not controlled by two or more appropriately chosen antiepileptic medications) and approximately 75% of epilepsy begins during childhood, regarding the susceptibility of the developing brain to seizures. With the development of genetic technology, an increasing number of genes associated with epilepsy are identified. These discoveries will improve diagnosis and treatment of epilepsy and provide the basis for including genetic tests in clinical practice. Researchers found 977 genes that are associated with epilepsy and classified these genes into 4 categories according to the manifestation of epilepsy in phenotypes and found 84 genes that are considered as epilepsy genes (genes that cause epilepsies or syndromes with epilepsy as the core symptom), 73 genes as neurodevelopment-associated genes (genes associated with both brain-development malformations and epilepsy) and several genes (536) that were epilepsy-related (genes associated with both physical or other systemic abnormalities and epilepsy or seizures). They also reported 284 additional genes putatively associated with epilepsy that requires further verification.

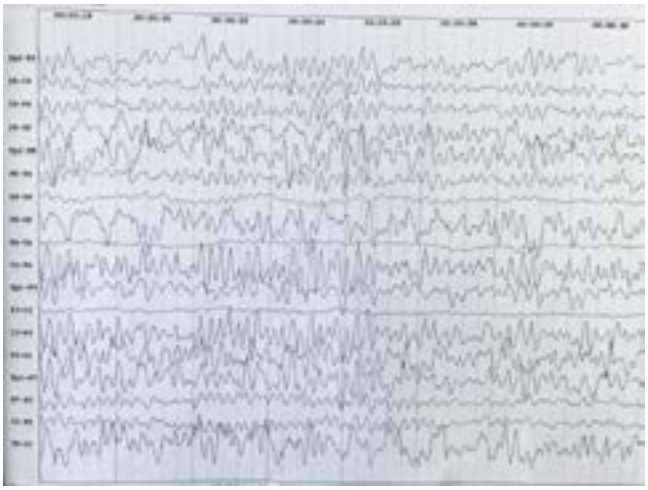
We report cases of epilepsy in two sisters with heterozygous ALDH7A1 and SLC6A1 gene mutations. Mutations in the ALDH7A1 gene, encoding β-aminoadipic semialdehyde dehydrogenase have been reported to cause Pyridoxine dependent epilepsy (PDE) in most patients. PDE is a rare autosomal recessive neurometabolic disorder characterized by intractable seizures in neonates

and infants. In the classical form, seizures are observed within the first month of life, while in the atypical form seizures appear later in life, sometimes as late as at the age of 3 years of life. Both types of seizures cannot be controlled with conventional anticonvulsant therapy, but respond both clinically and electrographically to large daily supplements of pyridoxine (vitamin B6). This enzyme converts β-aminoadipic semialdehyde (β-AASA) into β-aminoadipate (AAA), a critical step in the lysine metabolism of the brain. ALDH7A1 dysfunction causes an accumulation of β-AASA and β1-piperideine-6-carboxylic acid (P6C), which are in equilibrium with each other. P6C binds and inactivates pyridoxal 5'-phosphate (PLP), the active form of pyridoxine. Pipecolic acid (PA) and AASA are markedly elevated in urine, plasma, and cerebrospinal fluid (CSF) and thus can be used as biomarkers of the disease. SLC6A1 (The Solute Carrier Family 6 Member 1) encodes the gamma-aminobutyric acid (GABA) transporter 1 (GAT-1), which is one of the major GABA transporters in the brain and is responsible for re-uptake of GABA from the synapse. GABA is the most important inhibitory neurotransmitter in the central nervous system and its alterations are involved in the pathogenesis of epilepsy. The clinical picture of SLC6A1 gene mutations is characterized by a broader spectrum including a mild-to-moderate intellectual disability, speech difficulties, behavioral problems (such as hyperactivity, attention deficit, aggressiveness, and autistic traits), epilepsy (often with myoclonic-atonic and atypical absence seizures, characterizing a myoclonic-atonic epilepsy), and neurological signs (ataxia or unsteady gait, hypotonia, tremor, and fine-motor impairment).

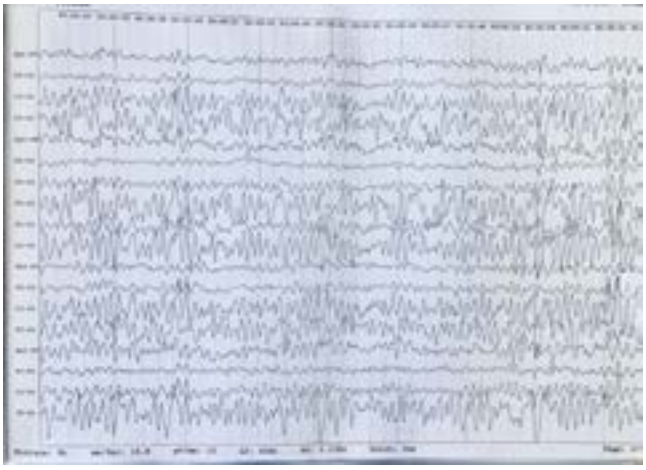
Aim: Including genetic tests in the clinical practice and evaluating the results of genetic tests with the goal to better characterize the association between genes and epilepsies and to further understand the mechanisms of underlying epilepsy.

CASE DESCRIPTION

Here, we report family cases of epilepsy with genetic mutations in two sisters, meaning, a three years old girl (patient 1) with normal development and episodes of seizures that appeared at the age of 13 months and her sister (patient 2), 6 years old with a normal development and episodes of seizures that appeared at the age of 9 months. There is a positive familiar history of epilepsy from their mother. Electroencephalography (EEG) in patient 1 (shown in picture 1) revealed alpha rhythm, symmetric sleep waves and high voltage slow waves temporal, occipital and parietal with spike wave complexes in both hemispheres, while in patient 2 it showed bihemispheric foci of spike wave complexes and high voltage slow waves temporal, central, occipital and parietal and spike waves (shown in picture 2).

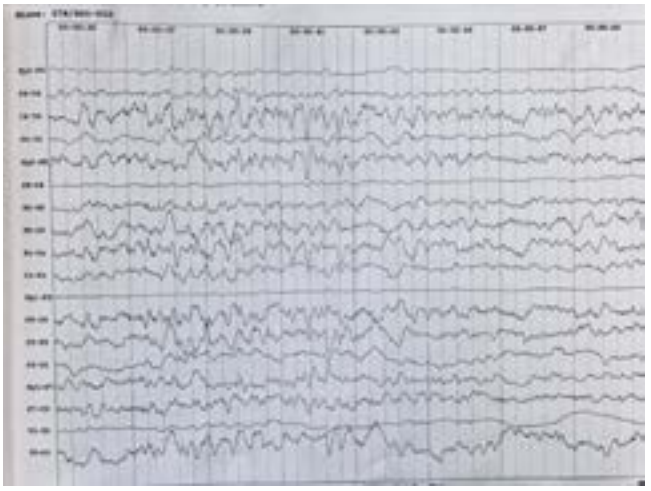


Picture 1: EEG of patient 1 before treatment

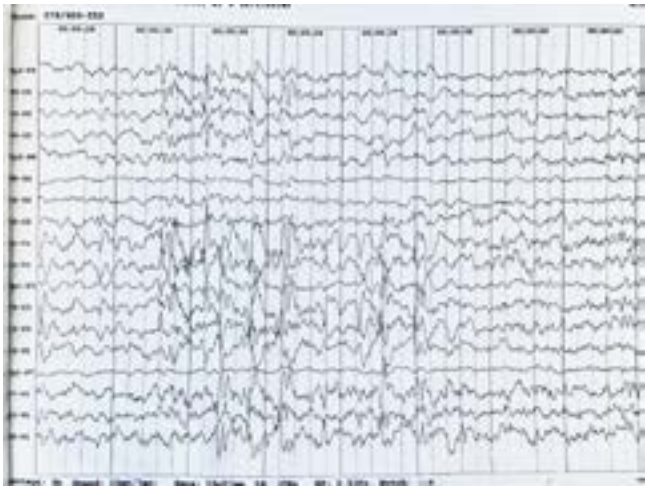


Picture 2: EEG of patient 2 before treatment

Magnetic resonance scan of the brain in both of them showed normal findings. Antiepileptic treatment with valproic acid was started in both of them and the seizures were controlled thereafter. Follow-up EEG in patient 1 revealed EEG in stabilization with a right-sides focus of spike wave complex (shown in picture 3), and in patient 2 it revealed bihemispheric foci of spike wave complexes (shown in picture 4).



Picture 3: follow-up EEG of patient 1



Picture 4: follow-up EEG of patient 2

By targeted resection of 4800 clinically significant genes, heterozygous mutations in ALDH7A1 (c.-17C>G) and SLC6A1 (c.1436G>A) genes were found in patient 1 and patient 2, as well as in their mother, changes with unknown clinical significance. Nowadays they are free of seizures and in antiepileptic therapy with valproic acid that is in reduction.

CONCLUSION AND DISCUSSION

Genetic tests are important to be included in the clinical practice of epilepsies. Evaluating the results of genetic tests is the goal to better characterize the association between genes and epilepsies and to further understand the mechanisms of underlying epilepsy. A genetic-first approach to inherited disorders is often challenged by determining the pathogenic nature of novel variants. Although several researchers reported EEG characteristics of PDE patients, no specific pattern of EEG abnormalities has been documented.

Mutations in SLC6A1 seem to occur specifically in individuals presenting with myoclonic atonic epilepsy (MAE). Most patients carrying pathogenic SLC6A1 variants have a MAE phenotype with language delay and mild/moderate intellectual disability before epilepsy onset, which is not the case here.

The variant c.-17C>G, in 5-UTR of ALDH7A1 gene is an unknown variant for causing a disorder of the normal translation of mRNA in ALDH7A1 gene. This mutation has not been reported in literature and is not present in database of pathogenic mutations in ALDH7A1 gene. This mutation has two contradictory criteria for classification, one which shows that this change is rare and is not found in the database and another, showing that this change is benign. Therefore, it has been classified as a variant with unknown clinical meaning.

The variant c.1436G>A(p.Arg479Gln) in exon 14 of SLC6A1 gene is a missense mutation causing exchange of arginine in position 479 with glutamine. This mutation has not been reported in literature and is not found in the database of pathogenic mutations of SLC6A1 gene. Therefore, this change is classified as a mutation with unknown clinical meaning.

The genetic findings showed that mutations with unknown clinical meaning, ALDH7A1 c.-17C>G and SLC6A1 c.1436G>A, were found in heterozygous form in patient 1 and 2 as well as their mother. The presence of variants with unknown clinical meaning should not be neglected and should not affect the clinical course and treatment.

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SPLENECTOMY FOR MASSIVE SPLENOMEGALY IN PATIENT WITH STEROID-REFRACTORY AUTOIMMUNE HEMOLYTIC ANEMIA–CASE RAPORT

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ABSTRACT

Introduction: Splenomegaly is a common finding in multiple diseases; however, massive enlargement of the spleen is seen in few conditions such as chronic myeloid leukemia, lymphomas, autoimmune hemolytic anemia, infectious and infiltrative conditions. Massive splenomegaly is indicated by spleen weight exceeding 1000 g and largest spleen dimension greater than 20 cm. The most common hematologic indications for splenectomy are immune thrombocytopenia purpura, hereditary spherocytosis, and autoimmune hemolytic anemia. Therapy is guided by the severity of the hemolysis, with first-line treatment being corticosteroids. In nonresponders, second-line therapy such as splenectomy should be considered and can lead to good short and long term results

Case presentation: We present a case of 29 year old female patient who was admitted at our institution with massive splenomegaly with autoimmune hemolytic anemia refractory to corticosteroids. Physical examination revealed cushingoid appearance, a pale conjunctiva, icteric sclera, and splenomegaly with spleen extension to the pelvic brim. Laboratory findings revealed normocytic anemia with low hemoglobin level. CT of the abdomen and pelvis revealed an enlarged spleen (22 cm by 13 cm). Left subcostal incision revealed massive splenomegaly and the open splenectomy was performed. The exctracted specimen measured 23cm in cranio-caudal diameter and was weighing 1250 g. She was discharged from the hospital on the fifth postoperative day in good overall condition and normal blood count. Three months after surgery she is disease free, taking no medications and has normal blood count.

Conclusion: Splenectomy is definitive treatment for massive splenomegaly and treatment of choice as second-line therapy for steroid refractory autoimmune hemolytic anemia.

Key words: splenectomy, massive splenomegaly, hemolytic anemia

INTRODUCTION

Splenomegaly is a common finding in multiple diseases; however, massive enlargement of the spleen is seen in few conditions such as chronic myeloid leukemia, lymphomas, autoimmune hemolytic anemia, infectious and infiltrative conditions1,2. Normal spleen size is considered with splenic length up to 13 cm and weight up to 300 g. Massive splenomegaly is indicated by spleen weight exceeding 1000 g and largest spleen dimension greater than 20 cm3.

The most common hematologic indications for splenectomy are immune thrombocytopenia purpura, hereditary spherocytosis, and autoimmune hemolytic anemia which is characterized by the development of immunoglobulin G (IgG) and/or IgM anti-erythrocyte autoantibodies and the destruction of erythrocytes, which causes moderate or severe anemia4.

Autoimmune hemolytic anemia (AIHA) is estimated to occur in 1 per 100,000 per year, with a prevalence of 17 per 100,0005. Both warm and cold antibodies have been reported. Warm antibodies react best at 98.6°F (37°C), account for the approximately 70% of cases, and are mainly due to IgG4. The presentation of warm AIHA is variable and includes vague constitutional symptoms consistent with anemia, such as weakness and dizziness. Symptoms vary with the severity of the hemolysis. Mild jaundice is often present and splenomegaly is seen in approximately half of cases. More than 95% of patients with warm AIHA have a positive Coombs test (direct antiglobulin test)5

Therapy is guided by the severity of the hemolysis, with first-line treatment being corticosteroids6. Approximately 80% of patients have a partial or complete response to steroids. In nonresponders or those requiring maintenance steroid dose greater than 10 to 15 mg of prednisone daily, second-line therapy should be considered. These options include splenectomy or rituximab, a monoclonal antibody against CD20 found on the surface of B cells.

Splenectomy can lead to good short-term results, with early response in approximately 70% of patients and cure in 20% to 60%.7,8 The first splenectomy for autoimmune hemolytic anemia (AIHA) was performed in 1911 by Micheli, thus stimulating the application of splenectomy for hematologic disease9. LS is now the gold standard for elective splenectomy in patients with normal-sized spleens, but hand-assisted and open splenectomy are an alternative of the laparoscopic approach in cases with massive splenomegaly, with spleens greater than 22 cm in craniocaudal length or 19 cm in width10.

CASE PRESENTATION

We present a case of 29 year old female patient who was admitted at our institution with massive splenomegaly and anemia with main complaint of fatigue, followed by night sweats, shortness of breath, left-upper-quadrant fullness, early satiety and generalized weakness. The patient was in her usual state of health until approximately 6 months before admission, when diagnosis of autoimmune hemolytic anemia with negative direct Coombs' test for IgG and complement was established. She was initially treated with iron supplementation, vitamin B12 and corticosteroids, starting with prednisone and continuing with dexamethasone 16 mg per day. Despite high doses of steroids she was refractory to treatment and constantly requiring blood transfusion up to 2 units per week in the last 3 months. Due to planed splenectomy, she received polyvalent vaccines against encapsulated organisms a week before.

Physical examination revealed cushingoid appearance, a pale conjunctiva, icteric sclera, and splenomegaly with spleen extension to the pelvic brim, with no evidence of systemic lymphadenopathy. Laboratory findings revealed normocytic anemia with hemoglobin level 7,3 g/dL, red blood cell count 2.95 x1012/ml, iron level 3.3 g/dl and hematocrit 0.27. Computed tomography (CT) of the chest, abdomen, and pelvis, performed after the intravenous administration of contrast material, revealed an enlarged spleen (22 cm by 13 cm). She was taken to the operation room with two units of blood received the day before surgery. Left subcostal incision revealed massive splenomegaly and the open splenectomy was performed. The exctracted specimen measured 23cm in cranio-caudal diameter and was weighing 1250 g. The postoperative course went without any surgical complication. During postoperative course she continued receiving corticosteroids with lower doses, 8 mg per day and started receiving low molecular heparin. She was discharged from the hospital on the fifth postoperative day in good overall condition and normal blood count. Histopathology, besides congestion, hypertrophy and zones of colliquative necrosis, did not revealed other underlying pathologies in spleen. A month after surgery she discontinued corticosteroids and three months after she is disease free, taking no medications and has normal

blood count.

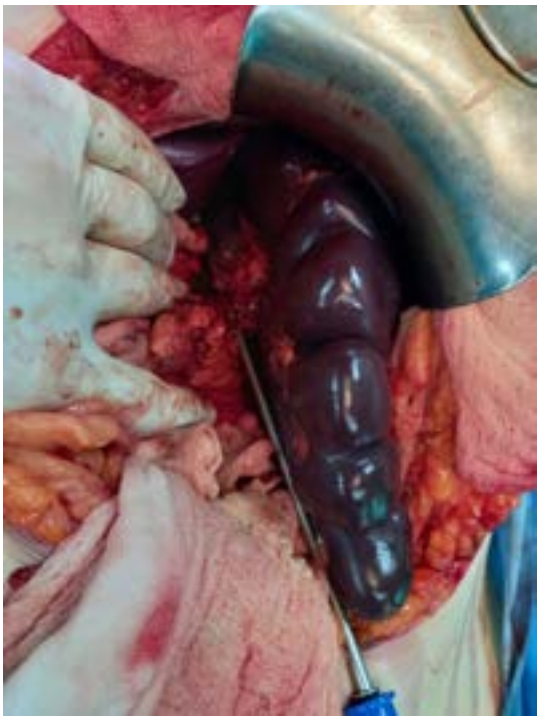

Figure 1. Intraoperative finding

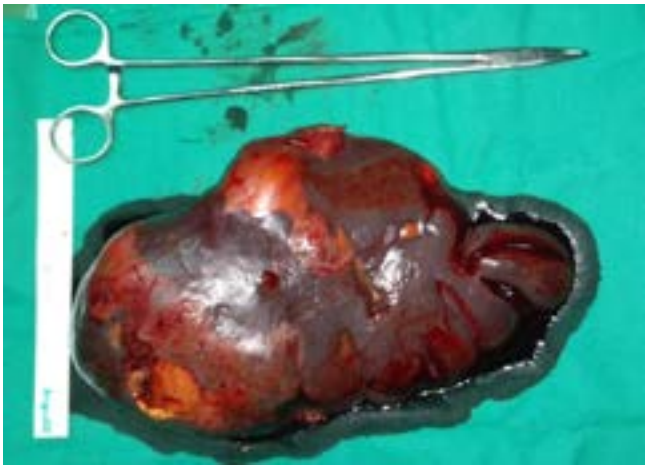

Figure 2. Extracted specimen measuring 23 cm in cranio-caudal diameter and weighing 1250 g

DISCUSSION

Although corticosteroids represent the first-line treatment for patients with autoimmune hemolytic anemia, approximately 30% of patients require second-line treatment. A second-line treatment is the definite treatment for underlying disease. Currently, splenectomy can be regarded as the most effective and best-evaluated second-line therapy5.

In experienced hands, a laparoscopic approach for normal size spleen is preferred over open surgery, with lower blood loss, lower or similar morbidity, and lower hospital stay,11,12,13 but it should be appreciated that splenomegaly cases are considerably more challenging than for normal-sized spleens. Several studies document increased risks associated with conventional laparoscopy in the setting of splenomegaly (>1000 g)9. Challenges with large spleens include difficulties manipulating and moving the large organ, perisplenic adhesions and inflammation, large collateral vessels, reduced surgical space, and difficulties with extraction of the specimen. Laparoscopic splenectomy for splenomegaly has longer operative time, increased blood loss, higher risk of conversion to open splenectomy, increased postoperative length of stay, and higher postoperative morbidity when compared to splenectomy for smaller spleens.14,15.

Conversion rates to open splenectomy start to increase with a spleen size of greater than 22 or 23 cm,16 and patients converted for complications likely suffer poorer outcomes than patients who undergo a controlled open operation. Splenic length >20 cm is a reasonable measure of anticipated difficulty, and a hand-assisted approach or open surgery for these patients is appropriate, depending on available expertise17,18. That's the reason that we "a priori" decided to use the open approach.

The major concern after splenectomy is overwhelming postsplenectomy infections (OPSI), defined as rapidly evolving sepsis, meningitis, or pneumonia caused by S pneumoniae, Haemophilus influenzae type B, and Neisseria meningitides19, with a high mortality rate of 40% to 50%.20,21. Patients undergoing splenectomy or partial splenectomy should be vaccinated against encapsulated organisms with recombinant polyvalent S pneumoniae, H influenzae type B, and N meningitides vaccines22.

CONCLUSION

Splenectomy is definitive treatment for massive splenomegaly and treatment of choice as second-line therapy for steroid refractory autoimmune hemolytic anemia. Open or laparoscopic splenectomy is feasible and reliable procedure with low complication rates.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article

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Articles to be published in *Medicus* will be **peer-reviewed**. The editorial board will take into account the reviewer's comments and may then promt the author for changes or further work.

Numri i faqeve (përfshirë tabelat dhe/ose figurat/ ilustrimet) varet nga lloji i artikullit:

punim origjinal hulumtues –deri ne12 faqe dhe jo më shumë se 6 tabela dhe/ose grafikone/fotografi;

punim profesional ose punim revyal – deri ne 8 faqe dhe jo më shumë se 4 tabela dhe/ose figura/imazhe;

prezantim rasti apo kumtesë e shkurtër – deri 6 faqe dhe maksimum 3 tabela dhe/ose figura/imazhe.

Letër redaksisë - deri 2 faqe

Së bashku me dorëshkrimin, dorëzoni një faqe me **titullin** e artikullit; **emrin/at e autorit/ve**, duke përfshirë emrin me jo më shumë se dy tituj shkencor; emrin e departamentit dhe institucionit në të cilin është bërë punimi; institucioni ku punon (për secilin autor); si dhe emri dhe adresa e autorit të cilit do ti adresohen kërkesat nga ana e Redaksisë (shihni Informacionet plotësuese për autorët)

Abstrakti duhet te jete me jo më shumë se 250 fjalë. Duhet të konsistojë në katër paragrafë, i klasifikuar në Hyrje, Metodat, Rezultatet dhe Diskutimi (Përfundimet). Ato duhet të përshkruhen shkurt, respektivisht, problem qenësor i studimit, se si është kryer studimi, rezultatet e fituara, dhe perfundimi.

Tabelat, figurat dhe legjendat (shihni Informacionet plotësuese për autorët)

Fjalët kyqe -Tri deri pesë flaje apo fraza te shkurtëra duhet t'i shtohen pjesës së fundme të faqes së abstraktit.

Citatet e referencave në tekst duhet fillimisht të jenë nga revistat e indeksuara në **PubMed**. Stili i referencave që kërkohet nga Medicus është i formatit Vancouver (shihni Informacionet plotësuese për autorët).

Shkurtimet (**akronimet**) përdoren për njësitë matëse, kurse në raste tjera kur përmendet për herë të parë, ai duhet të jetë i sqaruar me fjalën bazë bashkangjitur.

Për të gjitha barnat duhet të përdoren **emrat gjenerik** ndërkombëtar. Nëse në hulumtim janë të përdorura brendet e patentuara, përfshini emrin e brendit në kllapa në paragrafin e Metodave.

Dorëshkrimi i dërguar tek botuesi duhet të shënohet nga autorët , nëse janë në seksionin e "punimeve origjinale shkencore" apo në pjeset tjera përmbajtesore të revistës.

Autorët marrin dy kopje të botimit përkatës.

The number of pages (including tables and/or figures/ illustrations) is dependent upon the type of the article:

original research paper - up to 12 pages and no more than 6 tables and / or graphs / pictures;

professional or review paper - up to 8 pages and no more than 4 tables and / or figures / images;

case report or brief communication - up to 6 pages and a maximum of 3 tables and / or figures/images.

Leter up to 2 pages

With the manuscript, provide a page giving the title of the paper; the name(s) of the author(s), including the first name(s) and no more than two graduate degrees; the name of the department and institution in which the work was done; the institutional affiliation of each author; and the name and address of the author to whom reprint requests should be addressed. (see Additional Information for Authors)

Provide an **abstract** of not more than 250 words. It should consist of four paragraphs, labeled Backround, Methods, Results and Conclusions. They should briefly describe, respectively, the problem being in the study, how the study was performed, the salient results, and what the authors conclude from the results.

Tables, figures and legends (see Additional Information for Authors)

Three to five **key words** or short phrases should be added to the bottom of the abstract page.

Quotations of references in the text should primarily be from journals indexed in **PubMed** which have proven their significance. The style of references required by **Medicus** is the Vancouver format (see Additional Information for Authors).

Except for units of measurement, abbreviations are discouraged. The first time an abbreviation appears it should be preceded by the words for which it stands.

The international **generic names** should be used for all drugs. When proprietary brands are used in research, include the brand name in parentheses in the Methods section.

All manuscript sent to the editor should be noted by the authors whether they are meant for the "original research papers" section or the rest of the journal's content.

The authors receive two copies of the relevant issue.

Informacione plotësuese për autorët

I. Faqja e parë – *ballina*: Duhet të përmbajë: (a) titullin e punimit, të shkurtër, por informativ; (b) emri, inicialet e emrit të mesëm dhe mbiemrit të secilit autor; (c) institucioni; (d) emri i departamentit që i atribuohet punës shkencore; (e) emri dhe adresa e autorit për t'iu përgjigjur në lidhje me dorëshkrimin; (f) burimi/përkrahja në formë të granteve, paisjeve, barnave dhe në përgjithësi.

II. Faqja e dytë – *abstrakti dhe fjalët kyqe*: Abstrakti duhet të shkruhet me maksimum prej 150 fjalësh për abstraktet e pastrukturuara, dhe me 250 fjalë për abstraktet e strukturuara (pjesët përmbajtësore: objekti/ete studimit ose hulumtimit, procedurat bazë, siç është përzgjedhja e subjekteve apo kafshët laboratorike, metodat vrojtuese dhe analitike, pastaj, rezultatet/gjetjet përfundimtare (të dhënat dhe rëndësia e tyre statistikore, nëse është e mundur), dhe konkluzionet kryesore. Vini theksin mbi aspektet e reja dhe të rëndësishme të studimit apo vrojtimit. Nën abstraktin indentifikoni dhe shkruani fjalët kyqe: 3-5 fjalë apo fraza të shkurtëra që do të ndihmojnë në paisjen me tregues të punimit dhe publikimit të abstraktit. Përdorni terme nga lista e Index Medikus për Nëntituj Mjekësor (Medical Sub-Headings [MeSH]); nëse nuk ka term të përshtatshëm në MeSH për disa terme të reja, mund të përdorni termet e dhëna.

III. Faqja e tretë dhe të tjerat – *teksti i plotë i artikullit*: Teksti i plotë I artikujve hulumtues ose vrojtues normalisht, por jo domosdoshmërisht, duhet të jetë i ndarë në paragraf me këta nëntituj: hyrja, metodat dhe materialet, rezultatet dhe diskutimi.

1. Hyrja: Krijoni një kontekst apo prapavijë(trualli) të studimit (që në fakt është natyra e problemit dhe rëndësia e tij). Për të bërë këtë duhet të bëni një hulumtim të literaturës – duke kërkuar, gjetur dhe lexuar punimet përkatëse, që duhet të jenë si referencë në dorëshkrimin tuaj. Sqaroni hipotezat tuaja dhe planifikoni t'i testoni ato, si dhe përshkruani qëllimet tuaja. Kini qëndrim të qartë se çka prisni të gjeni dhe arsyet që ju udhëhoqën tek hipotezat që keni krijuar. Objekti i hulumtimit më së shpeshti fokusohet kur parashtrohet si pyetje. Mos përfshini të dhëna apo rezultate nga puna që do të raportohet.

2. Metodat & Materialet: Ky paragraf duhet të përfshijë atë informacion që ishte në dispozicion në kohën që plani apo protokoli i studimit po shkruhej. Të gjitha informacionet e marra gjatë studimit i takojnë paragrafit të Rezultateve.

Përshkruani përzgjedhjen tuaj të pjesëmarrësve së vrojtimit ose eksperimentit (pacientët ose kafshët laboratorike, përfshirë kontrollat) qartë, duke përfshirë kriteret e përshtatshme (inkluzive) dhe përjashtuese (ekskluzive).

Parimi udhëheqës duhet të jetë i qartë se si dhe pse studimi është bërë në një mënyrë të caktuar. Jepni detaje të mjaftueshme për metodat, mjetet dhe materialet (jepni emrin dhe adresën e prodhuesit në kllapa), dhe procedurat për të lejuar të tjerët të kuptojnë dhe riprodhojnë rezultatet tuaja.

Nëse një metodë e caktuar që është përdorur është e njohur, atëherë nuk është e nevojshme të jepet përshkrim komplet i saj. Mund t'i referoheni punimit në të cilin së pari herë është përshkruar dhe të

Additional Information for Authors

I. First page - *front page*: It should contain: (a) title of paper, a short, but informative; (b) the first name, initials of middle name and last name of each author; (c) the institution; (d) the name of the department that is attributable to the scientific work; (e) the name and address of the author with whom to correspond about the manuscript (f) source/support in the form of grants, equipment, drugs, or all.

II. Second page - *abstract and keywords*: The abstract should be written with a maximum of 150 words for unstructured abstracts and 250 words for structured abstracts (containing parts: objective(s) of study or research, basic procedures, such as selection of subjects or laboratory animals, observational and analytical methods, then, the main findings/results (data and their statistical significance, if possible), and the main conclusions. Emphasize the new and important aspects of the study or observation.

Below the abstract identify and write the keywords: 35 words or short phrases that will assist in indexing the paper and publication of the abstract.

Use terms from the list of Index Medicus for Medical Sub-Headings (MeSH); if there is no appropriate MeSH term for some newly introduced terms, we can use the given terms.

III. Third and further pages – *full text of the article*: The full text of research or observational articles should normally be, but not necessarily, divided into sections with the following headings: introduction, material and methods, results and discussion.

1. Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). To do this you must complete a literature review – searching for, finding and reading relevant papers, which must be referenced in your manuscript. Explain your hypotheses and the plan to test them, and describe your aims. Clearly state what you expect to find and the reasoning that led you to the hypotheses that you have made. The research objective is often more sharply focused when stated as a question. Do not include data or conclusions from the work being reported.

2. Methods & Material: This section should include only information that was available at the time the plan or protocol for the study was being written. All information obtained during the study belongs in the Results section.

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria.The guiding principle should be clarity about how and why a study was done in a particular way.

Give sufficient details of the methods, apparatus and materials (give the manufacturer's name and address in parentheses), and procedures to allow others to understand and reproduce your results.

If a particular method used is well known then there is no need to give a complete description. You can reference the paper in

përmendni ndonjë modifikim/ndryshim që keni bërë. Jepni arsyet për përdorimin e tyre dhe vlerësoni kufizimet e tyre. Në fund, përshkruani se si i keni analizuar të dhënat tuaja, duke përfshirë metodat statistikore dhe pakon programore që keni përdorur.

Autorët e doreshkrimeve të rishqyrtuara duhet të përfshijnë një paragraf që përshkruajnë metodat që kanë përdorur për lokalizimin, përzgjedhjen, ekstrahimin dhe sintetizimin e të dhënave. Përdorni formën joveprore të foljes, në vetën e tretë, kur dokumentoni metodat, gjë që do të fokusonte vëmendjen e lexuesit tek puna që është bërë e jo tek hulumtuesi (P.sh. Janë marrë, janë realizuar, janë prezantuar etj.)

2. a) Statistikat: Përshkruani metodat statistikore me detaje të mjaftueshme për t'ia mundësuar një lexuesi me njohje në atë fushë t'i qaset të dhënave origjinale për të verifikuar rezultatet e raportuara. Kur është e mundur, përcaktoni sasinë e zbulimeve dhe prezantoni ato me indikatorë përkatës të gabimeve në matje apo pasiguri (siç janë inter-valet e besueshmërisë). Evitoni mbështetjen vetëm në testet statistikore të hipotezave, siç janë vlerat p, që dështojnë të transmetojnë informacion të rëndësishëm mbi madhësinë e efektit. Jepni detaje rreth përzgjedhjes së rasteve (randomizimi) dhe përshkruani metodat dhe sukseset e vro¬jtimit gjatë realizimit të studimeve të verbuara. Definoni termet statis¬tikore, shkurtesat dhe më së shumti simbolet. Specifikoni programin kompjuterik që është përdorur.

3. Rezultatet: Ky paragraf duhet t'i bëjë gjetjet tuaja të qarta. Prezantoni rezultatet tuaja në rend logjik në tekst, tabela dhe ilustrime, duke dhënë së pari rezultatet kryesore ose më të rëndësishme. Mos i përsërisni të gjitha të dhënat në tabela apo ilustrime, në tekst. Nënvizoni ose përm-bledhni shkurtimisht vetëm vrojtimet më të rëndësishme.

Kur të dhënat përmblidhen në paragrafin e Rezultateve, jepni rezultate numerike jo vetëm si derivate (për shembull, përqindja) por gjithashtu si numra absolut nga të cilët derivatet janë llogaritur, dhe specifikoni metodat statistikore që janë përdorur për t'i analizuar ato.

Kufizoni tabelat dhe figurat në aq sa janë të nevojshme për të sqaruar argumentin e punimit dhe për të vlerësuar të dhënat ndihmëse. Duke përdorur grafikonet për të reprezentuar të dhënat tuaja si alternativë e tabelave, do të rrisë kuptueshmërinë e lexuesit. Mos i dyfishoni të dhënat në grafikone dhe tabela. Duhet të jeni të qartë se cili lloj i grafikoneve është i përshtatshëm për informacionet tuaja. Për shembull, për të reprezentuar korelimin mes dy ndryshoreve, preferohet grafiku vijëzor, krahasuar me grafikun rrethor apo në formë shtyllash.

Sa i përket të gjitha paragrafeve, qartësia dhe të qënit i thuktë është kyçe. Mos prezantoni të njëjtat të dhëna më shumë se një herë. Kufizojeni veten në të dhënat që ndihmojnë në adresimin e hipotezave tuaja. Kjo është e rëndësishme edhe nëse të dhënat i aprovojnë ose nuk i pranojnë ato. Nëse keni bërë analiza statistikore, duhet të jepni vlerën e proba¬bilitetit (p) dhe të tregoni se është shprehës (sinjig në nivelin që ju po testoni. Varësisht nga analizat e përdorura, gjithashtu mund të jetë e rëndësishme të jepni intervalet e besueshmërisë së rezultateve (Confidence Interval –

which it was first described and mentioned any modifications you have made. Give the reasons for using them, and evaluate their limitations. Finally,, describe how you analysed your data, including the statistical methods and software package used.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

Use the third person passive voice when documenting methods which would focus the readers' attention on the work rather than the investigator.(e.g. Were taken, was performed, were presented itd.)

2. a) Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as p values, which fail to convey important information about effect size. Give details about the randomization and describe the methods and success of observations while using blinded trials. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

3. Results: This section should make your findings clear. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text. Emphasize or summarize only the most important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.

Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Using graphs to represent your data as an alternative to tables will improve the reader's understanding. Do not duplicate data in graphs and tables. You need to be clear what type of graphs is suitable for your information. For example, to represent the correlation between two variables, a line graph is preferred to a pie chart or a bar chart.

As with all sections, clarity and conciseness is vital. Don't present the same data more than once. Restrict yourself to the data that helps to address your hypotheses. This is important whether the data supports or disproves them. If you have carried out a statistical analysis, you should give the probability (P) value and state it is significant at the level you are testing. Depending on the analysis used, it may also be important to give the confidence intervals of the results, or the statistical parameters such as the odds ratios. Provide a caption for each figure making the gen¬eral meaning clear without reference to the main text, but don't discuss the results. Let the readers decide for themselves what they think of the data. Your chance to say what you think comes next, in the discussion.

3. Tables: Each table should be inserted at the point of the text where they have to be placed logically, typed by the same rules

CI), ose parametrat statistikorë si proporcionet e rastit (odds ratio). Bëni përshkrimin tek secila figurë duke bërë të qartë domethënien e përgjithshme pa referencë në tekstin kryesorë, por mos diskutoni rezultatet në të. Lëreni lexuesin të vendosë vetë se çfarë men-don për të dhënat. Mundësia juaj për të thënë se çfarë mendoni, është në vazhdim, tek diskutimi.

3. Tabelat: Secila tabelë duhet të vendoset në vendin e tekstit ku duhet të vihet logjikisht, e plotësuar me të njëjtat rregulla sikur teksti i plotë. Mos i dërgoni tabelat si fotografi. Secila tabelë duhet të citohet në tekst. Tabelat duhet të jenë me numra ashtu që të jenë në koordinim me refer-encat e cituara në tekst. Shkruani një përshkrim të shkurtë të tabelës nën titullin. Çdo sqarim shtesë, legjendë ose sqarim i shkurtesave jostan¬darde, duhet të vendoset menjëherë poshtë tabelës.

4. Diskutimi: Ky paragraf është pjesa ku ju mund të interpretoni të dhë-nat tuaja dhe të diskutoni duke ballafaquar dhe krahasuar gjetjet tuaja me ato të hulumtuesve të mëparshëm. Rishikoni referencat e literaturës dhe shihni nëse mund të përfundoni se si të dhënat tuaja përkojnë me atë që keni gjetur.

Ju gjithashtu duhet të llogarisni rezultatet, duke u fokusuar në mekaniz¬mat në prapavij të vrojtimit. Diskutoni nëse rezultatet tuaja mbështesin hipotezat tuaja origjinale. Gjetjet negative janë aq të rëndësishme në zhvillimin e ideve të ardhshme sikur gjetjet pozitive.

E rëndësishme është se, nuk ka rezultate të këqija. Shkenca nuk të bëjë me të drejtën dhe të gabuarën, por merret me zgjerimin e njohjeve të reja.

Diskutoni si janë paraqitur gabimet në studimin tuaj dhe çfarë hapa keni ndërmarrë për të minimizuar ato, kështu duke treguar se ju çmoni ku¬fizimet e punës tuaj dhe fuqinë e përfundimeve tuaja. Duhet gjithashtu të merrni në konsideratë ndërlikimet e gjetjeve për hulumtimet në të ardhmen dhe për praktikën klinike. Lidhni përfundimet me qëllimet e studimit, por evitoni qëndrimet dhe përfundimet e pakualifikuara, që nuk mbështeten në mënyrë adekuate nga të dhënat. Shmangni prioritetet deklarative apo të aludoni në punën që nuk është krahasuar.

5. Referencimi: Referencat janë baza mbi të cilën është ndërtuar raporti juaj. Shqyrtimi i literaturës dhe leximi i referencave gjithmonë duhet të jetë pikë fillestare e projektit tuaj. Ky paragraf duhet të jetë i saktë dhe të përfshijë të gjitha burimet e informacionit që keni përdorur.

Në formatin " Vancouver" , referencat numërohen një nga një, sikur që shfaqen në tekst dhe identifikohen me numra në bibliografi..

Një punim mund të ketë më së shumti një autor dhe 4 koautor. Koautori i fundit duhet të jetë mentori ose koautori më i afëërt me punimin. Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

Referencat e librave duhet të jepen sipas emrit të autorit, titulli i librit (mund të citohet edhe titulli i kapitullit para titullit), vendi i botimit, botuesi dhe viti.

as for the full text. Do not send tables as photographs. Each table should be cited in the text.Tables should be numbered so that they will be in sequence with references cited in the text. Provide a brief explanation of the table below the title. Any additional explanations, legends or explanations of non¬standard abbreviations, should be placed immediately below the table.

4. Discussion: This section is where you interpret your data and discuss how your findings compare with those of previous researchers. Go over the references of your literature review and see if you can determine how your data fits with what you have found.

You also need to account for the results, focusing on the mechanisms be¬hind the observation. Discuss whether or not your results support your original hypotheses. Negative findings are just as important to the de¬velopment of future ideas as the positive ones.

Importantly, there are not bad results. Science is not about right or wrong but about the continuing development of knowledge.

Discuss how errors may have been introduced into your study and what steps you took to minimise them, thus showing that you appreciate the limitations of your work and the strength of your conclusions. You should also consider the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. Avoid claiming priority or alluding to work that has not been compared.

5. Referencing: The references are the foundation on which your report is built. Literature searches and reading of references should always be the starting point of your project. This section must be accurate and in¬clude all the sources of information you used.

In the Vancouver format, references are numbered consecutively as they appear in the text and are identified in the bibliography by numerals.

One article can have one author and 4 co-author. Last co-author is the mentor of the article or closest co-author of the paper." The authors' namer are fol-lowed by the title of the article; the title of the journal abbreviated ac-cording to the style of Index Medicus; the year of publication; the volume number; and the first and last page numbers.

References to books should give the names of any editors, place of publication, editor, and year.

In the text, reference numbers are given in superscript. Notice that issue number is omitted if there is continuous pagination through¬out a volume, there is space between volume number and page numbers, page numbers are in elided form (51-4 rather than 51-54) and the name of journal or book is in italics.The following is a sample reference:

Në tekst, numrat e referencave jepen me indeks të sipërm. Vëreni se çështja e numrave neglizhohet nëse ka numërtim të vazhdueshëm përg¬jatë gjithë vëllimit, ka hapësirë mes numrit të vëllimit dhe numrit të faqes, numrat e faqeve janë në këtë formë: 51-4 në vend të 51-54, dhe emri i revistës ose librit është në italic. Në vazhdim është një shembull i referencës:

Artikujt e revistave:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. *N Engl J Med* 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. *BMJ* 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. *Lancet* 1997;349: 1498-504.

Librat dhe tekste tjera:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. *National service framework for coronary heart disease*. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Kamberi A, Kondili A, Goda A, dhe bp; *Udhërrëfyes i shkurtër i Shoqatës Shqiptare të Kardiologjisë për parandalimin e Sëmundjes Aterosklerotike Kardiovaskulare në praktikën klinike*, Tiranë, 2006
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Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papub-likuara" dhe "komunikime personale". Referencat e pranueshme, por ende të papublikuara lejohet të merren, vetëm nëse shënoni se janë "në shtyp".

6. Mirënjohjet: Ju mund të keni dëshirë të falënderoni njerëzit që ju kanë ndihmuar. Këto mund të rangohen prej atyre që ju kanë përkrahur me teknika eksperimentale deri tek ata që ju kanë këshilluar deri në bër¬jen e dorëshkrimit final.

7. Formati i fajllit të të dhënave për **ilustrimet** (**figurat**): JPG

Nëse përdoren fotografitë e pacientëve, qoftë subjekti, qoftë fotografitë e tyre nuk duhet të jenë të identifikuara, ato duhet të shoqërohen me lejen e shkruar nga ta për përdorimin e figurës. Format e lejuara janë në dispozicion nga redaksia.

Nëse fajllet e të dhënave janë shumë të mëdha për t'u dërguar me e-mail, rekomandohet dërgimi me CD në adresën tonë.

8. Legjendat për Ilustrimet (Figurat)

Legjenda e tabelës duhet të vendoset mbi tabelë. Referenca e një tabeleje, e cila është marrë nga ndonjë publikim tjetër, duhet të vendoset poshtë tabelës. (Është përgjegjësi e autorit të sigurojë lejen e ribotimit nga botuesit e atij botimi) Legjenda e figurës duhet të vendoset në fund të faqes. Referenca e figurës e marrë nga ndonjë tjetër publikim vendoset në fund të legjendës. (Leja e ribotimit duhet të sigurohet nga botuesi i këtij botimi).

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Avoid using as references abstracts; "unpublished data" and "personal communications". References to accepted but yet unpublished articles are allowed to be made, only if you note "in press".

6. Acknowledgements: You may wish to acknowledge people who have helped you. These can range from those who supported you with exper¬imental techniques to those who read or offered advice on your final manuscript.

7. Data file format for **illustrations** (**figures**): JPG

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permis-sion to use the figure. Permission forms are available from the Editor.

If data files are too big for transmission as an Email attachment submis¬sion of a CD to our address is recommended.

8. Legends for Illustrations (Figures)

The legend of a table has to be placed above the table. The reference of a table, which has been taken from another publication, must be placed below the table. (It is the author's responsibility to obtain the permission of reproduction from the publishers of the publication.) Figure legends are to be placed at the end of the paper. The reference of a figure taken from another publication stands at the end of the legend. (Permission of reproduction must be obtained from the publishers of this publication).