Intracerebral Hemorrhage and Epileptic Seizures: Frequency, Localization and Seizures Types

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Original article

ML28133 -A MULTICENTER, OPEN-LABEL, LONG-TERM EXTENSION STUDY OF WA 19926 TO DESCRIBE SAFETY DURING TREATMENT WITH TOCILIZUMAB IN PATIENTS WITH EARLY, MODERATE TO SEVERE RHEUMATOID ARTHRITIS

ML28133 "МУЛТИЦЕНТРИЧНА,ОТВОРЕНА, СТУДИЈА ВО ЕДНА ГРАНКА, ПРОДОЛЖЕНИЕ НА WA19926 ЗА СЛЕДЕЊЕ НА БЕЗБЕДНОСТА ПРИ ЛЕКУВАЊЕ СО ТОЦИЛИЗУМАБ КАЈ ПАЦИЕНТИ СО РАН, УМЕРЕН ДО ТЕЖОК ОБЛИК НА РЕВМАТОИДЕН АРТРИТИС"

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Abstract

Introduction. Biologic DMARDs (Disease Modifying Anti Rheumatic Drugs) have shown to be effective in the treatment of rheumatoid arthritis (RA) resistant to the use of synthetic DMARDs. The primary goal of this study wasto assess the long-term safety of the use of tocilizumab in patients with early rheumatoid arthritis, moderate to severe disease activity. The secondary goal was to assess the efficiency of tocilizumab in achieving and maintaining clinical remission of the disease.

Methods. ML28133 is a long-term, extended study of 13 patients with rheumatoid arthritis treated with tocilizumab. Two patients were male (15.4%), 11(84.61%) female. The average age of patients was 53.27+/-10.68. Patients received 8mg/kg tocilizumab i.v. every four weeks, 104 weeks overall. Safety was assessed following side effects, blood tests, physical examination and vital signs. Efficiency was assessed by achieving and maintaining clinical remission according to DAS28 (Disease Activity Score 28), global assessment of disease activity, VAS score and HAQ-DI (Health Activity Score) questionnaire.

Results. Incidence of side effects was 76.92%. Infections were of special interest and were most common (15.3%). Four patients had serious adverse events, three of which associated with tocilizumab, and therapy was stopped. In 11 (84.6%) of the 13 treated patients clinical remission was achieved at times. At the end of the study, 8 out of 9 patients were in remission.

Conclusion. The results have shown significant therapeutic effect of tocilizumab even in the most severe forms of the disease, which gives hope for its use as a monotherapy.

Keywords: rheumatoid arthritis, tocilizumab, safety, adverse effects, efficiency

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Апстракт

Вовед. Биолошките DMARDs лекови (Disease Modifying Anti Rheumatic Drugs) се покажаа многу ефикасни во третманот на ревматоидниот артритис (RA), резистентен на синтетските DMARDs лекови. Примарна цел на студијата беше процена на долгорочната безбедност на терапијата со тоцилизумаб, кај пациенти со ран, умерен и со тежок ревматоиден артритис. Секундарна цел, процена на ефикасност на лекот, дефинирана со постигнување и одржување клиничка ремисија на болеста.

Методи. Во ML28133 долгорочна, продолжена студија-13 пациенти со ревматоиден артритис беа лекувани со тоцилизумаб. Двајца испитаници беа мажи (15.4%) и 11 жени (84.61%), со просечна возраст од 53.27±10.68. Пациентите примаа 8мг/кг тоцилизумаб iv, на секои четири недели, вкупно 104 недели. Безбедноста беше проценета со следење несакани настани, крвни анализи, физикален статус, витални знаци. Ефикасноста е проценета со постигнување и одржување клиничка ремисија со DAS28-ESR (Disease Activity Score28), глобална процена на активноста на болеста, со VAS скор, HAQ-DI (Health assessment questionnaire) прашалник.

Резултати. Инциденца на пријавени несакани настани, поврзани со лекот беше 76.92%. Инфекции од посебен интерес беа најчести (15.3%), при што четири пациенти беа со сериозни несакани настани, три од нив поврзани со лекот, што беше причина за прекинување на терапијата. Кај 11 (84.6%), од вкупно 13, третирани со тоцилизумаб е постигната клиничка ремисија во одредени визити во студијата. На крајот од студијата, во ремисија беа осум, од девет пациенти.

Заклучок. Добиените резултати, претежно се од терапискиот бенефит на лекот, и кај најтешка форма на болеста влеваат голема надеж и можност за давање на лекот како монотерапија.

Клучни зборови: ревматоиден артритис, тоцилизумаб, безбедност, несакани настани, ефикасност

Introduction

Rheumatoid arthritis (RA) is a multisystem, autoimmune disease characterized by peripheral synovitis. The natural course of the disease leads to disability. Long standing chronic synovitis leads to structural changes in the joints, deformities and malfunctioning leading to disability [1]. The use of an intensive treatment strategy is especially important in patients with aggressive disease and the presence of factors indicating difficult prognosis [2-4]. The treatment should be tailored to achieving remission or low disease activity quickly according to the recommendations (EULAR 2013). Biologic DMARDs (Disease Modifying Anti Rheumatic Drugs) specifically attack the molecules in the cascade of the inflammatory response and interfere with it. They calm the inflammation, the synovial hyperplasy, degeneration and degradation of the cartilage and the destruction of the subchondral bone and joints. They have been shown to be very effective in the treatment of rheumatoid arthritis, in the early forms of the disease, as well as in patients with developed disease and severe disease activity resistant to the standard treatment with synthetic DMARDs.

Tocilizumab (Actemra) is a first-line biologic agent for treatment of adult patients with moderate to severely active rheumatoid arthritis [5,9]. It can be used as a monotherapy, or in combination with methotrexate or other synthetic DMARDs [10,18]. Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6) receptor monoclonal antibody from the IgG1 subclass. It is the first biologic drug to specifically inhibit interleukin-6, a very important proinflammatory cytokine in the pathogenesis of RA. The drug connects to the membrane and soluble receptors for IL-6 and inhibits its action. It blocks signal transmission and cell activation through IL-6. Interleukin-6 is a proinflammatory cytokine which regulates many processes in the development of the autoimmune rheumatoid inflammation. It is associated with disease activity, as well as systemic manifestations of RA such as anaemia, osteoporosis and increased risk for cardiovascular diseases. Locally, in the joint itself, IL-6 is found in high concentrations in the rheumatoid synovium and actively supports the process leading to joint damage. IL-6 is the main stimulator in the producion of acute phase proteins such as C-reactive protein (CRP) and serum amyloid alpha [2]. Besides the multiple proinflammatory effects, CRP is an independent predictor of increased cardiovascular risk in patients with RA [1]. High levels of IL-6 contribute to anemia. Blocking its receptor leads to significant improvements in the signs and symptoms of the disease.

Aims

The primary aim of this study wasto evaluate the long-term safety of TCZ therapy in patients who had completed the WA19926 corestudy (a multicentric, randomized, double-blind study of parallel groups evaluating the safety, disease remission and the prevention of structural joint damage in patients treated with tocilizumab as a monotherapy, or in combination with methotrexate, compared to methotrexate monotherapy in patients with early rheumatoid arthritis, with medium to severe disease activity) and may have ben efited from TCZ treatment.

The secondary aims were to assess efficacy of TCZ overtime using end point ssuchas clinical remission based on the DAS28-ESR, total tender joint count (TJC) and total swollen joint count (SJC) andto assess sustained drug-free remission via DAS28-ESR remission criteria.

Materials and methods

This was a Phase III, open-label, single arm, multicenter, long-term extension study. The study population consisted of 17 enrolled patients, previously treated with TCZ, withearly, moderate to severe rheumatoid arthritis (RA) from 1 center at the University Clinic of Rheumatology in Skopje, Macedonia. Inclusion criteria were: patients who were able and willing to provide a written informed consent and to comply with the requirements of the study protocol, were aged >18 years, patients who completed WA19926 core study (visit at Week 104 and 2 follow-uptelephone visits) and who may have benefited from study medication according to theinvestigator's assessment, no current or recent adverse event (AE) or laboratory finding preventing the use of the study medication dose of TCZ 8 mg/kg at screening, receiving treatment on an outpatient basis; for women who were not postmenopausal (12 months of amenorrhea) or surgicallysterile (absence of ovaries and/or uterus), agreement was required to use at least 1 adequate method of contraception, including at least 1 method with a failure rate of < 1% per year (e.g., hormonal implants, combined oral contraceptives, vasectomized partner), during the treatment period, while females of childbearing potential must have had a negative serum pregnancy test at screening.

Exclusion criteria: females who were pregnant, patients who had prematurely withdrawn from the WA19926 core study for any reason, treatment with any investigational agent or cell-depleting therapies since the last administration of study medication in the WA19926 core study, treatment with an anti-tumor necrosis factor or anti-interleukin (IL) 1 agent, or a T-cellco-stimulation modu-

lator since the last administration of study medication in the WA19926 core study, immunization with a live/ attenuated vaccine since the last administration of the study drug in the WA19926 core study, diagnosis since visit at Week 104 of the core WA19926 study of rheumatic autoimmune disease other than rheumatoid arthritis (RA), including systemic lupuserythematosus, mixed connective tissue disease, scleroderma, and polymyositis, or significantsystemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis or Felty' ssyndrome). Secondary Sjögren's syndrome and/or nodulosis with RA were permitted, diagnosis since visit at Week 104 of the core WA19926 study of inflammatory jointdisease other than RA (e.g., gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease), laboratory parameters at screening period:aspartate aminotransferase (AST) or alanine aminotransferase (ALT)1.5 timesupper limit of normal (ULN), total bilirubin >ULN, absolute neutrophil count <1000/mm3 (1x109/L), platelet count <100,000/mm3 (100x109/L), history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or hypersensitivity to TCZ (the active substance or to any of the excipients), evidence of serious uncontrolled concomitant cardiovascular, nervous system, pulmonary (including obstructive pulmonary disease), renal, hepatic, endocrine (including uncontrolled diabetes mellitus), immunologic or gastrointestinal (GI) disease; history ofdiverticulitis, diverticulosis requiring antibiotic treatment or chronic ulcerative lower GI diseasesuch as Crohn's disease, ulcerative colitis or other symptomatic lower GI conditions that mightpredispose to perforations for whom a favorable benefit/risk assessment for study continuation could not be documented, known active or history of recurrent bacterial, viral, fungal, mycobacterial or otherinfections (including but not limited to tuberculosis (TB) and atypical mycobacterial disease, clinically significant abnormalities on chest X-ray as determined by the investigator, humanimmunodeficiency virus [HIV], hepatitis B [hepatitis B surface antigen {HBsAg} and total hepatitis B core antibody {HBcAb}] and hepatitis C virus [HCV] antibody and Herpes zoster, but excluding fungal infections of nail beds), or any major episode of infection requiring hospitalization or treatment with intravenous (IV) antibiotics within 4 weeks prior to baseline ororal antibiotics within 2 weeks prior to baseline, evidence of active malignant disease, malignancies diagnosed within the previous 10years (including hematological malignancies and solid tumors, except basal cell carcinoma ofthe skin that had been excised and cured), or breast cancer diagnosed within the previous 20 years, uncontrolled disease states, such as asthma or inflammatory bowel disease whereflares were commonly treated with oral or parenteral corticosteroids, current liver disease as determined by the investigator, active TB requiring treatment within the previous 3 years. Patients were required to bescreened for latent TB following local practice guidelines and should not have been admittedto the study if latent TB was detected. Patients should have had no evidence of active TB infection at enrollment. Patients treated for TB with no recurrence in 3 years were permitted.

There were 17 patients enrolled, with 13(76.47%) treated with TCZ (3 patients with a history of infection or active infection and one patient with latent TB).

Demographic and disease characteristics at baseline were consistent with the patient population andthe requirements of the study protocol. Of the enrolled patients 2(15.4%) were male and 11(84.6%) were female. The mean (standard deviation [SD]) age of all patients in the intent-to-treat (ITT) population. Population was 53.27 (10.68) years with a range of 32 to 72 years. Majority of patients belongs in group 18 to 64 year (92.3%), and 1 patient belongs in the age group 65 to 72 years (7.7%).

A detailed physical examination was conducted in all patients (cardiovascular, pulmonary, abdominal, neurological, head, neck, extremities, lymph nodes, skin, musculosceletal system) at baseline and on weeks 12, 24, 56, 80 and at the end of the study. Vital signs (heart rate, systolic and diastolic blood pressure), body temperature, laboratory testing including hematologic tests (hemoglobin, hematocrit, erythrocyte, leukocyte, neutrophil, basophil, eosinophil, lymphocyte count, platelets, erythrocyte sedimentation rate, MCV, MCH, MCHC), bloot tests (AST, ALT, ALP, the highly sensitive CRP, total proteins, albumin, LDL, HDL, total cholesterol, urea, creatinine, uric acid, sodium, potassium, chloride, calcium, phosphorus, triglycerides), urine analysis (for potential presence of protein, blood or sugar) were done at baseline and on weeks 12, 36, 48, 56, 80, 92 and at the end of the study. All data were analyzed electornically in the eCRF.

The effect of the therapy with tocilizumab was assessed through the changes of DAS28-ESR, total number of tender joints and total number of swollen joints; the percent of patients who achieved clinical remission according to DAS28-ESR <2.6 in two following visits (every 12 weeks); physicians global assessment of disease activity with visual analogue score (VAS) scale; patient global assessment of disease activitywith visual analogue score (VAS) scale; pain assessment with visual analogue score (VAS) scale; health assessment questionnaire (HAQ). All of these parameters were assessed with the same dynamic as the vital signs, lab tests, meaning at baseline and on weeks 12, 36, 48, 56, 80, 92 and at the end of the study.

Eligible patients, who met all inclusion criteria, received an IV infusion of 8 mg/kg TCZ(maximum of 800mg for patients over 100kg) every 4 weekson an outpatient basis for a total of 104 weeks (with two phone controls at weeks 108 and 112). Dose modifications of TCZ were allowed for safety reasons, which was done in two

patients because of viral infections. A concomitantnon-biologicdisease-modify in gantirheumatic drug (DMARD) could be added atany visitatthe investigator's discretion and as tolerated by the patient. Of all ITT patients (13), 11 patients (84.61%) reported at least 1 concomitant background medication. There were 11(84.61%) patients who received concomitant DMARDs, 12(92.30%) MTX, 5(38.46%) patients who received non-steroidal anti-inflammatory drugs (NSAIDs)and 2(15.38%) patients who received corticosteroids. The most frequently reported concomitant medications were methotrexate (92.30%) and folic acid(76.9%). Two (2) patients (15.38%) reported at least 1 prior medication. It was 1 NSAIDs (ketoprofen) and onefolic acid.

Safety was assessed using the ITT Population and by reporting of adverse events (AEs) with special emphasison infections and other AE sofspecial interest, clinical laboratory results, and physical examination including vital signs. Adverse events were summarized by intensity and by relationship to study drug. The primary safety outcome measures were as follows: incidence and severity of AEs, incidence and severity of serious adverse effects (SAEs), incidence and severity of Aes of specialinterest (AESIs) including: infections including all opportunistic infection sand non-serious infections as defined by those treated with IV anti-infective drugs, myocardial infarction/acute coronary syndrome, gastroin-testinal perforation sandrelated events, malignancies, anaphylaxis/hypersensitivity reactions, demyelinating disorders, stroke, bleeding events, hepatic events, rates of Aes leading to dose modification or study with drawal, incidence of clinically significant laboratory abnormalities. All safety data were reported regarding all patients enrolled inthe study and who received at least 1 TCZ dose during the study. A total of 13 patients were reportedin this population.

For statistical analysis we used nonparametric statistical tests (Friedman test, Kruskal Wallistest, Spearman's correlation test). Baseline was defined as the day of first TCZ dose in the study. Statistical signification was on level $p<0.05$, $p<0.01$ and $p<0.001$. Changes in parameters were analyzed by nonparametric Friedman test (for differences between morethan two times periods). For analysis of differences between two periods Wilcoxon test was performed. Categorical data were analyzed by Chi-square and Fisher's exact test, as appropriate. In all tests, p value <0.05 was considered to be statistically significant.For laboratory test data (N), mean, standard deviation, median, minimum, maximum was reported, whereas for qualitative variables absolute and relative frequency distribution was described. The incidence of clinically significant laboratory adverse effects, death or discontinuation of treatment were reported with percents. The incidence of adverse effects was taken from the total number of patients with a particular adverse effect divided by the number of years treated (number of patients/patient years).

Results

ML28133 is a local study to evaluate the long-term safety of tocilizumab in patients who have successfully completed the WA19926 study and had benefited from the treatment. A total of 17 patients were screened and enrolled for the study of whom 13(76.47%) were treated withTCZ and included in the Population. Of the 4 patients who were screening failures anddid not receive treatment, 3 were due to active (or known history of) recurrent bacterial, viral, fungal, mycobacterial or other infections and 1 had active tuberculosis treatment. About half of treated patients (10[58.82%]) completed the study according to the protocol. Of the 3(23.07%) patients who did not completethe study, the primary reason was an adverse event (patient ID 3 hadtumor on right ovarium, patient ID 13 had thrombocytopenia and patinet ID 16 had paronychia). Threepatientshad temporary discontinuation because of an adverse event (patient ID 1-bronchopneumonia, patent ID 2-rhino-rrhea and nasopharyngeal inflammation and patient ID 7-tonsillopharyngitis). Aftertemporary termination, all of thesepatients returned to the study.

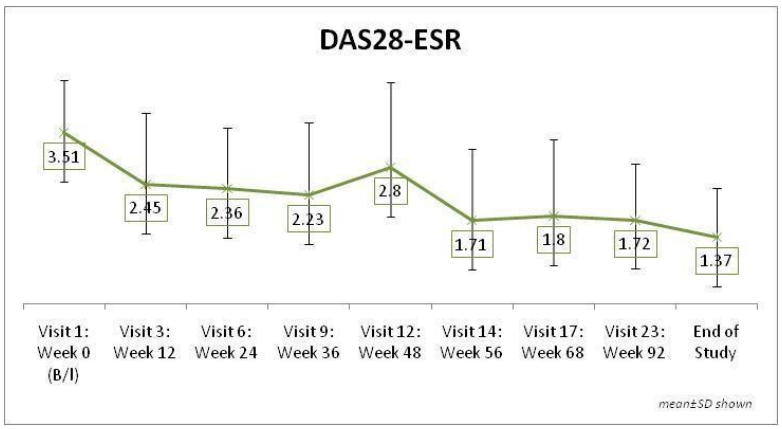

Fig 1. Mean DAS28-ESR scores by visit (ITT Population)

At screening, 5(38.46%) patientsreported a previous or ongoing clinically significant medicalcondition other than RA. These patientshad 6 clinically significant previous or concomitant diseases. Two (33.33%) of theseevents has resolvedstatus, while 4(66.66%) are ongoing with treatment.At baseline, the mean (SD) DAS28-ESR, total TJC, and total SJC valueswere: 3.51 (1.09), 5.38 (4.62),and 2.1 (2.30), respectively. The mean values across all 3 measures were numerically lower thanbaseline (indica- ting improvement) at all subsequent visits from Week 4. At the end of the study the mean(SD) DAS28-ESR, total TJC, and total SJC valueswere: 1.37 (1.01), 2.11 (4.59), and 0.0 (0.0), 19 respectively (Table 6). This change is statistically significant ($p<0.01$). Graph shown in appendix (Figure 1).

Mean values for the changes for TJC scores in patients treated with tocilizumab in visit 1 (week 0), 3 (week 12), 6 (week 24), 9 (week 36), 12 (week 48), 14 (week 56), 17 (week 68), 23 (week 92) and at the end of the study (week 104) were 2.15, 1.08, 1.08, 1.0, 0.91, 0.58, 0.44, 0.56 and 0 respectively, showing a significant decrease of the number of swollen joints. At the end of the study all patients were without swollen joints.

DAS28-ESR was categorized according to the EULAR criteria defining the therapeutical response using the DAS28 index:

Range	Remission	Low	Moderate	High
0-9.4	<2.6	≥2.6-<3.2	≥3.2-≤5.1	>5.1

The mean values of the DAS28-ESR measures were continually numerically lower than baseline (indicating improvement) at all subsequent visits from Week 4 (Figure 2), showing disease suppression by the medication.

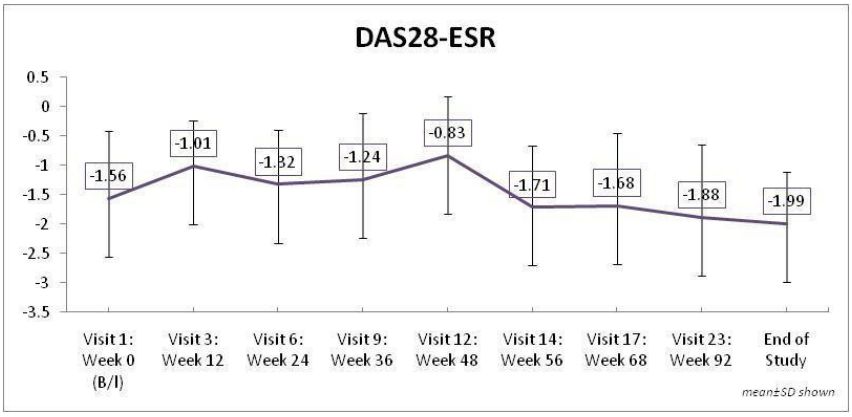

Fig 2. Mean changes of DAS28-ESR scores from baseline

There were 11 patients (84.6%) who achieved clinical remission at any time during the study, definedas DAS28-ESR <2.6. At baseline, 2 patients (16.6%) had achieved clinical remission, rising to 8patients (88.9%) at the end of the study. After 4 weeks the number of patients in remissionjumped from 2 (16.6%) to 8 (66.6%) (Figure 3).

At baseline, the mean (SD) PGA of disease activity, patient's global assessment (PtGA) of disease activity and Patient's Assessment of Pain VAS values were 24.30 (13.04), 30.15 (13.95) and 29.69 (13.99), respectively. The mean values across all 3 measures were numerically lower than baseline (indicating improvement) at all subsequent visits from Week 4. This change is statistically significant ($p<0.01$).

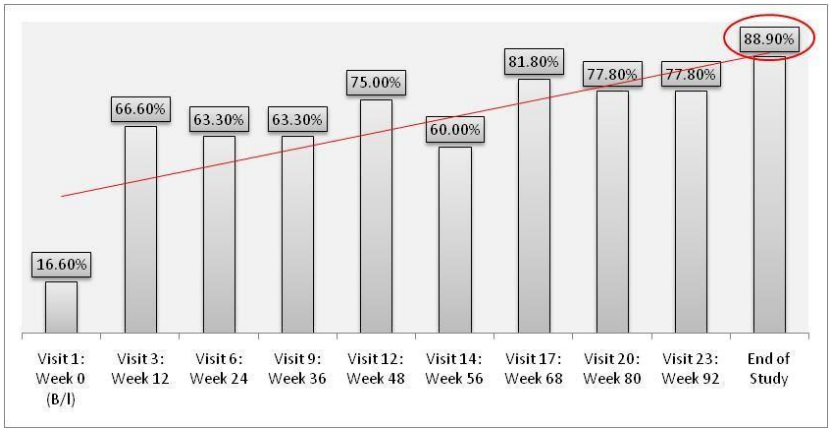

Fig 3. Summary of clinical remission by visit (ITT Population)

At baseline, the mean (SD) HAQ-DI was 0.43 (0.43). The mean value was lower across all subsequent visits. This change is statistically significant ($p<0.01$).

All enrolled patients received 8 mg/kg tocilizumab. Two patients required dose modification, thereason forboth patients being AEs (virosis). In case of 2 patientswith body weight above 100 kg, 800 mg tocilizumab was administered in line withthe provisions of the study protocol.

Overall, 10 patients (76.92%) experienced 16 events during the study. The mean number of AEs perpatient was (M±SD) (1.60±1.26). Maximum number of AEs experienced by one patient was5 AEs. Onepatient had AEs of ovarian tumor as a severe intensity AEs, all other AEs were mild or moderate inintensity. There were 6 patients (46.15%) who experienced 7 AEs that were considered remotely, possibly, orprobably related to TCZ. There were 9 unrelated AEs.There were no

Table 1. Overallsummaryofadverseevents (ITT Population)n/totalpatients

	n/total patients (%)	n Events
Any AEs	10/13 (76.92%)	16
RelatedAEs	6/13 (46.15%)	7
SAEs	4/13 (30.76%)	4
Related SAEs	3/13 (23.07%)	3
Severe AEs	1/13 (7.69%)	1
Related Severe AEs	1/13 (7.69%)	1
AEs of Special Interest	2/13 (15.38%)	3
Infections	2/13 (15.38%)	2
Myocardial Infarction/Acute Coronary Syndrome	0/13 (0.00%)	0
Gastrointestinal Perforations and Related Events	1/13 (7.69%)	1
Malignancies	0/13 (0.00%)	0
Anaphylaxis/Hypersensitivity Reactions	0/13 (0.00%)	0
Demyelinating Disorders	0/13 (0.00%)	0
Stroke	0/13 (0.00%)	0
Bleeding Events	0/13 (0.00%)	0
Hepatic Events	0/13 (0.00%)	0
Related AEs of Special Interest	2/13 (15.38%)	3
SAEs of Special Interest	2/13 (15.38%)	2
AEs Leading to Dosage Modification	2/13 (15.38%)	2
Related AE Leading to Dosage Modification	0/13 (0.00%)	0
Withdrawn from Study Due to AEs	1/13 (7.69%)	1

Abbreviations: AE=adverse event, ITT=Intent-to-Treat, N=number of patients in group, n=number of events, SAE=serious adverseevent

Table 2. Summary of all adverse (ITT Population) events?

SOC/ PT	n/total patients (%)	n Events
Infections and infestations	5/13 (38.46%)	8
Tonsillitis	1/13 (7.69%)	1
Virosis	2/13 (15.38%)	2
Tonsillopharyngitis	2/13 (15.38)	2
Bronchopneumonia	1/13 (7.69%)	1
Paronychia	1/13 (7.69%)	2
Gastrointestinal signs and symptoms	1/13 (7.69%)	1
Unknown* (Chronic gastritis, reflux esophagitis gr. A)	1/13 (7.69%)	1
Vomiting	1/13 (7.69%)	1
Respiratory, thoracic and mediastinal disorders	1/13 (7.69%)	1
Rhinorrhea	1/13 (7.69%)	1
Reproductive system and breast disorders	1/13 (7.69%)	1
Ovarian tumors	1/13 (7.69%)	1
Investigations	1/13 (7.69%)	3
Blood triglycerides increased	1/13 (7.69%)	1
Blood cholesterol increased	1/13 (7.69%)	1
Thrombocytopenia	1/13 (7.69%)	1
Injury, poisoning and procedural complications	1/13 (7.69%)	1
Traumatic fracture	1/13 (7.69%)	1

Abbreviations: AE=adverse event, ITT=Intent-to-Treat, N=number of patients in group, n=number of events, SAE=serious adverse, SOC=system organ class, PT=preferred term
*Unknown-patient had AE with "unknown" name in database, classified as "Gastrointestinal Perforations and Related Events". Afterinvestigation of patient file, investigator confirmed that respected AI is chronic gastritis, reflux esophagitis gr. A (Documented in NTF from 13-Sep-2016)

deaths, life-threatening AEs. There was one SAEs possibly related to TCZ.Two (2) patients had 2 AEs, which led to dosage modification. Six (6) patients had 7 AEs, which led todiscontinuation of drug administration. Three (3) patients had temporary discontinuation and three (3) permanent discontinuation. Theprimary reason why 3 (23.07%) patients permanently discontinued the study was an adverse event (patient ID 3 had tumor on right ovarium, patient ID 13 had thrombocytopenia and patinet ID 16 had paronychia). In three patientswho had temporary discontinuation the reason was also an adverse event (1-bronchopneumonia, 2-rhinorrhea and nasopharyngeal inflammation and 3-tonsillopharyngitis). After temporarydiscontinuation, all 3 patients returned to the study treatment. There were no mortalities during the study. None of the AEs led to discontinuation of the medication application. There were no vitally dangerous AEs. There was only one possible SAE associated with tocilizumab (Table 1 and Table 2).
Investigators rated initial intensity of adverse events as moderate in 4(25.00%) cases and mild in 12 cases (75.00%). The intensity of AEs was: mild 11 (68.75%), moderate 4 (25.00%) andsevere 1 (6.25%) of all AEs.
Regarding laboratory tests, 1 patient (7.69%) had elevated triglyceride levels, 1(7.69%) had elevated cholesterol and 1(7.69%) had thrombocytopenia.

Discussion

The primary goal of this study was to evaluate the safety of tocilizumab used for a long time period, in patients who had completed the basic WA 19926 study and who had benefited from the treatment. The secondary goals were to assess the efficacy of tocilizumab, using clinical remission of the disease as defined by the Disease Activity Index 28 with erythrocyte sedimentation rate (DAS28-ESR), total number of tender joints (TJC), total number of swollen joints (SJC) and the assessment of remission persistence using the DAS28 criteria. All patients recruited were diagnosed with rheumatoid arthritis and had moderate to severe disease activity without a satisfactory response to synthetic DMARDs, at a single center at the University Clinic of Rheumatology in Skopje, Macedonia. Patients were treated with tocilizumab i.v. 8mg/kg every 4 weeks. A total of 17 patients were considered for participation in the study, of whom 13 were included, having satisfied the inclusion criteria. Of the 4 patients that were not included, 3 had active (or a history of repetitive) infections, and one was being actively treated for tuberculosis. The safety of tocilizumab was assessed with a special accent on following potential infections, serious adverse effects and events of special significance associated with the study medication. The incidence of adverse effects was 46.15%. Out of all adverse effects, infections were the most common (15.3%). Four patients had serious adverse events (SAEs). Three of these were associated with the tested drug (pneumonia, ovarian tumor, paronychia). All three had stopped the treatment, two permanently. A serious adverse event was reported in a single patient. There were no deaths or life-threatening events. Two patients (15.3%) had a total of 3 adverse effects of interest, two of which were infections and one with chronic gastritis with esophagial reflux gradus A. To assess the safety of the drug, laboratory tests, physical examinations, EKG recordings, tuberculosis testing, chest x-rays, data regarding admission to hospital/death were used. The mean value of the data collected to assess the efficacy of tocilizubam, such as DAS28-ESR, TJC and SJC showed significant improvement compared to baseline after the week 12 visit (visit 4) in all three measurments ($p< 0.05$). Of the 13 treated patients, 11(84.6%) had achieved clinical remission in certain visits during the study. At the last visit, 8 out of the 9 remaining patients were in remission (DAS28-ESR<2.6).
Tocilizumab (Actemra) is a first-line biologic agent for treatment of adult patients with moderate to severely active rheumatoid arthritis. It can be used as a monotherapy, or in combination with methotrexate or other synthetic DMARDs [4,5]. Tocilizumab was registered in Macedonia in 2009 [5] as it was in Europe, but it was used for the first time in 2008 in Japan. It is the first biologic drug which specifically inhibits the actions of interleukin-6 (IL-6), an important proinflammatory cytokine in the pathogenesis of RA [7].
Tocilizumab is used at a dose of 8mg/kg of body weight in an intravenous infusion, in duration of one hour. Premedication is not needed. The infusion is repeated every 4 weeks.
Searcing the literature showed that over 4000 patients were included in clinical developmental programs before the official registering of the medication. They confirm that the inhibition of the IL-6 receptor with tocilizumab results in significant clinical improvement and a clear benefit for patients with RA and a stable safety profile. Tocilizumab was studied as a monotherapy in patients previously not treated with methotrexate (AMBITION) [13], in combination with methotrexate in patients with an inadequate response to DMARDs (OPTION, TOWARD and LITHE) [14,15], and in patients with an inadequate reponse to anti-TNF therapy (RADIATE) [16]. Tociluzumab was proven to be effective in all three investigated groups, used as a monotherapy or in combination with methotrexate or other synthetic DMARDs in treatment of patients with an inadequate response to synthetic DMARDs or TNF antagonists. Time to effect of the clinical response to tocilizumab is fast and is seen after just 2 weeks of application, and the magnitude of the effect increases with the increase of the time treated. Treatment with tocilizumab at the dose of 8mg/kg shows powerful inhibition of joint damage. Tocilizumab is an approved biologic agent with proven superiority compared to methotrexate in

monotherapy for 6 months in patients with RA with moderate to severe disease activity [18,19]. This therapy also provides a clinical remission which is stable and the effect improves with every following application according to the DAS28-ESR. The reports from the multycentric study, phase III, with 4211 patients [19] shows that tocilizumab is generally well tolerated, most of the adverse effects are mild to moderate in severity. Of these, the most common are infections, mainly upper respiratory, such as nasopharyngitis. Pneumonia, mainly bacterial, is the most common serious adverse effect. There are reports of rare SAE, such as gastrointestinal perforation of the lower GI tract, mostly associated with infections and diverticulitis. Neutrophilia has been reported, but it is unclear whether it is associated with the medication and its dosing or with an infection.

Conclusion

Our study data has shown that the safety profile, the efficiacy and benefit of the treatment with tocilizumab, even in the most severe forms of RA resistant to previous DMARD therapy is excellent. Thus, tocilizumab provides a great and positive hope. This drug has been shown to be efficient in treating systemic manifestations of the disease. It can also be applied as a monotherapy. Data regarding the efficiency and the safety profile of this drug support the positive attitude towards the "cost-benefit"in using tocilizumab in early rheumatoid arthritis with moderate to severe disease activity.

Conflict of interest statement. None declared.

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Original article

IMPACT OF POST-TRANSPLANT DYSGLYCEMIA ON RENAL ALLOGRFAT FUNCTION IN KIDNEY TRANSPLANT RECIPIENTS ON CYCLOSPORINE- BASED IMMUNOSUPPRESSION

ВЛИЈАНИЕ НА ПОСТ-ТРАНСПЛАНТАЦИОНАТА ДИСГЛИКЕМИЈА ВРЗ ФУНКЦИЈАТА НА БУБРЕЖНИОТ АЛОГРАФТ КАЈ ПАЦИЕНТИ ПО РЕНАЛНА ТРАНСПЛАНТАЦИЈА НА ЦИКЛОСПОРИН - БАЗИРАНА ИМУНОСУПРЕСИЈА

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Abstract

Introduction. Post-transplant diabetes (PTDM), impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are common complications of immunosuppressive therapy (IT) and are associated with increased cardiovascular morbidity and impaired graft function (GF).
Methods. Fifty-nine living donor kidney transplant recipients (KTR) were included in a combined cross-sectional and 8-month-observational prospective study about the impact of impaired glucose homeostasis (IGH) on GF. All patients were on standard IT including cyclosporine A (CsA), steroids and mycophenolate mofetil (MMF). In all patients a standard oral glucose tolerans test (OGTT) was performed. Results were classified according to the criteria of the American Diabetes Association: normal-with fasting blood glucose level (FGL) <5.6, IFG with FGL of 5.6-6.9, IGT with FGL of 7.8-11.1 and DM between > 6.9 FGL and >11 mmol / l. According to the results, all patients were divaded into two groups: Group 1 with impaired and Group 2 with normal GH. GF was estimated by GFR-Cockroft Gault (CG) and by degree of proteinuria in the beginning and end of the study.
Results. Twenty of 59(33.9%) patients showed overt IGH after transplantation while the remaining 39(66.1) were normal. The principal dysglycemia in KTR were PTDM (2 patients-3.3%), IGT (18 patients-30.5%) and IFG (7 patients-11.8%). In Group 1, postprandial glucose was higher (8.1±2.3 vs 5.8±0.7), more KTR were male (70% vs 33.3%), higher CsA levels were observed (160.9±81.2 vs 115.1±59.9) and time after the surgery was shorter (24.5±21.3 vs 41.4±28.). After a follow-up period of approximately 18 months in Group 1 a significant decline in GFR (62.6-52.7 ml/min) was noted, with no significant change in proteinuria. The correlation analysis was positive between CsA level and IGH and the time after transplantation and IFG.
Conclusion. Post-transplant dysglycemia and associated metabolic abnormalities are a significant factor for the deterioration of GF. CsA higher levels are associated with the occurrence of IGH and they affect the GF.

Keywords: renal transplantation, dysglycemia, graft function

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Апстракт

Вовед. Дисгликемиските состојби во кои спаѓаат пост-трансплантацискиот дијабет (ПТДМ), нарушената гликемија на гладно (НГГ) и нарушената гликозна толеранција (НГТ) се чести неимунолошка компликација на имуносупресивната терапија и се асоцирани со зголемен кардиоваскуларен морбидитет и нарушена функција на графтот.
Методи. Во оваа опсервациона пресечна и проспективна едноцентрична студија беше испитувано можното влијание на нарушената глукозна хомеостаза врз функцијата на алографтото кај 59 пациенти поренална трансплантација од жив донор кои се на иста тројна имуносупресивна терапија во дози на одржување, без претходна историја за дијабет, и без претходни епизоди на отфралање на графтот. За процена на гликозните нарушувања беше изведен ОГТТ со 75 грама анхидрирана гликоза. Согласно резултатите пациентите беа поделени водве групи: група со дисгликемии (ДМ, НГТ, НГГ) и група без гликозни нарушувања. Функцијата на графтот беше следена преку стапката на гломеуларната филтрација (ГФР-КГ) и степенот на протеинурија на почетокот и крајот на студијата. Просечното време на следење на пациентите изнесуваше 18 месеци.
Резултати. Групата со дисгликемија (група А) ја сочинуваа 20/59 пациенти или 33.9%, а нормогликемични (група Б) беа 39/59 или 66.1%. Превален-

цата на ПТДМ, НГТ и НГГ беше 3.39% (2/59), 30.5% (18/59), 11.86 (7/59) соодветно. Во групата пациенти со дисгликемија постпрандијалните гликемии беа повисоки (8.19±2.33 vs 5.80±0.70, P <0.05), имаше повеќе реципиенти од машки пол (70% vs 33.3% P<0.05), беа нотирани повисоки нивоа на Циклоспорин (160.90±81.21 ng/ml vs 115.10±59.90 ng/ml, P<0.05), а времето по трансплантација беше пократко (24.50±21.32 vs 41.48±28.06, p<0.05). По период на следење од приближно 18 месеци во групата со дисгликемија беше нотиран сигнификантен пад на ГФР (62.64-52.77 ml/min, P<0.05), безначајна промена на протеинуријата. Корелационата анализа покажа позитивна корелација меѓу нивоата на Циклоспорин и постпрандијалните гликемии и меѓу гликемиите на гладно и времето по трансплантација.
Заклучок. Пост-трансплантационата дисгликемија и асоцираните метаболни абнормалности се значаен фактор за влошување на функцијата на графтот. Повисоките нивоа на Циклоспоринските се асоцирани со настанување на гликозните нарушувања и директно или индиректно влијаат и на влушување на бубрежната функција.

Клучнизборови: ренална трансплантација, дисгликемија, функција на графтот

Introduction

The occurrence of post-transplant diabetes and other dysglycemic conditions such as IGT are associated with increased cardiovascular morbidity and mortality [1] and may adversely affect patient and graft survival [2]. The most significant diabetogenic risk factors associated with transplantation are immunosuppressive drugs, especially use of calcineurin inhibitors (CNI-Tacrolimus, Cyclosporin A) and glucocorticoids which may cause beta cell toxicity and insulin resistance. Diabetogenic effect of Cyclosporin A (CsA) was described in the early 1980s [3].
The role of end-stage renal disease (ESRD) and dialysis in glucose homeostasis is underestimated. At first, patients with ESRD have decreased clearance of insulin [4] and it leads to compensatory increase in insulin secretion [5], which is often insufficient to achieve satisfactory glucose control resulting in a high prevalence of IGT. On the other hand, dysglycemia leads to deterioration of the graft function. It is known that any increase in postprandial glucose by 1 mmol/l leads to a 3% increase in the risk of the graft failure [6].
OGTT remains the best diagnostic test for various dysglycemic conditions and has increased sensitivity and specificity compared to fasting glucose alone in diagnosing diabetes in the general population [7].
Independent of the etiology of the underlying kidney disease, laboratory assessment of kidney function involves calculation of the estimated glomerular filtration rate (e GFR) from the serum creatinine and assessment of kidney damage by measurement of proteinuria. Proteinuria occurs commonly after kidney transplantation. Because it is often a marker of allograft damage and is a potentially modifiable risk factor, its early recognition is important. Proteinuria is an important marker of progression for non-transplant CKD. Kidney Disease Improving Global Outcomes (KDIGO) CKD guidelines define renal transplant recipients as having CKD regardless of whether the GFR is normal. The KDIGO guidelines recommend monitoring of proteinuria as part of a routine transplant follow-up (at least once within the first month after transplantation, every 3 months during the first year and annually later on) [8].
However, it has been shown that nephrotoxicity is associated with longer treatment duration, larger cumulative doses and higher daily dose of CsA [9].
The aim of this study was to determine the prevalence of post-transplant dysglycemia and the possible impact of immunosuppressive therapy on its occurrence as well as the difference in renal function in patients with and without dysglycemia after a period of follow-up.

Materials and methods

In this cross-sectional and prospective study 59 patients were examined, with mean age of 35.15±8.75 years (range 14-53) after successful living donor kidney transplantation, satisfactory graft function (mean GFR 60.55 ±13.77 ml/min), and mean period after transplantation of 35.73±27.03 months. All patients were on the same triple immunosuppressive therapy including Mycophenolate mofetil (MMF), Cyclosporine A (CsA, formulation Neoral) and Prednisolone (PRED).
Inclusion criteria were: age over 14 years, the absence of a history of DM, normal or impaired fasting glycemia before testing the glucose metabolism (OGTT), satisfactory graft function and a minimum of 6 months follow-up after surgery.
Exclusion criteria were: previous episodes of acute graft rejection, steroid use due to other comorbidities and DM occurring before testing of glucose metabolism.
All investigations in the study were done in accordance with the rules of the WHO and the Declaration of Helsinki. All patients gave an informed consent for participation in the study.
After twelve hours of fasting, OGTT was performed in all enrolled patients with 75 grams of anhydrous glucose (as recommended by the WHO). Postprandial samples were harvested 2 hours after administration of glucose. Results of the survey were classified according to the revised criteria of the American Diabetes Association (ADA): normal-with fasting blood glucose level of <5.6 mmol/l, impaired fasting glucose (IFG)-fasting blood glucose level between 5.6-6.9 mmol/l, impaired glucose tolerance (IGT)-glucose level between 7.8-11.1

mmol/l-2 hours after the load, DM->6.9 fasting glucose and >11 mmol/l-2 hours after the load.
According to the performed OGTT, patients were divided in two groups: dysglycemic group (IFG/IGT, DM) and control group of patients with normal glucose metabolism.
Glucose levels were measured in venous blood samples using glucose-oxidase method in the automatic analyzer (Beckman). CsA trough levels were determined from the same blood samples using FPIA (fluorescence polarization immunoassay) technique in an automatic analyzer (Abbott).
In order to correlate multiple factors presumably associated with pre-diabetes and diabetes we used data from the files of the patients and biochemical analyses made on the same day with OGTT. The necessary data were entered in special questionnaires including: CsA trough level, daily steroid dosage, triglyceride levels, cholesterol levels, estimated glomerular filtration rate (e-GFR-Cockcroft-Gault formula), blood pressure, gender, age, BMI, HCV infection, time after transplantation, family history of diabetes, underlying renal disease, duration of dialysis, HCV seropositivity.
In order to assess renal function in the prospective part of the study, the following parameters were observed: proteinuria/24 h, GFR, presence of HTA (defined as blood pressure over 140/90 mmHg or need for antihypertensive therapy) and body mass index (BMI).
Cockcroft-Gault equation was used as a method for estimating GFR as follows:

$$eCrCl = \frac{(140 - Age) \times Weight\ (kg)}{72 \times Creatinine_{serum\ (mg/dL)}} \times 0.85 \text{ if female}$$

Body mass index-BMI was calculated by the formula BMI=weight (kg)/height (m2).
BMI categories: underweight=<18.5, normal weight= 18.5-24.9, overweight=25-29.9, obesity=BMI of 30 or greater.

Immunosuppressive protocol

A standard maintenance immunosuppression was used in all patients including CsA, formulation Neoral, MMF and PRED. The dose of Cyclosporine in renal transplant patients was based on the drug levels in the blood. Monitoring of CsA trough levels was done periodically at different times and dose was adjusted consequently. In our therapeutic strategy, target therapeutic levels of CsA were 200-300 ng/ml during the first three months, 100-250 ng/ml 4-12 months and 100-200 ng/ml after 12 months of transplantation.

Statistical analyses

The statistical software SPSS for Windows (version 13.0) was used. For a descriptive statistics mean and standard deviation for continuous data were used while categorical data were expressed as a percentage. Pearson's correlation coefficient was used for certain risk factors. Continuous data were analyzed by Student's t-test for unbound samples to detect intergroup differences. Categorical data were analyzed with chi-square test and Fisher′s test for equivalent pairs of frequencies. A P-value of <0.05 was defined as statistically significant in this study.

Results

A total of 59 patients with successfully transplanted kidney from a living donor was included in the study. Twenty-two (37.29%) were females, while 37 (62.71%) were men, with a mean age of 35.15±8.75 years (range 14-53). The mean follow-up after renal transplantation was 35.73±27.03 months. All included patients had no prior history of diabetes. Most of the patients (49-83.05%) were anti-HCV negative while 10(16.94%) were anti-HCV positive. The mean levels of CsA were 130.62±70.64 ng/ml, and the average daily dose of prednisone was 7.45±2.68 mg.
BMI average value was 25.61±4.29. At the time of performance of OGTT, the average GFR was 60.55± 13.77 ml/min. The mean values of total lipids were 9.08±1.56, triglycerides 2.20±0.82, total cholesterol 5.67±1.05, LDL-c 3.63±1.02 and HDL-c 1.29±0.29 mmol/l. Most of the patients (55/59-77%) had HTA with regular intake of antihypertensive drugs. Only 4/59 (22%) had normal blood pressure.
According to primary diagnosis as a cause of transplantation most of the patients had ESRD (end-stage renal disease)-20 patients (33.89%). Obstructive nephropathy had 9(15.25%), SLE (systemic lupus erythematosus) 5(8.47%), GN (glomerulonephritis, mesangioproliferative, with minimal changes, undifferentiated) 16(27.11%), 4 had amyloidosis (6.77%), GIHT 2(3.38%) and focal glomerular sclerosis (Sy. Alport) 3(5.08%) patients.
All 59 patients included in the study had fasting blood glucose levels less than 6.9 mmol/l. In the whole group the mean fasting blood glucose was statistically significantly lower-5.31 mmol/l than glucose after loading-6.59 mmol/l. ($p<0.001$). Before the OGTT 13.55% (8/59 patients) were classified as IFG, and 86.44% (51/59 patients) were normal based on fasting blood glucose level alone. After performing OGTT the prevalence of PTDM, IGT and IFG was 3.39% (2/59), 30.5% (18/59), 11.86 (7/59), respectively. The overall prevalence of glucose disorders (patients with diabetes and pre-diabetes) was 33.9% (20/59) versus 66.1% (39/59) of patients with normal glucose values. Statistical analysis showed significantly smaller number of patients without glucose disorders (difference between two proportions=0.025 $p<0.05$), and significantly higher number of patients with dysglycemia ($p<0.05$) when

classification was based on OGTT compared with the classification based on fasting blood glucose.
All patients were divided in two groups according to the presence of dysglycemic disorders. Group 1, predominantly with some degree of glycemic disorders and group 2 without any of them. Patients in both groups did not differ among themselves in age, underlying disease, the prevalence of HTA, BMI, family history of diabetes and values of lipid parameters, prevalence of HCV seropositivity, and the values of proteinuria and GFR during the performance of the OGTT. In the group of patients with dysglycemia, postprandial glucose was higher (8.19±2.33 vs 5.80±0.70, P <0.05), more recipients were male (70% vs 33.3% P <0.05), higher CsA levels were observed (160.90±81.21 vs 115.10± 59.90, P<0.05) and shorter observation time after transplantation than in normal patients (24.50±21.32 vs 41.48±28.06, P <0.05).

Table 1. Differences between group A and group B. GFR, proteinuria, BP, BMI-before and after follow-up (18 months)

Parameters	Group A (n=20)	Group B (n=39)	P
Postprandial glucose	8.19±2.33 0.70	5.8±0.70	<0.05
CsA (ng/ml)	160.90±81.21	115.10±59.90	<0.05
Gender-male (%)	70	33	<0.05
Time since Tx (months)	24.50±21.32	41.48±28.06	<0.05
GFR 1* (ml/min)	62.64*	59.49	n.s.
GFR 2 * (ml/min)	52.77*	61.19	<0.05
Proteinuria 1 (g/24h)	1.1	0.9	n.s.
Proteinuria 2 (g/24h)	1.3	1.1	n.s.
BP 1 (mmHg)	150/90	145/100	n.s.
BP 2 (mmHg)	145/95	150/100	n.s.
BMI 1 (kg/m^2)	26.38	25.21	n.s.
BMI 2 (kg/m^2)	26.95	26.19	n.s.

GFR-glomerular filtration rate, BMI-body mass index, BP-blood pressure (1-basic and 2-after the follow-up)

There were also changes in the values of HTA and BMI, factors which often promote chronic allograft nephropathy. In the prospective part of the study between groups we did not note differences in BMI, presence of hypertensive syndrome, lipid status, neither in terms of proteinuria. The only significant difference was noted in the values of GFR (62.64 ml/min to 52.77 ml/min, p <0.05) after an average of 18 months of follow-up, indicating the deterioration of renal function in patients with dysglycemia. Also, after the period of follow-up GFR showed a significant difference between groups (52.77 ml/min vs. 61.19 ml/min, p <0.05).

In further analysis many categorical and non-categorical variables associated with the occurrence of abnormalities in glucose metabolism were correlated with postprandial glucose using the Pearson's coefficient. In the whole group time after transplantation (r=-0.26 - p<0.05), CsA higher levels (r=0.37-p<0.05), increased levels of total lipids (r=0.31- p<0.05) and LDL-c (r= 0.28, p<0.05) were significantly associated with the occurrence of glucose metabolism abnormalities through significant correlation of risk factors listed with postprandial glucose. Analyzing the correlation among certain

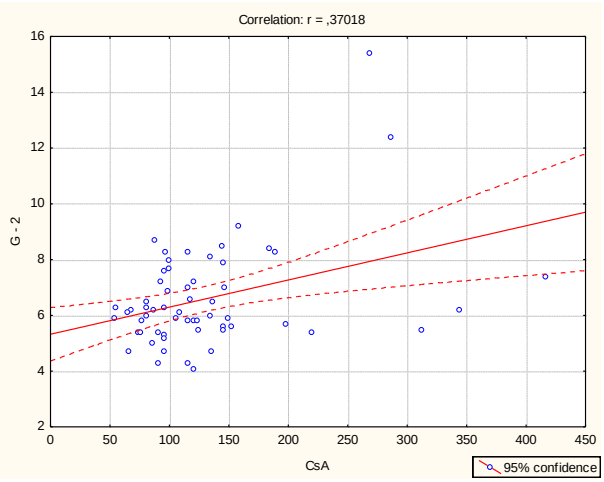

Fig. 1. Correlation of CsA trough levels with postprandial glucose

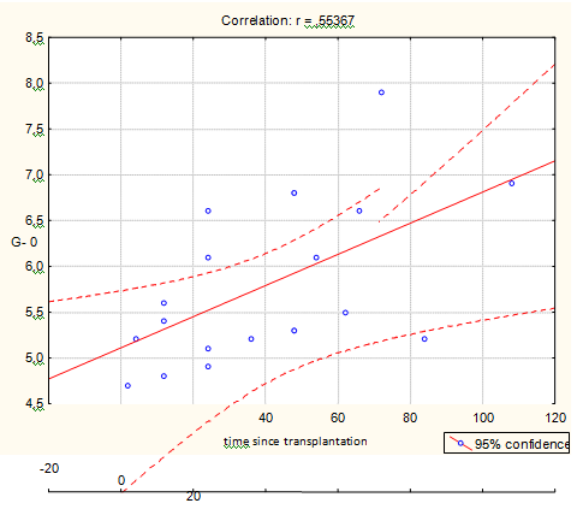

Fig. 2. Correlation of the time since transplantation and fasting glucose

risk factors and dysglycemia (pre diabetes and diabetes), the positive coefficient of correlation was confirmed with CsA trough level (r=0.38, p<0.05), total lipids (r= 0.44, p< 0.05) and LDL-c (r=0.51, p< 0.05).
A positive correlation between fasting glucose and time since transplantation was confirmed (r=0.55, p<0.05).

Discussion

Cyclosporine (CsA) has revolutionized transplant medicine and is currently one of the most important immunosuppressive agents for a wide range of organ transplantations and autoimmune and inflammatory diseases. Its application is associated with numerous immunological and non-immunological complications. The most serious non-immunological complications are nephrotoxicity, hyperlipidemia, hypertension and disorders in glucose metabolism.

PTDM- general

Postrenal transplantation dysglycemia, including new onset diabetes after transplant (NODAT), impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), is a relevant clinical problem. However, despite more than two decades of research the pathogenesis of post-transplant dysglycemia is incompletely understood and there is no consensus how to screen, diagnose and manage this important clinical problem [1]. Usually hyperglycemia is a consequence of imbalance between pancreatic β cell insulin production and required insulin by target tissues to regulate effectively fasting glucose production and postprandial glucose disposal [10].
The incidence of post-transplant glycemic disorders varies from 2%-50% in different studies, due to major differences in the definitions of dysglycemias, different populations of patients included in the studies and various immunosuppressive protocols [11]. Most of the studies that use only fasting glucose, underestimate the prevalence of PTDM and other glycemic disorders in kidney transplant recipients. Thus, pre-diabetic states such as IFG and/or IGT are very important because of the increased risk of developing diabetes and cardiovascular disease [12]. Several recent studies that used OGTT and ADA criteria for the diagnosis of diabetes and pre-diabetes have shown similar prevalence. In the study of Tillmann *et al.*, 187 patients with normal or IFG underwent OGTT and 130 patients (69.5%) had normal test results, whereas 57 patients (30.5%) had pre-diabetes [13]. In the cross-sectional study of Hoi Weong Chan, 31 of 119 patients from China showed dysglycemia after performing OGTT: 4/31 (12.9%) patients were diagnosed as IFG, 8/31 (25.8%) as IGT and in 4/31 (12.9%) patients PTDM were confirmed. In the entire group of 119 patients overall prevalence of abnormal glucose metabolism was 31.9% [14].
Our results showed prevalence of PTDM, IGT and IFG of 3.39% (2/59), 30.5% (18/59), 11.86% (7/59) respectively, which represents a lower prevalence of DM and similar prevalence of pre-diabetes in comparison with the abovementioned studies.
Baseline risks that predispose individuals to PTDM are: advanced age, obesity, male gender, non-white race, and a family history of diabetes [10,15]. These traditionally non-modifiable characteristics reflect inherited and acquired defects in insulin sensitivity and β cell function that contribute to glucose dysregulation. There is consistent evidence that PTDM is more common in older individuals. Cosio *et al*. (2001) reported that recipients above 45 years old were 2.9 times more likely to become diabetic post-transplant when compared with younger recipients [16]. A similar association of age with the development of abnormal glucose metabolism was found in two other studies, but their examined patients were older at the time of transplantation [14,16]. Our results did not confirm significant association between age at the time of transplantation and the development of pre-diabetes and diabetes. The possible explanation could be in the fact that our patients were much younger (35.15±8.75) compared to those in the other studies. However, in the group of patients without glucose metabolism impairment it has been shown that with increasing the time since transplantation there is a rise in the value of fasting glucose. This correlation was statistically significant (r=0.55, p<0.05) and it confirms that aging favors increase in fasting glucose.
In the group with dysglycemia male patients predominated, which is consistent with the findings of other authors [10,15].

PTDM and Immunosuppression

The high incidence of transplant-associated hyperglycemia (TAH) in the months after transplantation reflects a superimposition of new, transplant-related factors on the baseline metabolic milieu of predisposed individuals [15,17]. According to our study a significant inverse correlation was confirmed between postprandial glucose and time since transplantation.
The best elucidated transplant-specific exposures include immunosuppressive agents such as glucocorticoids, calcineurin inhibitors (CNIs) and sirolimus, post-transplantation weight gain, HCV infection.
There is some evidence that dysglycemic states are related with the degree of CNI exposure. The dose response effect of Cyclosporine on NODAT has also been described with the use of low dose of Cyclosporine protocols with less post-transplant glycemia compared to those with standard CsA immunosuppression [18]. Nevertheless, some studies have not confirmed a significant correlation between CNI and NODAT probably due to lower doses of CNI used in their centers [14,16]. Our study confirmed a statistically significant correlation between the use of CsA and postprandial blood gluco-

se levels. Also dysglycemic group had a higher CsA trough levels than normal, which confirms the CNI dose response effect on NODAT. One of the possible explanation of this effect could be the critical role of CNI on β cell growth and function [19]. This strongly suggests that CNIs contribute to TAH by impairing insulin secretion.
Glucocorticoids (GC) affect glucose metabolism by increasing hepatic glucose production and by reducing peripheral tissue insulin sensitivity. In transplant patients the use of steroids, and in particular the prescribed cumulative dose of steroids is often associated with an increased risk of PTDM [20,14]. Many authors stated that the number of rejection episodes positively correlated with pre-diabetes, which was due to the high cumulative doses of GC. On the other hand, the standard dose of steroids below 7.5 mg/day did not affect glucose metabolism in renal transplant patients [13,14]. Some of the patients (23%) were on a steroid-free immunosuppressive protocol and did not show a lower prevalence of pre-diabetes as compared to patients with low-dose steroids [13]. With the use of PRED of 7.45 ±2.68 mg/day, we did not find a significant correlation between daily doses of corticosteroids and pre-diabetes and post-transplant diabetes. All patients who had episodes of acute graft rejection were excluded from our study due to the need for increased doses of immunosuppressive therapy and consecutively higher exposure of higher cumulative corticosteroid dose for treatment of acute rejection.

PTDM and obesity

Obesity increases markedly in the first 1 to 2 yr after transplantation because substantial weight gain is typical [21,22]. Multiple factors contribute to post-transplant weight gain, including GC and reversal of the uremic state, stimulating appetite and food intake [22]. In many studies obesity expressed as BMI≥30 kg/m2 has been demonstrated as a risk factor for the development of PTDM [23,24]. In contrast to other publications, in our study BMI as a continuous and categorical variable was not associated with deranged glucose metabolism. Our results are consistent with the results presented by several authors [25,13,14]. The reason lies probably in the fact that our patients were relatively thin and the average BMI was 25.61±4.29, indicating overweight but not obesity.

HCV and PTDM

Epidemiologic data have demonstrated strong associations between HCV infection and hyperglycemia in the general population [26]. The pathogenic mechanisms that link HCV infection and hyperglycemia remain unclear. Fabrizi F *et al.* (2005) using a meta-analysis have also shown a significant relationship between anti-HCV seropositive status with the development of PTDM [27]. The prevalence of HCV positivity among our patients was small, around 16% in both groups, so that we could not verify connectivity of dysglycemic conditions and anti-HCV seropositive status.

PTDM, nephrotoxicity and graft function

The fact that CsA was nephrotoxic was discovered early after its initial use, when Calne *et al.* found a significant and unexpected nephrotoxicity [28]. Currently, it is well known that renal damage may be an important side effect of CsA therapy, but it is also known that nephrotoxicity is associated with longer treatment duration, larger cumulative doses and higher daily dose of CsA. It is also related to individual susceptibility [29,30]. This association between CsA nephrotoxicity and higher CsA doses (>5 mg/kg/day) was confirmed by others [31]. It has been demonstrated that levels of CsA in the renal tissue are much higher than in blood [32,33]. A combination of CsA-induced hemodynamic changes and direct toxic effects of CsA on tubular epithelial cells is thought to play a role [34].
Renal dysfunction can be functional or structural. Functional impairment, which may begin soon after the beginning of the treatment, can be subdivided into vascular dysfunction and tubular dysfunction. Vascular dysfunction is caused by vasoconstriction of the afferent glomerular arterioles, leading to increased vascular resistance. This results in decreased renal glomerular filtration rate (GFR) and renal blood flow with decreased clearance of creatinine [30].
Our results showed a greater functional impairment in the dysglycemia group, where significantly higher CsA level was noted, thus confirming the dose-dependent nephrotoxicity. After the follow-up, control GFR was significantly lower in the group with glucose disorders than in the control group.

PTDM, proteinuria and hypertension

Proteinuria (PTN) after kidney transplantation has been recognized as a risk factor for the progression of chronic allograft nephropathy and cardiovascular disease [35]. Proteinuria and albuminuria can be quantified with a 24- hour collection or by using spot urine collections (Albumin-Creatinine Ratio (ACR) or Protein-Creatinine Ratio (PCR)). KDIGO suggest that ACR and PCR are reasonable screening tests in the renal transplant recipients. Any positive screen should be confirmed by a 24-hour urine collection [8]. The accuracy of the spot PCR has been studied in renal transplant recipients. In one of the earliest studies, analyzing the PCR of 133 kidney transplant recipients, a high correlation ($r=0.93$; $P<0.001$) between the PCR and the 24-hour urine collection was demonstrated and the sensitivity to detect nephrotic range proteinuria was 99%. In other study in this analysis, sensitivity of the PCR to detect low levels of proteinuria (<150 mg/d) was limited (73%) but

remained high (96%) for the detection of nephrotic range proteinuria. In contrast to these two studies, other authors found that the sensitivity of the PCR to detect 24-hour protein excretion >500 mg/d was only 85% and dropped even lower for the detection of nephrotic-range proteinuria [36,37]. So, 24-hour urine protein excretion is the gold standard for quantitative protein assessment [38].

The etiology of post-transplant proteinuria is multifactorial [39], and we can mention chronic allograft nephropathy, transplant glomerulopathy, repeated or recurrent glomerulonephritis, chronic pyelonephritis, nephrotoxicity by calcineurin inhibitors and diabetic nephropathy [39].

Male recipients, transplantation from a living donor and the presence of post-Tx hypertension were associated with a higher likelihood of developing post-renal Tx PTN. Renal function at 12 months (measured by creatinine) was significantly lower in patients with post-transplant PTN. Proteinuria should be assessed in all recipients after renal transplantation, since, in addition to being a marker of kidney disease, it has also been considered a risk factor for the progression of chronic allograft nephropathy, and cardiovascular disease [40].

In both groups of patients we noted a similar prevalence of hypertension, and all transplantations were from a living donor, which explains the relatively high proteinuria and the small difference between groups. In dysglycemia group we did not find a significant increase in proteinuria, probably due to the relatively short follow-up period.

Dysglycemia has a relatively high prevalence in renal transplant recipients. Major risk factors for glucose disorder after transplantation are higher CsA trough levels, elevated total lipid concentrations and LDL-c. Glucose disorders are a significant factor for deterioration of renal function.

As glucose disorders and associated metabolic abnormalities are part of the effects of calcineurin inhibitors, we can indirectly conclude that the deterioration of renal function over a long period of time is the effect of cyclosporine, not only as a direct toxic effect on the kidney structures (endothelium, interstitium), but also by disturbed glucose metabolism and metabolic syndrome. Thus, modern immunosuppressive treatment means true individualization or customization of treatment according to the patient's needs and its own risk factors.

Limitations of the study: Lack of mandatory use of OGTT in the pre-transplant examination might include patients with dysglycemia in our study and over estimate the prevalence of pre-diabetes after transplantation. Although all of our patients were on a maintenance immunosuppressive protocol, the point at the time of testing was not pre-determined by the study protocol. This resulted in marked differences in the time-delay from transplantation to OGTT between patients. There was a significant difference in this time-delay between the two study populations.

Conflict of interest statement. None declared

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ММР

Original article

PATIENT-CONTROLLED ANALGESIA (PCA) WITH REMIFENTANIL VERSUS INTERMITTENT EPIDURAL BOLUSES FOR LABOR ANALGESIA

ПАЦИЕНТ-КОНТРОЛИРАНА АНАЛГЕЗИЈА СО РЕМИФЕНТАНИЛ НАСПРОТИ ИНТЕРМИТЕНТНИ ЕПИДУРАЛНИ БОЛУСИ ЗА БЕЗБОЛНО ПОРОДУВАЊЕ

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Апстракт

Вовед. Ремифентанилот станува се популарен за безболно породување како алтернатива на невроаксијалната аналгезија. Во оваа студија јаспоредуваме јачината на болката, задоволството на родилките и несаканите ефекти од страна на мајката.
Методи. 80 пациентки АСА 1 или 2, прворотки, во термин за раѓање, беа вклучени во студијата и поделени во 2 групи. Првата група (35 пациентки) добија интравенски ремифентанил на пумпа за пациент-контролирана аналгезија (ПКА) во болус дози. Втората група (45 пациентки) добија интермитентни епидурални болуси со силно дилуиран локален анестетик и опиоид (Bupivacain и Fentanil). Анализиравме пулсна оксиметрија (SpO_2), број на респирации, крвен притисок, пулс, седација, гадење и повраќање како и скоровите за болка и задоволството на родилките преку 2 различни VAS скали.
Резултати. Средната SpO_2 беше значително пониска во групата на ПКА со ремифентанил 96.2%±1.6 наспроти 98.2±1.2 во епидуралната група. Респираторна депресија (број на респирации <9 или SpO_2<90%) не беше најдена во двете групи. Скоровите на седација беа значително повисоки во групата наПКА со ремифентанил, P<0.05. Инциденцата на гадење и повраќање беше иста во двете групи, без сигнификантна разлика. Во однос на скоровите за болка ПКА со ремифентанил беше инфериорна во однос на епидуралната аналгезија во сите временски точки, но без сигнификантна разлика измеѓу двете групи во задоволството на родилките.
Заклучок. Интравенска пациент контролирана аналгезија со ремифентанил обезбедува задоволително ниво на обезболување, со понизок SpO_2 и повеќе седација. Може да биде одлична алтернатива на епидуралната аналгезија, но континуиран мониторинг и достапност на кислород е задолжително.

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Клучни зборови: ремифентанил, епидурална аналгезија, безболно породување

Abstract

Introduction. Remifentanil is becoming more and more popular for labor analgesia as an alternative for neuroaxial anesthesia. In this study we comparedthe severity of pain, patient satisfaction and side effects between two different types of labor analgesia.
Methods. Eightyprimiparous patients ASA I or II, atterm pregnancy, were included in the study and divided in two groups. The first group (35 patients) received intravenous remifentanil on patient control pump in bolus doses. The second group (45 patients) received intermittent epidural boluses with highly diluted local anesthetic and opioid (Bupivacain and Fentanil). We analyzed oxygen saturation (SpO_2), respiration rate, heart rate, blood pressure, sedation, nausea and vomiting as well as patient pain scores and satisfaction scores through 2 different VAS.
Results. Mean SpO_2 was significantly lower in the PCA remifentanil group 96.2%±1.6 versus 98.2±1.2 in the epidural group. Respiratory depression (RR<9 or SpO2 <90%) was not found in both groups. Sedation scores were significantly higher in the PCA remifentanil group, P<0.05. Incidence of nausea and vomiting was similar between the two groups, without significant difference. PCA remifentanil was inferior to epidural analgesia with respect to pain scores at all time points, but without significant difference in patient satisfaction between the two groups.
Conclusion. Intravenous patient-controlled analgesia with remifentanil provides satisfactory level of labor analgesia, with lower SpO_2 and more sedation. It could be an excellent alternative to epidural analgesia but continuous monitoring and oxygen supply is mandatory.

Keywords: remifentanil, epidural analgesia, labor analgesia

Introduction

Epidural analgesia provides reliable and effective analgesia during labor and it is considered a gold standard in obstetric anesthesia [1]. However,there are conditions that limit the use of epidural analgesia: when it is contraindicated (coagulopathies, long term use of anticoagulants, infections on the place of the punction, spine abnormalities) or when the parturient simply does not wantit because it is an invasive procedure as well as due to side effects, which although rare, can be very serious. But, it is clear that effective and safe alternative should be established.

Remifentanil with its pharmacokinetic capacities can be an ideal medicine for labor analgesia. It is an ultrashort acting, μ-1 opioid receptor agonist, metabolized to an inactive metabolite by plasma and tissue esterases. It is characterized with fast onset of analgesia (30-60 seconds), with a maximum effect in 2.5 minutes, analgesic half-life of 3.5-6 minutes and without accumulation effect after long-term use. Plasma concentrations of remifentanil in pregnant women are approximately half of those found in women not pregnant due to the greater volume of distribution and higher clearance. It crosses the placenta very quickly, but it is rapidly metabolized and redistributed in the fetus [2]. All these characteristics make remifentanil ideal for labor analgesia [3,4].

In recent years many studies have been published examining remifentanil in terms of efficacy and safety. One large multicenter randomized study conducted by Freeman *et al.* [5] from 2015 was specifically focused on the satisfaction of patients, while another large retrospective study by Lin *et al*. [6] from 2014 as well as the meta-analysis of Stourac *et al.* [7] from 2015 were focused on the effectiveness and maternal and neonatal side effects. Many issues still remain insufficiently clarified and leave space for much more research before we can carelessly use it for pain relief. It was the aim of our study to compare the analgesic efficacy of patient-controlled analgesia (PCA) with remifentanil to epidural analgesia with bupivacain/fentanil and to analyze any maternal side effects.

Materials and methods

This was a prospective randomized clinical study performed at the University Clinic for Gynecology and Obstetrics in the period from 09.2015 to 03.2016. The study was approved by the Ethics Committee of the Medical Faculty in Skopje.

Inclusion criteria for the study were: primiparous, patients older than 18 years, healthy or with mild systemic disease (ASA 1 or 2) and at term for birth (gestational age> 34 weeks). Eighty patients that matched the inclusion criteria were included in the study. All patients after admission to hospital for childbirth signed an informed consent and were randomly assigned into two groups, remifentanil intravenous PCA group (RG) and epidural analgesia group (EG). Parturients in both groups were adequately prepared by placing a peripheral venous line and basic monitoring (non-invasive blood pressure, pulse oximetry, respiratory rate). We began with pain relief at 4-5 cm cervical dilatation, always in agreement with the gynecologist-obstetrician.

Thirty-five patients were included in the remifentanil group (RG) and they received intravenous remifentanil in bolus doses on a pump for patient-controlled analgesia in 2 minutes locked interval. We started the remifentanil analgesia with smaller doses and increased them gradually. We started with 0.15 μg/kg remifentanil (solution 20 μg/ml), gradually increased for 0.1 μg/kg up to the maximum bolus dose of 1 μg/kg. All patients were explained how to operate the pump and when to give the bolus dose. We advise all patients to apply the bolus when they feel pain is coming. Few labor pains are enough and patients know when to give the bolus. Analgesia was stopped 10 minutes before the expected expulsion of the newborn.

Forty-five patients were distributed in the epidural group (EG) and they received epidural analgesia with intermittent bolus dosing. After placement of the epidural catheter and negative test dose all patients received a bolus dose of 10 ml 0.1% Bupivacain with Fentanil 0.05 mg. Further on, all patients hourly received epidural bolus of 10 ml 0.0625% Bupivacain with Fentanyl 2 μg/ml. The last bolus dose patients received at least 30 minutes before the expected completion of the birth.

At all times during labor analgesia parturients were monitored: oxygen saturation and heart rate continuously, respiratory rate and noninvasive blood pressure every 15 minutes, continuous cardiotocograph recording for fetal monitoring. The level of sedation was evaluated every 30 minutes by Ramsey sedation score - RSS (0- alert; 1- anxious, restless; 2- cooperative, oriented; 3- responding to commands; 4- brisk response to stimulus; 5- weak and slow response to stimuli; 6- does not respond to strong painful stimuli). The incidence of nausea, vomiting and itching was also recorded.

If oxygen saturation of the parturient fell <95%, a nasal catheter with $O_2$2-3 l/min was immediately placed. If the parturient SaO_2fell <92% or respiratory rate (RR) decreased <9 or RSS was 4 or greater than 4, then we temporarily stopped with analgesia. After normalization of physiological parameters the analgesia was started again with one step lower doses.

During the birth both groups of patients were asked to answer two separate questions. First they were asked to determine the level of pain on a specially designed scale for pain (visual analogue scale-VAS) from 0 (no pain) to 100 (highest possible pain) of "how strong pain is during contraction" in every 30 minutes during childbirth starting with the first question before starting analgesia. The second question was designed to determine the patient satisfaction with analgesia. Parturients

were asked to determine their satisfaction with labor analgesia on different VAS scale from 0 (extremely dissatisfied) to 100 (very satisfied) with the answer to the question "are you satisfied with the analgesia".

Results

Between 09.2015 and 03.2016 eighty (80) patients were randomized to receive either intravenous PCA remifentanil (35 patients) or epidural analgesia (45 patients) for painless delivery. Sixty-five patients were ASA 1 (76.5%), while 15 patients were with mild systemic disease, ASA 2 (23.5%).

The average $SpO_2$was significantly lower in the PCA remifentanil group 96.2%±1.6 versus 98.2±1.2 in the epidural group (Figure 1), with statistically significant difference ($p<0.01$). Nasal catheter with O_2 2-3 L/min was set only if SpO_2 fell less than 95%. Nineteen patients (54%) from the RG needed O_2 support, while only 3 patients (7%) from the EG neededO_2. None of the patients in both groups had a drop in saturation less than 92% or respiratory rate less than 9.

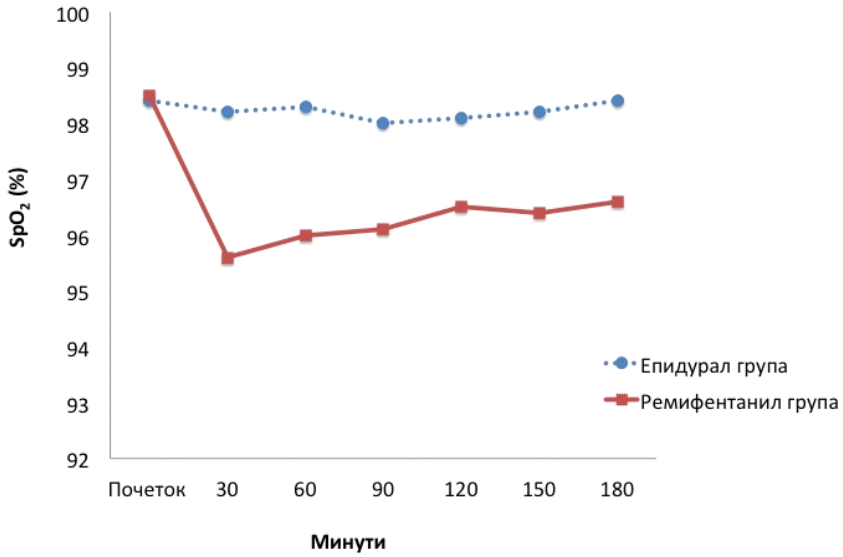

Fig. 1. Comparison of SpO_2 between the two groups of patients
Start-Minutes; Epidural group-Remifentanil group

Noninvasive blood pressure, measured in every 15 minutes was all the time stable in both groups of patients during birth. Mild hypotension appeared in 2 patients from the EG, but without need for vasopressors.

Sedation was significantly higher in the RG at all times during birth ($p<0.05$). Four patients from the RG reached the sedation score 3 according to RSS, while only 1 patient in the RG reached score 4. Remifentanil was stopped temporary and after 3 minutes the analgesia was proceeded with one step lower doses.

Nausea, vomiting and itching were approximately the same in both groups, with no statistically significant difference.

VAS pain scores with starting mean value of 92±8.1 immediately after initiation of analgesia were significantly reduced in both groups, but still remained higher in the RG. As the labor continued pain scores were elevated in both groups, more in the RG, but still far from initial scores (Figure 2). Mean values of the VAS pain scores after onset of analgesia in the remifentanil group were 45±4.3 and in the epidural group 30±3.9, with statistically significant difference of $p<0.01$.

On the other hand, satisfaction scores were all the time almost the same in both groups (Figure 3). Mean VAS satisfaction scores in the remifentanil group were 89± 7.8 and in the epidural group 90±9.2, with no statistically significant difference in both groups ($p=0.6$).

Table 1. Side effects and complications

		RG (n = 35)	EG (n = 45)
Hypotension		/	2 (4.4%)
Nausea		4 (11.4%)	5 (11%)
Vomiting		3 (8.6%)	3 (6.7%)
Itching		1 (2.8%)	2 (4.4%)
Sedation according to RSS	1	15 (42.8%)	35 (77.8%)
	2	16 (45.7%)	10 (22.2%)
	3	3 (8.6%)	0
	4	1 (2.9%)	0

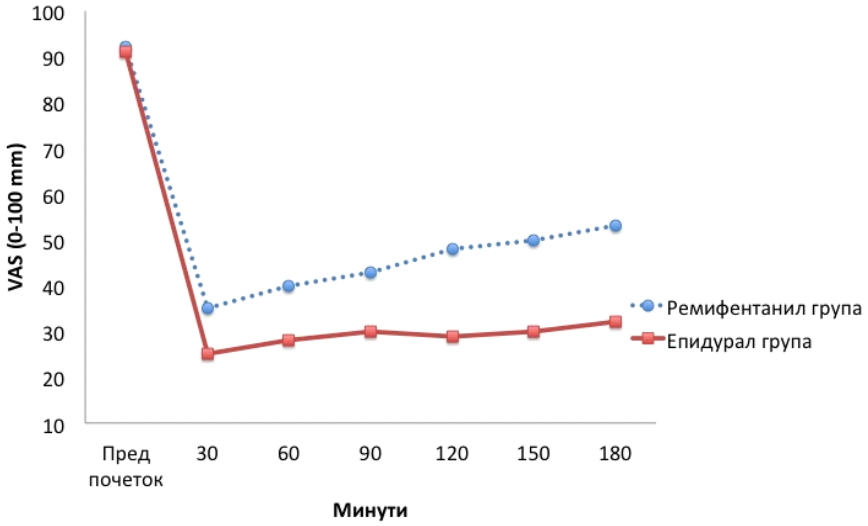

Fig. 2. Comparisonof VAS pain scores between the two groups of patients
before start-Minutes
Epidural group-Remifentanil group

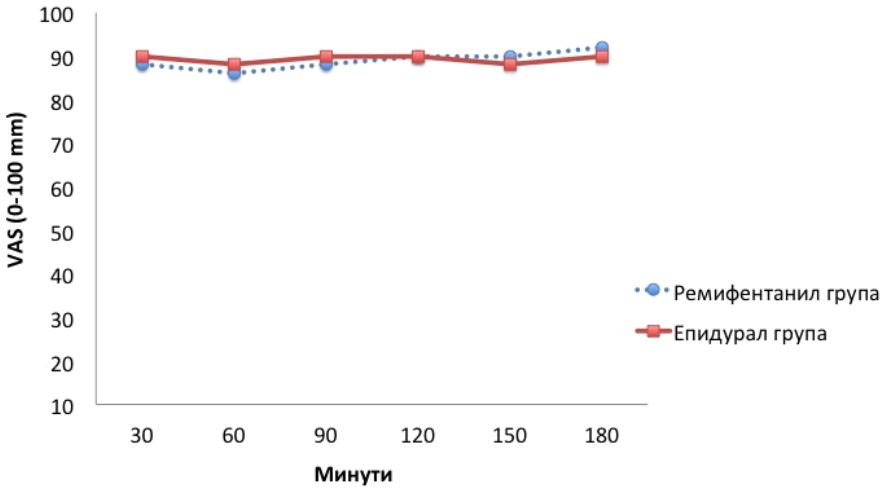

Fig. 3. Comparison of VAS satisfaction scores between patients in remifentanil and epidural group
Minutes
Epidural group-Remifentanil group

Discussion

Desaturation is the main side effect during intravenous analgesia with remifentanil. Incidence of maternal desaturation in analgesia with remifentanil beneath 95% was observedin 25-75% of cases [8-12]. It is not higher than desaturation during analgesia with meperidine or Entonox, but is far higher than with epidural analgesia. In our study 19 patients (54%) from the RG and only 3 patients (7%) from the EG showeddecrease in the saturation less than 95%. Episodes of desaturation associated with remifentanil are usually short-termed and easily correctable with application of nasal oxygen and stimulation of the mother. In our study all patients immediately normalized SpO_2 with nasal oxygen 2 L/min, without the need for temporary stop of the remifentanil pump. There are several case reports [13-16] of obstetric patients that showedvery serious cases of desaturation resulting in apnea, all of them started as remifentanil labor analgesia. These cases required further caution, continuous SpO_2 monitoring and the possibility of application of oxygen during intravenous analgesia with remifentanil.

Sedation also appears as a frequent side effect of remifentanil analgesia. Different levels of maternal sedation are common [12,18,19], while in some studies [20,21] incidence of sedation of nearly 100% has been observed. In our study there was a significantly higher level of sedation in the RG than in the EG, which was expected. Fourpatients in the RG reached score 3 according to RSS, and only 1 patient in the RG reached RSS score 4, which meant suspension of analgesia and return to 1 step lower doses. All this was short-lived, easily corrected, but again implying the need for continuous and obligatory monitoring.

The incidence of nausea, vomiting and itching were similar in both groups, shown in many previous studies [6,12,19]. As it is already known the use of opioids whether given by intrathecal, intravenous or epidural administration can lead to nausea, vomiting and itching. But these symptoms may develop during childbirth, even when there is no analgesia.

The difference in analgesic efficacy between PCA with remifentanil and epidural analgesia at all times during childbirth was visible and statistically significant ($p < 0.01$). It has been proven in many older and recent scientific papers [5,6,8,22]. After initiation of analgesia pain scores decreased in both groups, but more in the epidural group. As the labor progressed pain scores in the RG increased. Remifentanil bolus dose in our study varied from 0.15 μg/kg up to 0.8 μg/kg. In 30 patients (85.6%) the bolus dose of remifentanil was increased up to maximum0.6 μg/kg, because the pain scores were really low or because the patients felt that the pain was reduced and that dose was sufficient. We did not reach the maximum bolus dose of 1 μg/kg in any patient. However, side effects are dose-dependant and increasing the dosage of remifentanil side effects (mostly sedation) increased. The only patient that reached RSS score 4 was run at the moment with 0.8 μg/kg PCA remifentanil.

Latest researches go towards improving the efficiency of bolus doses of remifentanil [23]. The overlap of pain with the peak of remifentanil can be improved by the prediction of contractions, but it is not known yet whether the technique will improve the safety.

On the other hand, satisfaction scores of the patients in our study were all the time almost the same in both groups, with no statistically significant difference ($p=0.6$). But, it is very important that many studies [18,20,24,25] found no significant difference in maternal satisfaction between these two groups of labor analgesia. This probably indicates that remifentanil provides weaker but highly acceptable maternal analgesia. One explanation may be opioid-induced euforia [12], or simply easy applicability.

Conclusion

Intravenous PCA analgesia with remifentanil provides a satisfactory level of pain relief with lower $SpO_2$and more sedation. It can be a great alternative to epidural analgesia, but continuous monitoring and availability of oxygen is mandatory.

Conflict of interest statement. None declared.

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Original article

GASTROINTESTINAL LYMPHOMA IN TERTIARY GASTROENTEROLOGY CENTER: EPIDEMIOLOGICAL, CLINICAL AND ENDOSCOPIC FEATURES

ГАСТРОИНТЕСТИНАЛНИ ЛИМФОМИ ВО ТЕРЦИЕРЕН ГАСТРОЕНТЕРОЛОШКИ ЦЕНТАР: ЕПИДЕМИОЛОШКИ, КЛИНИЧКИ И ЕНДОСКОПСКИ КАРАКТЕРИСТИКИ

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Abstract

Introduction. Within the heterogeneous group of extranodal lymphoma, the gastrointestinal tract is the most frequently involved extranodal site accounting for 30-50% of all extranodal cases. Gastrointestinal involvement most oftenoccurs secondarily, while the primary gastrointestinal lymphomasare relatively rare accounting for 30%-45% of all extranodal lymphomas and 0.9% of all gastrointestinal tumors. Within the gastrointestinal tract, lymphoma can arise in any region but the stomach is the most commonly involved organ being affected in 50-70% of all the gastrointestinal lymphomas, followed by the small intestine and ileocecal region. The aim of the study was to analyze and present data regarding the endoscopic aspects and clinical presentation of patients with gastrointestinal lymphoma.

Methods. We retrospectively reviewed the medical records of patients with primary or secondary gastrointestinal lymphoma diagnosed at our Clinic over a fifteen-year period (January 1, 1999 to December 31, 2013). We analyzed the demographic data, clinical presentation, anatomic distribution, endoscopic aspect of the lesion, extension of the neoplastic process and occurrence of different histological subtypes.

Results. We discovered 18 patients with gastrointestinal lymphoma (7 males and 11 females). Fourteen patients (77.7%) were considered primary, while 4 patients (22.2%) were considered secondary gastrointestinal lymphoma. The stomach was affected in 14 cases (11 primary and 3 secondary), there were 2 duodenal lymphomas, 1 lymphoma of the terminal ileum and 1 peritoneal lymphoma. In most patients (10) massive and diffuse gastrointestinal infiltration was diagnosed, 5 patients had ulcerated lesions in the stomach and 3 patients presented with polyploid mass. Six patients presented with upper gastrointestinal bleeding, 1 patient with biliary tract obstruction, one patient with protein losing enteropathy, malabsorptionand consecutive bowel perforation and one patient presented only with ascites and pleural effusion. All the malignant lymphomas were Non-Hodgkin type and among them we registered only one T-cell lymphoma. Being diagnosed in 6 patients (33.33%), diffuse large B-cell lymphoma was the most prevalent histological type. The lymphoma was limited to the gastrointestinal tract in 6 patients, 7 patients had regional nodal involvement, in 2 patients there was an intra-abdominal spread and in 3 patients there was an extra-abdominal dissemination. Most patients received chemotherapy and only 2 patients were treated surgically. Two patients had rapidly progressive clinical course and lethal outcome shortly after the diagnosis was established and before chemotherapy was administered.

Conclusion. The gastrointestinal lymphoma has a variable clinical presentation and endoscopic aspect that often makes the diagnosis challenging. Substantial level of diagnostic awareness and comprehensive clinical approach are necessary in order to establish the correct diagnosis, provide appropriate treatment and prolong survival.

Keywords: gastrointestinal lymphoma, extranodal lymphoma, primary gastrointestinal lymphoma

Апстракт

Вовед. Гастроинтестиналниот тракт е најчестата екстранодална локализација, застапена кај околу 30-50% од сите екстранодални лимфоми. Гастроинтестиналната засегнатост, најчесто настанува секундарно, додека примарните гастроинтестинални лимфоми се релативно ретки и на нив отпаѓаат 30-45% од сите екстранодални лимфоми и 0.9% од сите гастроинтестинални тумори. Во рамки на гастроинтестиналниот тракт, лимфомите може да потекнуваат од која било локализација, но 50-70% од нив се локализирани во желудникот, по што следат тенкото црево и илеоцекалната регија. Цел на студијата беше да

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се анализираат и презентираат податоци, во врска со ендоскопскиот аспект и клиничка презентација на пациентите со гастроинтестинални лимфоми.
Методи. Ретроспективно беа ревидирани медицинските истории на пациентите со примарен или со секундарен гастроинтестинален лимфом, дијагностицирани на нашата клиника, во рамки на временски период од 15 години (од јануари 1999 до декември 2013). Беа анализирани демографските податоци, клиничката презентација, анатомската дистрибуција, ендоскопскиот аспект на лезијата, екстензивноста на неопластичниот процес и застапеноста на различни хистолошки подвидови.
Резултати. Во рамки на овој временски период беа детектирани 18 пациенти со гастроинтестинален лимфом (7 мажи и 11 жени). Примарен гастроинтестинален лимфом беше утврден кај 14 пациенти (77.7%), додека кај 4 пациенти (22.2%) беше утврдено присуство на секундарен гастроинтестинален лимфом. Лимфомите беа локализирани во желудникот кај 14 пациенти (11 примарни и 3 секундарни), беа нотирани 2 дуоденални лимфоми, 1 лимфом на терминален илеум и 1 перитонеален лимфом. Кај повеќето пациенти (10) беше утврдено присуство на масивна и дифузна гастроинтестинална инфилтрација, 5 пациенти имаа улцеративна лезија во желудникот и кај 3 пациенти беше утврдено присуство на полипоидна маса. Шест пациенти клинички се презентираа со горнодигестивно крварење, 1 пациент со билијарна опструкција, 1 пациент со енеропатија асоцирана со губење протеини, малапсорпција и цревна перфорација и 1 пациент се презентираше само со асцит и со плеврални изливи. Сите лимфоми беа Нон-Хоџкин тип, и меѓу нив регистриравме само еден Т клеточен лимфом. Дијагностициран кај 6 пациенти (33.33%), Дифузниот лимфом на големи Б клетки, беше најчестиот хистолошки тип. Лимфомот беше лимитиран на гастроинтестиналниот тракт кај 6 пациенти, кај 7 пациенти беше нотирано присуство на зголемени лимфни јазли, кај 2 пациенти беше утврдена интраабдоминална дисеминација и кај 3 пациенти беше регистрирана екстраабдоминална дисеминација. Повеќето пациенти беа третирани со хемотерапија и само 2 пациенти беа третирани хируршки. Двајца пациенти се презентираа со рапидно прогресивен клинички тек и летален исход, набргу по поставување на дијагнозата и пред третман со хемотерапија.
Заклучок. Гастроинтестиналните лимфоми имаат варијабилна клиничка презентација и ендоскопски аспект, што честопати го отежнува дијагностичкиот процес. Оттука, присуството на високо ниво дијагностичка свест и сеопфатен клинички пристап се неопходни за да се обезбеди точна дијагноза, соодветно лекување и продолжено преживување

Клучни зборови: гастроинтестинални лимфоми, екстранодални лимфоми, примарни гастроинтестинални лимфоми

Introduction

Although lymphoma as an entity refers to malignant proliferation of lymphoid cells within the lymphoid organs, it is well known that lymphoma can arise from any other organ or tissue comprising a large heterogeneous group of extranodal lymphomas (EL). EL refers to a lymphoma arising primarily from a site other than a lymph node, spleen, bone marrow or mediastinum (lymph node and thymus) [1]. Apart from the lymphoid organs, the extranodal lymphoid proliferation can occur in organs that contain associated lymphatic tissue such as small intestine, or even in organs that do not contain their own lymphoid tissue such as stomach [2]. EL can arise in every anatomic site of the body and it has been reported in almost every organ and tissue such as the gastrointestinal tract (GIT), Waldeyer's ring, nasopharynx and paranasal sinuses, salivary glands, skin, central nervous system, bone, testis, thyroid, breast, orbit, and rarely in adrenal glands, pancreas, and the genitourinary tract [3-16]. The extranodal involvement most commonly occurs secondaryas a consequence of an extension from the nodal site, while the primary extranodal lymphoma (PEL) are less frequent and are defined by a presence of a dominant lymphoid tumor mass and/or related symptoms in an extranodal organ with no or minor nodal involvement [17]. Most of the EL were Non-Hodgkin type (NHL) and in the literature there are only several extranodal Hodgkin lymphoma cases described. The GITis the most common extranodal site involved by lymphoma,being affected in up to 30-50% of all EL [18,19], in around 5%-20% of all lymphoma cases [20,21] and GIT lymphoma accounts for 0.9-6.5% of all gastrointestinal malignancies [22,23]. As other extranodal sites, the GIT is also mainly involved seconddarily, as a result of a spread from the mesenteric and retroperitoneal lymph nodes that are frequently involved in patients with generalized lymphomas [24]. Although primary gastrointestinal lymphomas (PGL) are relatively rare (approximately 0.9% of all GIT tumors [23]), they are still the most common type of PEL accounting for30%-45% of all extranodal NHL [25]. The primary sites of origin in decreasing order of frequency include the stomach (50-70%), small bowel (20-35%), colon (especially cecum) (5-10%), and esophagus (<1%) [26-28]. The diffuse large B-cell lymphoma (DLBCL) and the marginal zone B-cell lymphoma (MALT type) are the most frequent histological types among the PEL[2].
The aim of the study was to analyze and present data regarding the age and sex distribution, clinical presentation, endoscopic aspect, anatomic localization and occu-

rrence of different histological subtypes in patients with gastrointestinal lymphoma.

Material and methods

The study was carried out at the University Clinic of Gastroenterohepatology, a tertiary care hospital in Skopje, Macedonia. After searching our computer database, we retrospectively analyzed the medical files of all the patients with histologically proven primary or secondary NHL of the GIT (esophagus, stomach, large and small bowel) diagnosed at our institution over a fifteen-year period (January 1, 1999 to December 31, 2013). Patients with abdominal nodal disease or liver and spleen involvement, but without evidence of gastrointestinal involvement were not included in the study. After careful review of the medical records and taking into account the Lewin's diagnostic criteria [29], all cases were categorized as PGL or secondary gastrointestinal lymphoma (SGL). Lymphoma in patients who presented with morphologically and clinically dominant lesion in the GIT with/without nodal affection in the regional lymph nodes were considered PGL. The gastrointestinal lymphoma (GL) with distant GIT involvement from the dominant nodal disease/tumor mass and the GL in patients who were previously diagnosed with nodal disease, which later recurred in the GIT were considered SGL.The diagnosis was established by histopathological analysis of the material provided by endoscopic biopsy or surgical resection and the specific lymphoma type was confirmed by using an immunohistochemical study for B and T-cell markers. Patients were analyzed regarding the demographic data, immunological status, clinical presentation, histopathological features, endoscopic appearanceand distribution of different localization within the GIT and the results were compared with the data from the recent literature.We attempted to determine the clinical stage by using the Ann Arbor classification [30], but we were not able to conduct a complete clinical staging in all patients because of lack of informationin the available medical records. The HIV status for most of the patients was not known.

Results

During the last fifteen year, we discovered 18 patients with GL diagnosed in our institution; 16 patients were hospitalized at our Clinic and 2 patients were diagnosed through the outpatient endoscopy unit. Seven patients (39%) were male and 11 patients (61%) were female (Figure 1), male to female ratio 1:1.6. The average age of presentation of the GL was 53.12 years (range 32-80), while the average age of the initial lymphoma occurrence was 52.76 years (four patients were previously diagnosed with generalized nodal disease which latter reoccurred in the GIT). The peak incidence of the GL was in the 6th decade (6 patients, 33.33%). At the time of presentation, most of the patients were immunocompetent. One patient had diabetes, one patient had

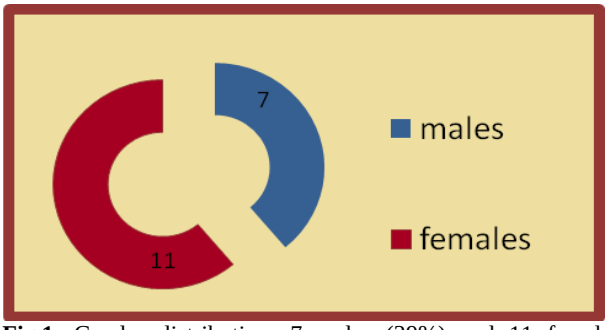

Fig.1. Gender distribution: 7 males (39%) and 11 females (61%)

liver cirrhosis, one patient had coronary artery disease, one patient was previously diagnosed with cervical cancer, one patient had chronic hepatitis B and one patient had chronic hepatitis C. Fourteen patients (77.77%) presented with a dominant gastrointestinal mass and were considered PGL, while 4 patients (22.22%) besides

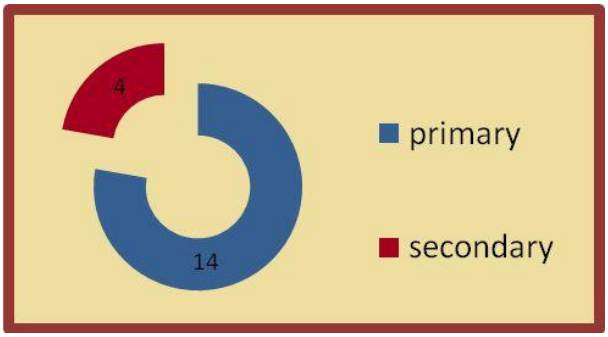

Fig.2. PGL vs SGL: 14 cases of PGL(77.7%) and 4 cases of SGL(22.2%)

the gastrointestinal involvement had a massive abdominal lymphadenopathy and/or splenic involvement and were considered SGL (Figure 2). The stomach was the most prevalent extranodal localization, being affected in 14 cases (11 PGL and 3 SGL); there were 2 duodenal lymphoma, 1 lymphoma of the terminal ileum and 1 peritoneal lymphoma (Figure 4) Six of the gastric lymphomas were infiltrating the corpus, in 5 cases there was infiltration of the corporal and proximal gastric segment, in 2 cases the gastric antrum and pyloric region were involved and one case was restricted to the subcardial region. In most patients (10) massive and diffuse gastrointestinal infiltration was diagnosed (7 gastric lymphomas, one duodenal, one ileal and one peritoneal lymphoma), 5 patients had ulcerated lesions in the stomach, and 3 patients presented with polyploid mass (two gastric and one duodenal tumor). In most patients (14) the gastrointestinal involvement was the initial manifestation of the lymphoma and 4 patients were previously diagnosed with generalized nodal disease additionally relapsing within the GIT. Six of the 14 ca-

ses of gastric lymphomas presented with upper gastrointestinal bleeding (Figure 3.). One patient who was previously diagnosed with abdominal nodal disease later presented with biliary tract obstruction as a consequence of secondary involvement of the duodenum.The lymphoma of the terminal ileum was initially discovered in a 35-year-old female during her early pregnancy. She presented with protein losing enteropathy, malabsorption and nutritive deficiency and later she developed bowel obstruction symptoms and bowel perforation discovered during surgery. The female patients with primary peritoneal lymphoma presented only with ascites and pleural effusion without lymph node enlargement, tumor formation or specific gastrointestinal symptoms.The remaining patients presented with abdominal pain and nonspecific constitutional symptoms (9 patients with abdominal pain and 10 patients with weight loss, Figure 3). In most patients (16) the diagnosis was established from the endoscopic biopsies while the patients with ileal and peritoneal lymphoma were diagnosed during surgery. All malignant lymphomas were Non-Hodgkin type and among them we registered only one T-cell lymphoma. There were 6 DLBCLs, 4 MALT lymphomas, 3 lymphocytic lymphomas, 1 anaplastic large cell lymphoma, 1 precursor B lymphoblastic leukemia/ lymphoma, 1 peripheral T-cell lymphoma, anaplastic type (the lymphoma of the terminal ileum) and 2 lymphomas were not classified at the time being (Figure 5). The lymphoma was limited to the GIT in 6 patients, 7 patients had regional nodal involvement, in 2 patients there was an intra-abdominal spread of the neoplastic process and in 3 patients there was an extra-abdominal dissemination. Most patients received chemotherapy and only 2 patients were treated surgically. Two patients (aggressive peritoneal DLBCL and peripheral T-cell lymphoma of the terminal ileum) had rapidly progressive clinical course and lethal outcome shortly after the diagnosis was established and before chemotherapy was administered.

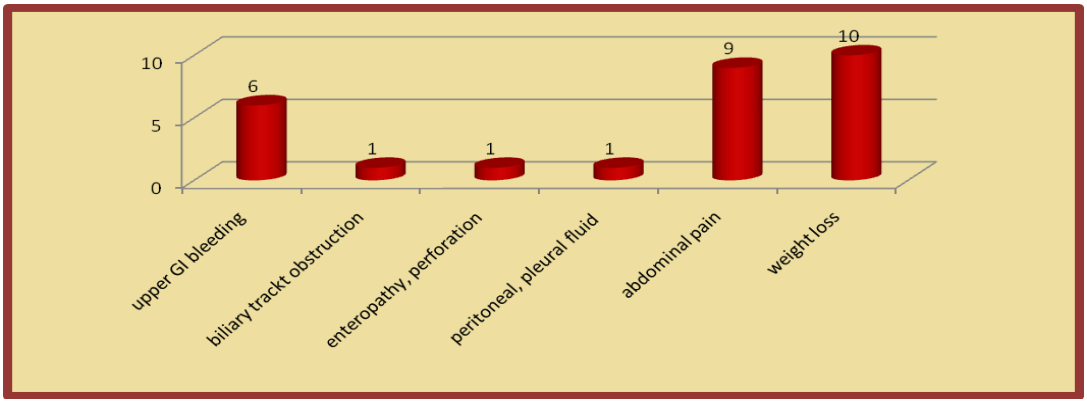

Fig. 3. Clinical presentation of patients with GL

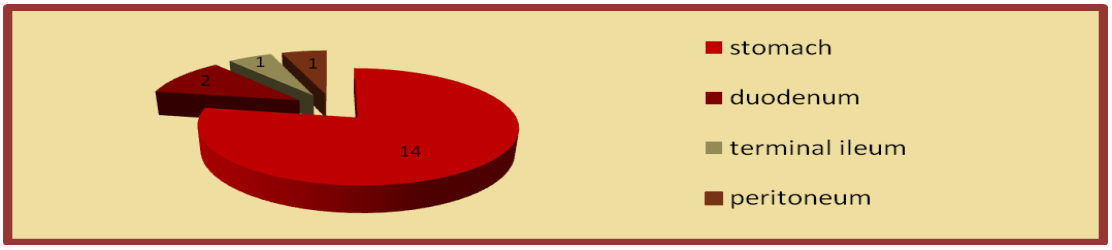

Fig. 4. Distribution of GL within the gastrointestinal tract: the stomach was the most prevalent extranodal localization, 14 cases (11 primary and 3 secondary)

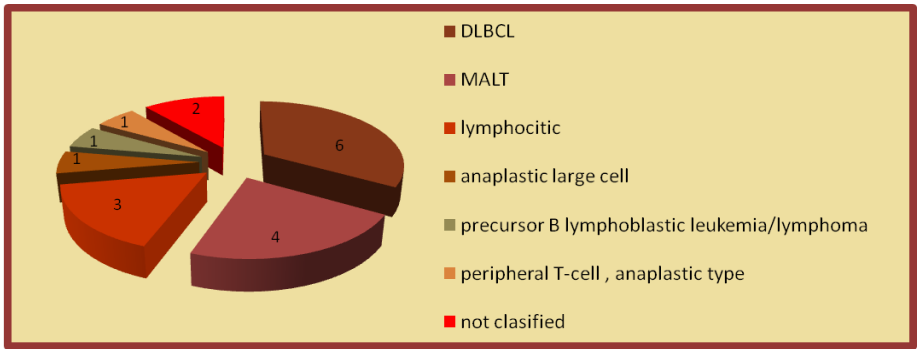

Fig. 5. Presence of different histological types: all malignant lymphoma were Non-Hodgkin type; there were 15 B-cell and only one T-cell lymphoma and DLBCL was the most prevalent subtype

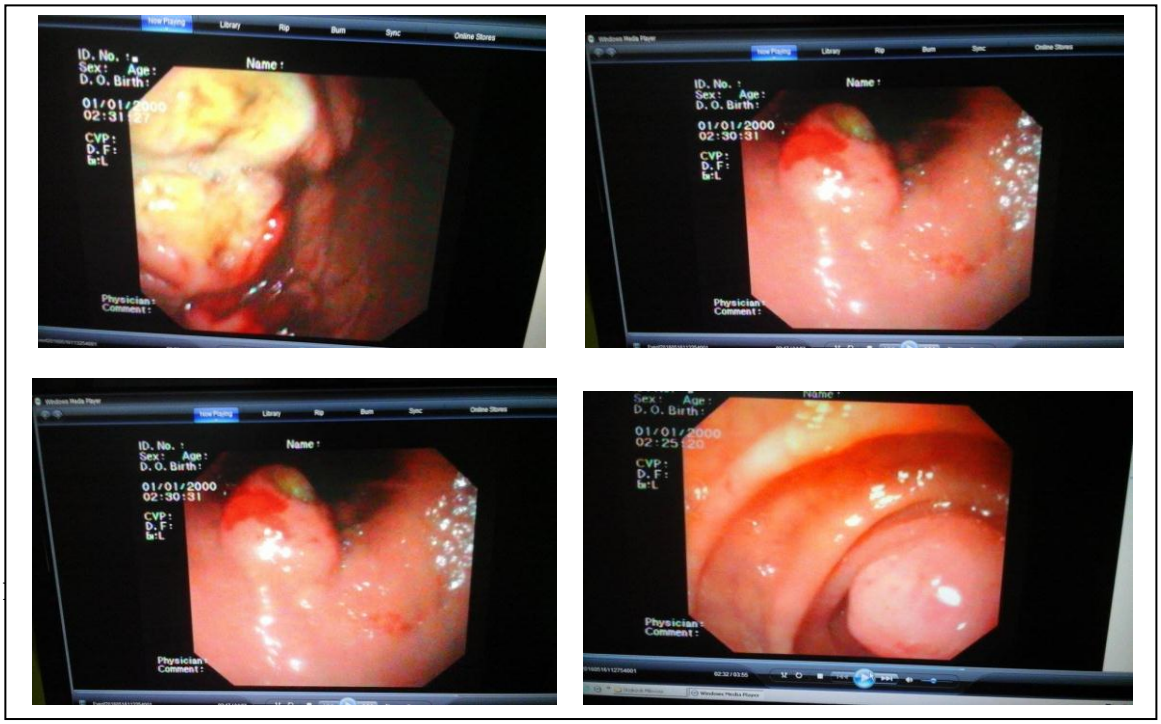

Fig. 6. Endoscopic appearance of gastric lymphoma (DLBCL)

Discussion

Epidemiological studies that deal with PEL and GL report that incidence and distribution of different lymphoma types vary in different geographic regions of the world, probably as a result of the geographic variations in the prevalence of viral or bacterial infection, celiac disease, diet or other environmental factors [25,31-34]. The incidence of PEL is around 15-25% of NHL in the United States and around 30-42% in parts of Europe [20,28,35], but it is higher in Middle East and Far East (Pakistan and Saudi Arabia up to 50%, 45% in Kuwait, 48.3% in Northern Iraq, 47.2% in Taiwan, 46.6% in Japan, 55% in Korea, 58.7% in Thailand, 44.9-61.4% in China, 22% in India) [4,9-11,14-16,36]. Primary small intestinal lymphoma is more prevalent in the Middle East and Mediterranean basin in comparison to the Western countries and the incidence of Burkitt lymphoma in Africa is approximately 50-fold higher than it is in the US [37,38]. There are some specifics related to some regions in Europe, suggesting that some lymphoma types, for example, the marginal zone lymphoma of MALT type occurred less frequently in South-East European countries (6.6%) than in West-European countries (10.5%), but it was still relatively common in Macedonia (7.6%) and Croatia (7.4%) [39]. Moreover, over the past two decades, many epidemiologic studies reported a rise in the incidence of NHL, extranodal lymphoma and GL in most parts of the world [12,13, 40-44]. Surprisingly, despite the thorough search through our database, within these 15 years we discovered only 18 cases of GL, a number much lower than we expected. This could possibly be explained by the fact that some patients diagnosed and managed at the Hematology Clinic could have had a gastrointestinal involvement that was not clinically dominant and remained unrecognized. Since we were only searching our gastroenterology database, it is possible that some of these patients were not detected and recruited within the study population. Moreover, the small number of patients prevented us from performing a more thorough analysis and making more reliable conclusions.

The distinction between PGL and SGL is complex and rather difficult. There were several previous attempts to create a suitable definition for EL, but the suggested diagnostic criteria are still not particularly precise. In the late 1961 Dawson and the coworkers set a diagnostic criteria for PEL, defining it by: 1) absence of palpable superficial lymph nodes on first physical examination; 2) absence of mediastinal lymphadenopathy detected on plain Chest X-ray; 3) dominant lesion at extranodal sites; 4) involvement of lymph nodes in the vicinity of the primary lesion; and 5) white blood cell count within normal range [27]. There was also a need to define the lymphoma with gastrointestinal involvement as PGL and to distinguish this entity from the lymphoma with secondary gastrointestinal involvement. Lewin *et al*. in a large series of 117 PGL patients defined the PGL as a lymphoma presenting with dominant lymphoid mass and/or associated symptoms within the GIT [29]. Later in 2003 Krol *et al*. suggested a liberal definition of PGL as a NHL that apparently originated at an extranodal site, even in the presence of disseminated disease, as long as the extranodal component was clinically dominant [45].

These definitions are still in wide use, especially as inclusion criteria in studies that deal with the PGL. But it is important to stress that in the routine clinical practice this distinction is sometimes very difficult to make. There is a significant number of patients that are diagnosed in an advanced stage where there is a large mesenteric mass along with a gastric infiltration. In these circumstances it is very difficult to define the dominant mass and to distinct the leading symptoms, which makes the definition of PGL rather challenging.

According to the two largest studies of GL of German and Greek population, being affected in 68-75%, stomach is the most prevalent GIT localization followed by small intestine including duodenum (9 %), ileo-cecal region (7%), more than one gastrointestinal localization (6-13%), rectum (2%) and diffuse colonic involvement (1%) [19,34]. Although there are studies in which most GL were located in the small bowel, [31,46,47] most studies report the gastric lymphoma as the most prevalent PEL [13,29,36,43,48,49]. In our report the stomach was also the most prevalent extranodal localization, being affected in 14 cases (11 PGL and 3 SGL), followed by small bowel (including duodenum and terminal ileum) in 3 cases. According to the literature, the primary gastric lymphoma is an uncommon tumor and accounts for about 2% of all lymphomas and for less than 15% all gastric malignancies [27]. However, primary gastric lymphoma is the most common EL, representing 30%-40% of all EL and 60%-75% of all GL [19,20,34,50]. Most of the primary gastric lymphomas (more than 90%) are either DLBCL or MALT lymphoma [51,52]. The primary gastric lymphoma was also the most prevalent entity in our group. We detected eleven cases of primary gastric lymphoma. Among them there were 4 DLBCL (Figure 6), 4 MALT lymphomas, 2 lymphocytic type lymphomas and one remained undetermined. Six of these patients presented with upper GI bleeding, which is not very common presentation of gastric lymphoma. DLBCL is the most prevalent GL and the most prevalent NHL in the western countries comprising 30-40% of all NHL cases [41,53]. Although the occurrence of DLBCL in our study was much lower than in most reports, DLBCL was still the most prevalent histopathological type being present in 6 cases (33%).

PGL is related to some risk factor such as Helicobacter pylori (H. pylori) infection, celiac disease and immunosuppression [23]. The relation between H. pylori and gastric MALT lymphoma is well established, but the role of H. pylori in gastric DLBCL is uncertain and still a matter of debate [54,55]. The H. Pylori infection has been involved in the pathogenesis of gastric MALT lymphoma and the bacteria can be identified in the gastric mucosa of more than 90% of these cases [56]. The H. pylori infection causes an immunological response leading to chronic gastritis with aggregation of T CD4+ and B lymphocytes and formation of lymphoid follicles in the gastric lamina propria [57]. The treatment of gastric MALT lymphoma involves eradication of H. pylori infection and the regression of the lymphoma in response to the eradication strengthens the causal theory between H. pylori and the entity [58]. Considering the retrospective nature of our research, we were not able to register and analyze the H. pylori status in most patients and to provide data and conclusion on this matter.

Despite the small number, we registered several interesting and unusual findings in our study. In most reports the GL was more prevalent in male than in female patients [1,13,43,48,49], which was not the case in our group, but taking into account the small number of patients, this deviation has no particular relevance. We registered a case of peripheral T-cell lymphoma that is very rarely found in the literature [58,59]. On the contrary, we did not detect a single case of colonic lymphoma which is rather unusual. It is also remarkable that there was a rare and unusual case of peritoneal lymphoma presented with ascites and pleural fluid accumulation without solid organ involvement or peripheral lymph node enlargement, which makes it a possible case of primary effusion lymphoma. Unfortunately, we were not able to confirm this with certainty because of the rapid clinical progression and the premature lethal outcome before the immunohistochemical and genetic analyzes were performed.

Conclusion

NHL is a heterogeneous group of lymphoproliferative malignant disorders with variable localization, presentation, natural course and malignant potential. The gastrointestinal involvement along withthe nonspecific clinical presentation and variable endoscopic appearance additionally contributes to the difficulty in the diagnostic process. Moreover, the new therapeutic protocols change the prognostic prospective of the lymphoma from potentially lethal to potentially curable disease. These are the reasons why a substantial level of diagnostic awareness and comprehensive clinical approach are necessary in order to establish the diagnosis correctly, provide appropriate treatment and prolong survival.

Conflict of interest statement. None declared.

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Original article

CEREBRAL OXYGENATION NON INVASIVE MONITORING IN TRAUMATIC BRAIN INJURY - A PILOT STUDY

НЕИНВАЗИВЕН МОНИТОРИНГ НА ЦЕРЕБРАЛНА ОКСИГЕНАЦИЈА КАЈ ТРАУМАТСКИ МОЗОЧНИ ПОВРЕДИ - ПИЛОТ СТУДИЈА

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Abstract

Introduction. Cerebral oximetry obtained with Near Infrared Spectroscopy (NIRS) provides noninvasive monitoring of microvasculature in the brain allowing for early recognition and preventive treatment of impaired cerebral oxygenation in traumatic brain injuries. Optimizing cerebral oxygenation is advocated to improve outcome in traumatic brain injury (TBI) hence the goal of this study was to determine the benefit of non invasive monitoring of cerebral oxygenation.
Methods. Noninvasive monitoring was conducted in fifteen patients with traumatic brain injury. The values and changes in cerebral oximetry were analyzed and compared with others tracked parameters: Glasgow Coma Scale on admission to determine the severity of traumatic brain injuries, systolic arterial blood pressure, mean arterial blood pressure, pulse oximetry, and regular laboratory test. Regional cerebral oxygenation was measured using cerebral oxymetar INVOS 5100 Somanetics®.
Results. According to data obtained, we noticed that any change in hemodynamic profile directly influenced the regional cerebral oxygen saturation. Higher changes of 15 % and more than basal values correlate with unfavorable outcome as neurologic sequels. Decreased values of rSO2 in our study were rectified with several simple interventions. In our cases decreased mean arterial blood pressure was the most prominent cause for disturbed rSO2.
Conclusion. Stable hemodynamic profile leads to optimized cerebral oxygenation. Monitoring the regional oxygen saturation influenced by several factors is important step for forehanded detection of adverse secondary brain injuries. NIRS technology as a monitoring system has potential diagnostic value and enables right therapeutic decisions and consequently better prognosis in TBI. Continued study of the benefits of cerebral oxygen monitoring is warranted.

Key words: cerebral oxygenation, mean arterial pressure, near-infrared spectroscopy, traumatic brain injury, noninvasive neuromonitoring

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Апстракт

Вовед. Церебрална оксиметрија, користејќи спектроскопија, со зраци близу до инфрацрвените (НИРС) обезбедува неинвазивен мониторинг на микроваскулатурата во мозокот овозможувајќи препознавање и превентивен третман на нарушена мозочна оксигенација кај пациентите со трауматска мозочна повреда. Оптимизирање на мозочната оксигенација го подобрува исходот кај мозочните повреди, па оттаму и целта на оваа студија е да се детерминира корисноста од неинвазивното мониторирање на церебралната оксигенација.
Методи. Невромониторинг со спектроскопија близу инфрацрвеното зрачење беше спроведен кај 15 пациенти со присутна траума на мозокот. Вредностите и промените во церебралната оксиметрија се споредуваа со другите следени параметри, се следеа: Глазгов Кома Скала при прием за одредување на клиничката тежина на трауматските мозочни повреди, систолен артериски притисок, среден артериски притисок, периферната кислородна сатурација и стандардни лабораториски наоди. Регионалната мозочна оксигенација се мереше користејќи го церебралниот оксиметар INVOS Somanetics®.
Резултати. Според добиените податоци се констатираше дека било каква подрастична промена во хемодинамиката директно влијае на мозочната сатурација. Поголеми промени во вредностите од 15 % и повеќе од базалните корелираат со лош исход и невролошки секвели. Намалените вредности на мозочната оксиметрија беа исправени со едноставни

интервенции. Кај нашите пациенти намалување на средниот артериски притисок беше пратен и со пореметување во мозочната оксигенација.

Заклучок. Стабилна хемодинамика води кон оптимизирана церебрална оксигенација. Мониторирање на регионалната мозочна сатурација е важен чекор за предвремено детектирање на несаканата секундарна мозочна повреда. Технологија користејќи спектроскопија со зраци близу до инфрацрвените има потенцијал во дијагностиката и секако во пружањето на правилен третман и подобра прогноза на трауматските мозочни повреди. Пожелно е континуирано истражување на корисноста од неинвазивен мониторинг на мозочната оксигенација.

Клучни зборови: церебрална оксиметрија, среден артериски притисок, трауматска мозочна повреда, неинвазивен невромониторинг

Introduction

Traumatic brain injuries without any doubt present enormous health and socio economic issue accompanied with high percent of mortality and morbidity especially in young population [1].

It is well known that traumatic brain injuries (TBI) initiate whole cascade of events leading to secondary brain injury. These secondary changes consist of ischemic, electrolytic, neurochemical and immunological processes which subsequently damage the already disturbed brain [2,3].

The causes for secondary brain injuries can be intracranial and extra cranial. The intracranial causes are intracranial hypertension, cerebral edema, disturbances in regional cerebral blood flow, seizures, excitotoxicity, mitochondrial dysfunction and metabolic disturbances. The extra cranial causes are systemic disturbances as hypoxemia, hypotension, anemia, disturbance in glucose metabolism and other metabolic abnormalities. If possible causes can be recognized on time, treatment and outcome will be much more beneficial. Prevention of possible causes can decrease the secondary brain injuries and hence is the main therapeutic goal in TBI management [4,5].

There are continuous achievements in quality of care for patients with TBI in operating rooms and in intensive care units. Despite this progress secondary brain injuries remain the biggest concern which can happen intraoperatively and in intensive care units [6,7]. Medical treatment of patients with traumatic brain injury (TBI) consists of three main pathways: to maintain cerebral oxygenation within normal ranges, to maintain cerebral perfusion pressure (CPP) and to control raised intracranial pressure (ICP) within normal ranges. Consequently, monitoring of these parameters in neurocritical care is strongly advised. Neuromonitoring is a much more essential tool in intensive care unit and its primary goal is trauma brain injury management with identification of causes and prevention of secondary brain injuries and therapy guiding [8].

This requirement initiates development of new technologies for monitoring and new strategies for early detection of brain dysfunction and appropriate neuroprotection.

Standard methods for monitoring still do not provide direct measurements of brain processes. Nowadays we are talking about multimodal monitoring which provides monitoring of several parameters of brain physiology and function and consists of several invasive and noninvasive techniques. The revised *Guidelines for the Management of Severe TBI* advocate (class III evidence) monitoring of cerebral oxygenation by jugular oximetry or measurement of brain tissue oxygen pressure via a parenchymal probe [9]. Jugular oximetry provides a more global estimate of oxygen extraction by the brain, whilst brain tissue oxygen monitoring represents a very local measurement, averaging the oxygen tension in a relatively small volume of tissue. Both techniques are widely accepted in clinical practice [10] and support management in TBI, but carry the disadvantage of being invasive [11]. More ideal would be noninvasive measurements of cerebral oxygenation. In this regard, near-infrared spectroscopy (NIRS) offers hope.

In 1996, Samra *et al*. suggested that noninvasive monitoring technique with cerebral oximetry-using spectroscopy with electromagnetic waves near infrared light spectroscopy can be clinically useful in management of patients with TBI, neurosurgical procedures and open heart surgery [12].

Cerebral oximetry with Near-Infrared Spectroscopy (NIRS) method provides noninvasive monitoring of microvasculature under the sensors measuring the oxyhemoglobin and deoxyhemoglobin in venous and arterial blood in ratio of 75:25 percent. This results in a sensitive, real time measurement of venous oxygen reserve i.e. measuring the blood oxygen which remains after the extraction from the tissue. This method enables absolute measurement of oxygen cerebral saturation (rSO2) and parameter reflects the balance between oxygen delivery and oxygen consumption [13].

The NIRS as a method is based on transmission and absorption of electromagnetic rays in area near the infrared light spectrum (700-100 nm) on different lengths passing the tissue. Since oxy-and deoxyhemoglobin have different absorption spectrum, cerebral oxygenation is assessed according to their relative absorption of near the infrared radiation. Factors that influence the absorption are scalp thickness, myelin sheets, liquor and changes in extracranial blood flow [14].

Pulse oximetry uses the spectroscopy of near the infrared radiation to estimate noninvasively and continuous changes of blood oxygen saturation. The main difference is that cerebral oxymetry directly monitors

the changes in regional oxygen saturation (rSO2) of predominately venous blood in the brain.
Since this system provides direct measurement of oxygen saturation in cerebral cortex any imbalance is an early warning sign of potential cerebral ischemia and impairment of brain function.
Normal values of basal rSO2 are 50-78% with 10 % variation up and down (critical moment is the value which is 15-20% lower than the basal one). Threshold for critical value is more individual and depends on accompanied disease, hence the most important necessary step is to establish the basal value of rSO2 in every patient [15]. When changes in oxygen delivery and consumption occur they can be intervened with simple procedures before irreversible brain secondary injury might happen.
Using this parameter enables indirectly monitoring of brain perfusion. It can be a sign of impairment in patient condition much earlier than other systemic measurements and laboratory tests which can remain normal besides the already occurred brain ischemia [16].

Aim of the study

Optimizing cerebral oxygenation is advocated to improve outcome in head-injured patients hence the purpose of this study was to determine the benefit of non invasive monitoring of cerebral oxygenation. The significance of this method is in early recognition of impaired cerebral oxygenation as a cause of secondary brain injury in TBI and preventive treatment of these changes.

Materials and methods

This is a randomized observational study. It has been performed at the Neurosurgical Intensive Care Unit of the University Clinic of Neurosurgery in Skopje from November 2015 and it is still going on. The study includes patients with traumatic brain injury and condition which allow placement of Somasensor® in the frontal part of the cranial vault. We applied standard diagnostic and resuscitation methods for trauma patients and specific methods for treatment of traumatic brain injury according to novel guidelines for treatment of neurotrauma patients.
In addition to standard therapy, a therapy for stabilization of the shock condition was given to all patients. On admission the following parameters were examined: Glasgow Coma Scale (GCS) to determine the severity of TBI, systolic blood pressure (SBP), mean arterial pressure (MAP), pulse oximetry (SpO2), and regular laboratory tests, ECG and temperature monitoring. Tracking the invasive arterial pressure is enabled through cannulation and placement a catheter in the right radial artery.
Regional cerebral oxygenation was measured noninvasively using cerebral oximetar INVOS 5100 Somanetics® in every patient on admission determining the basal cerebral values in the right and left hemisphere It is performed with two sensors i.e. Somasensors which are placed on the frontal part of patient's head. Spectroscopic radiation near infrared light passes through the frontal part of the scalp entering brain. The big letters R and L are used for determining the value of cerebral oxygenation in the right and left hemisphere. Non-invasive monitoring of cerebral oxygenation until now has been conducted in fifteen patients with TBI. The values and changes in cerebral oximetry were analyzed and compared with others tracked parameters.

Results

This pilot study investigates 15 patients suffering from traumatic brain injury. Demographic data are displayed in Table 1 as M ±SD and show distribution by sex, age, weight and height.

Table 1. Demographic data of examined patients (n=15) (M±SD)

Number	Sex		Age		Weight		Height	
n=15	M	F	M	F	M	F	M	F
	10	5	53.13±12.52	60±11.56	75.73±11.4	54.55±6.75	174±8	156±7

Table 2. Mechanism of injury

Mechanism of injury	n=15	%
Traffic accidents	7	46.6666
Pedestrians	4	26.66
Fall from height	3	20
Other	1	6.66
Total	15	100

According to mechanism of injury 46.6% of patients were victims of traffic accidents, 26.6% were victims as pedestrians. Patients due to mixed diagnosis belonged to several groups in same time.
Tables 4 and 5 present parameters examined in patients at the moment of admission in the intensive care

Table 3. Distribution of patients by diagnosis

SAH traumatica	Hematom epidurale	Hematom subdurale	Contusi cerebri	F-ra bazeos	F-ra impressiva
3	4	9	12	1	2

Table 4. Distribution of patients related to GCS

GCS	n	%	M±SD
1 - severe neurotrauma (GCS 3)	1	6.6	
2 - severe neurotrauma (GCS 4-5)	1	6.6	
3 - severe neurotrauma (GCS 6-8)	3	20	
3 - moderate neurotrauma (GCS 9-12)	6	40	
4 - mild neurotrauma (GCS13-15)	4	26.6	
Total	15	100	9.73±3.34

Shortcuts: GCS-Glasgow Coma Scale

unit: Glasgow Coma Scale (GCS), systolic arterial pressure (SAP), mean arterial pressure (MAP), pulse oximetry (SpO2) and rSO2 basal in the right and left hemisphere. The first parameter GCS in five patients showed severe neurotrauma (GCS 3-8), 6 patients had moderate neurotrauma (9-13) and four patients were with mild neurotrauma (GCS 14-15). One patient died after the first 24 hour. Hemodynamic profile on admission as systolic arterial pressure (SAP) and mean arterial pressure (MAP) were far below the threshold

Table 5. Data on admission in ICU

	GCS	SAP	MAP	SpO2	rSO2 basal R	rSO2 basal L
1	3	86	53	83	46	48
2	12	154	112	97	74	73
3	13	148	95	96	75	77
4	9	114	83	92	59	67
5	7	80	54	88	54	51
6	10	145	113	95	64	62
7	8	130	102	92	72	69
8	5	78	56	76	48	53
9	13	153	93	93	66	62
10	15	124	87	99	78	75
11	10	135	95	98	75	77
12	13	113	72	94	68	69
13	7	82	54	88	57	61
14	9	104	62	92	66	58
15	12	165	114	95	75	74
M±SD	9.73±3.34	120±29.66	83±22.89	91.86±6.08	65.13±10.28	65.05±9.24

Shortcuts: GCS - Glasgow Coma Scale, SAP - systolic arterial pressure, MAP - mean arterial pressure, SpO2- pulse oximetry

for optimized cerebral perfusion pressure in three patients

In Table 6 values for regional cerebral oxygenation (rSO2) are illustrated in the first 24 hour. The basal values were determined in the first hour and values were monitored in next hours. We noted the biggest change i.e. decreas or increas and they were connected with algorithm for possible causes. The procedures for increasing the oxygenation were performed as soon as possible. After the intervention values returned to near the basal ones i.e. cerebral oxygenation increased.

Table 6. Regional cerebral oxygenation rSO2

patient	SpO2 %	rSO2 basal %		rSO2 max change %		rSO2 difference %		Intervention
		R	L	R	L	R	L	
1	83	46	48	54	55	17.3	14.5	↑MAP,↑FiO2, head position
2	97	74	73	66	67	10.8	8.2	↓ MAP
3	96	75	72	76	73	1.3	1.3	MAP >70 mmHg
4	92	59	67	66	70	11.8	4.4	↑MAP,↑FiO2, head position
5	88	54	51	65	64	20.3	25.4	↑MAP,↑FiO2,
6	95	64	62	65	67	1.5	8.06	MAP >70 mmHg
7	92	72	69	74	73	2.7	5.7	MAP >70 mmHg
8	76	48	53	43	47	12.5	11.3	↓ MAP
9	93	66	62	72	71	9.09	14.5	↑MAP,↑FiO2 head position
10	99	78	75	78	76	0	1.3	MAP >70 mmHg
11	98	75	77	76	78	1.3	1.3	MAP >70 mmHg
12	94	68	69	72	74	5.8	7.2	↑MAP,↑FiO2
13	88	57	61	68	72	19.2	18.02	↑MAP,↑FiO2
14	92	66	58	73	67	10.6	15.5	↑MAP,↑FiO2 head position
15	95	75	74	77	75	2.6	1.3	MAP >70 mmHg
M±SD	91.8±6.0	65.1±10.2	65.05±9.2	68.3±9.4	68,6±7.9	8.5±7.3	9.2±7.2	

Shortcuts: SpO2-pulse oximetry, rSO2-regional cerebral oximetry

Discussion

Monitoring of cerebral oxygen saturation presents a window for the processes running on cellular level in that actual moment. Near-infrared spectroscopy (NIRS) as a method monitors the changes of cerebral oxygen which is a result of mechanic and hemodynamic processes.

McCarthy in his investigation in 2009 [17] used three month Glasgow Outcome Score (GOS) that revealed clinically meaningful 18% benefit in patients undergoing cerebral oxygen monitoring and optimization.

According to data obtained in several patients we noticed that any changes in hemodynamic profile directly influenced the regional cerebral oxygen saturation. In four patients we observed values higher than 15 % and more from the basal ones which correlated with more unfavorable outcome in terms of neurologic sequels. Decreased values of rSO2 in our cases were rectified with several simple interventions [18]. Some of these interventions were: correct head position in neutral position enabling permanent drainage of venous circulation from the brain; decrease cerebral metabolism with deeper sedation; decrease body temperature as a protective measure, increase oxygen delivery associated with increase in FiO2, increase cerebral blood flow, increase PaCO2 to normal values, increase blood pressure using inotropes and increase hematocrit value by giving red blood cells.

Decrease of rSO2 under the critical value of 20% occurred in one patient who died after 24 hours, but a more warning sign were the changes in the values higher than 15% and more from the basal ones, which occurred in three patients. Using simple interventions we successfully returned the values of rSO2 to almost basal ones [19].

Decreased mean arterial pressure (MAP) was the most prominent cause for decreased rSO2 in our patients. This indicates the importance of maintaining stable hemodynamics in patients with TBI. It corresponds with the randomized blind study of Murkin *et al*. [20] who investigated 200 patients undergoing coronary bypass surgery. They found that monitoring of cerebral rSO_2 by NIRS permitted earlier detection and treatment of systemic events causing cerebral desaturation. The most frequent interventions in this study were increasing mean arterial blood pressure, increasing pump flow, and correction of hypocapnia.

Normalizing the cerebral oxygen saturation as cause that can initiate severe secondary brain injuries is a beneficial step for optimized management of patients with traumatic brain injury.

Conclusion

By analyzing the results obtained by now we can conclude that NIRS signals of cerebral hypoxygenation reacted first to mean arterial pressure changes. Aggressive approach in maintaining stabile hemodynamic profile leads to optimized cerebral oxygenation. Monitoring the regional oxygen saturation influenced by several factors is an important step in a forehanded detection of adverse secondary brain injuries. NIRS technology as a monitoring system has potential diagnostic value and enables right therapeutic decisions and consequently better prognosis in TBI. Continued study of the benefits of cerebral oxygen monitoring is warranted.

Conflict of interest statement. None declared.

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Original article

INTRACEREBRAL HEMORRHAGE AND EPILEPTIC SEIZURE: FREQUENCY, LOCALIZATION AND SEIZURES TYPES

ИНТРАЦЕРЕБРАЛНА ХЕМОРАГИЈА И ЕПИЛЕПТИЧНИ НАПАДИ: ФРЕКВЕНТНОСТ, ЛОКАЛИЗАЦИЈА И ТИПОВИ НА НАПАДИ

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Abstract

Introduction. Between 2.8-18.7% of patients that suffer from spontaneous intracerebral hemorrhage (ICH) develop seizures. Previous studies suggest that the most important factors for developing subsequent seizures are: volume and localization of hematoma, cortical involvement and age. Aims: To determine the occurrence of new epileptic seizures in patients with spontaneous intracerebral hemorrhage and to analyze it with respect to patient's age, gender, presence of premorbid risk factors, localization of the hematoma and type of the seizures.

Methods. This is a retrospective study in design, comprising a sample of 308 patients with spontaneous intracerebral hemorrhage admitted the University Clinic for Neurology in the period between 2008 and 2014. The following premorbid risk factors for ICH were analyzed: hypertension, smoking, alcohol consumption. According to computer tomography (CT) of the brain patients were divided in two groups: lobar and thalamic (deep). According to the time of manifestation of seizures, they were classified as early (within 1 week of ICH) or late (more than 1 week after ICH). Also we analyzed seizure type and we divided them in four groups: simple partial, partial complex, secondary generalized and tonic clonic generalized seizures.

Results. Arterial hypertension was revealed in 78% of patients with spontaneous supratentorial ICH. Epileptic seizures developed in 8.2% of analyzed patients, most of them in the first week of brain bleeding. Lobar ICH had 78.6% of patients, with frontal localization in 44% of patients with lobar ICH, and most of them had simple partial and partial complex seizures.

Conclusion. Cortical involvement, large volume of hematoma, may be a factor for provoked seizures, especially in the first days of brain bleeding.

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Keywords: epilepsy, seizure, intracerebral hemorrhage

Абстракт

Вовед. Нови епилептични напади кај 2.8-18.7% од пациентите со интрацеребрална хеморагија (ИЦХ) се јавуваат нови епилептични напади. Претходните студии сугерираат дека најзначајни фактори кои придонесуваат за развојот на епилептични напади по ИЦХ се: волуменот и локализацијата на ИЦХ, инволвираност на кортексот и на возраста.

Цели на студијата. Да се одреди степенот на застапеност на епилептични напади кај пациенти со спонтана интрацеребрална хеморагија и да се постави зависност со полот и возраста, преморбидните ризик фактори, локализацијата на хематомот и типот на епилептичниот напад.

Методи. Студијата беше ретроспективна, со студиска популација од 308 пациенти со спонтана супратенторијална ИЦХ примена на Универзитетска клиника за неврологија во периодот од 2008-2014. Анализирани беа ризик фактори за ИЦХ: покачен крвен притисок, пушење, алкохол. Според наодот за ИЦХ на компјутеризирана томографија на мозокот (КТМ), пациентите беа поделени во две групи: лобарни и таламични. Според времето на појава на епилептичниот напад беа групирани во две групи: први 7 дена и после првата недела од ИЦХ.

Резултати. ХТА беше регистрирана кај 78% од пациентите. Епилептични напади имале 8.2% од анализираните пациенти, повеќето во првата недела од настанувањето на ИЦХ. Лобарни ИЦХ имаа 78.6% од пациентите, од тие 44% беа со фронтална локализација, а најголем број од нив имаа едноставни парцијални и парцијални комплексни напади.

Заклучок. Кортикалната инволвираност, големината на хематомот, кај пациенти со спонтана ИЦХ е значаен фактор во појава на епилептични напади, особено во првите денови од мозочното крварење.

Клучнизборови: епилепсија, епилептичен напад, интрацеребрална хеморагија

Introduction

Intracerebral hemorrhage (ICH) is an acute cerebrovascular disease (CVD), which occurs with rupture of a brain artery and extravasation of blood into the surrounding brain parenchyma [1]. Ischemic strokes are represented by 85-90%, and ICH are 10-15% of the total number of CVD. The majority of ICH is hypertensive (60%), and most of them are located supratentorially (85%). Supratentorial ICH is divided into two groups: lobar and deep (thalamic). Supratentorial lobar ICH according to the affected lobe is divided into: frontal, temporal, parietal and occipital ICH [2,3]. According to previous studies, 2.8-18.7% [4-7] of the patients with ICH developed subsequent seizures. The provoking factors of seizures in patients with ICH are volume of ICH, localization of hematoma in the frontal lobe and cortical involvement [8,9]. There are doubts about the prophylactic administration of antiepileptic therapy in patients with ICH, but the most recent studies indicate that there is no significant effect on the occurrence of epileptic seizures [10].

Aims of the study

The aim of the study was to quantify the occurrence of subsequent seizures in patents that suffered from acute, supratentorial intracerebral hemorrhage. In addition, we analyzed the gender and age of the patients and the following premorbid risk factors: presence of arterial hypertension, diabetes mellitus, smoking and alcohol consumption.

Material and Methods

The study was retrospective, conducted in a period of 6 years (January 2008-January 2014), at the University Clinic for Neurology in Skopje, Department of cerebrovascular disease and Department for early prevention of cerebrovascular disease. Data were collected from medical records (history of disease) of hospitalized patients in those departments.The inclusion criteria were defined as: clinical presentation of acute cerebrovascular accident and evidence of fresh haemorrhagic changes on CT scans. According to ICH findings of computed tomography of the brain (CT), patients were divided into two groups: lobar and thalamic (deep). According to localization lobar hemorrhages were divided into four groups: frontal, temporal, parietal and occipital lobar ICH [11-13].
Post-stroke seizures (PSS) were defined as new occurrence of seizure after ICH. According to timing, PSS were divided into two groups: early seizures (which were defined as new seizures in the first week after ICH) and late seizures (new seizures after the first seven days of ICH) [14-15].
According to the type of seizures, patients were grouped by using the classification of the International League for Epilepsy Seizures: simple partial seizures (SPS), complex partial seizures (CPS), and SGPS-partial seizures with secondary generalization seizures [16].
The statistical analysis of data was made with the descriptive statistics using the program Statistics for Window.

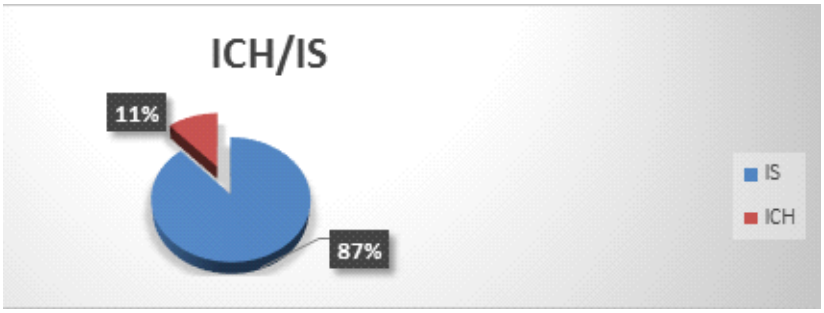

Fig. 1. Proportion of patients with ICH compared to total number of patients

Table 1. Description of patients: gender distribution, average age description

Patient demographics n=308		
	Gender (percentage)	**Mean age at presentation ± 2SD (age range)***
Male	162 (52.6%)	59±9.3 (41-78 y)
Female	146 (47.4%)	63±7.3 (47-89 y)
Total	308	64±8.1 (44-89 y)

*Age is expressed in years

Results

The total number of hospitalized patients with CVB in the analyzed period was 2368 of whom 308 were patients with spontaneoussupratentorial ICH (Figure 1).
In the analyzed period gender distribution of patients with spontaneous ICH was similar between males (n=162) and females (n=146). The average age of patients with ICH was 64 ± 8.1 years. (Table 1).

Predominantly high premorbid risk for the occurrence of spontaneous ICH was showen to be HTA (78% of patients). They were underrepresented mostly by alcohol intake (42.6%) and smoking (29.7%). Diabetes mellitus was found in a very small number of patients 7% (Figure 2).

Lobar ICH had 78.6% of patients, 44% of those were with frontal localization, 27% were parietal, 13% temporal and 16% of patients with ICH had occipital localization. Deep (thalamic) ICH had 21.4% of patients (Figure 3).

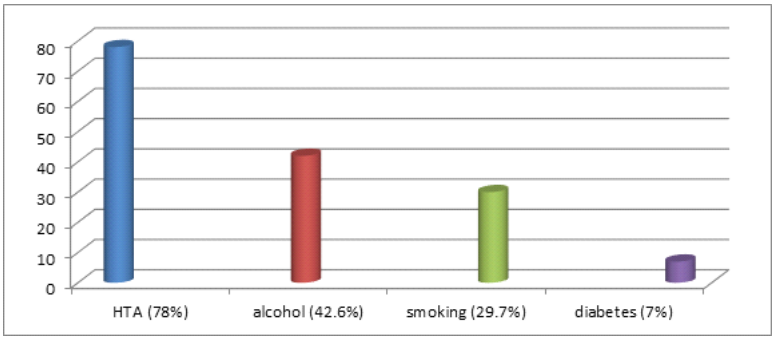

Fig. 2. The most common co morbidities as risk factors for occurrence of ICH

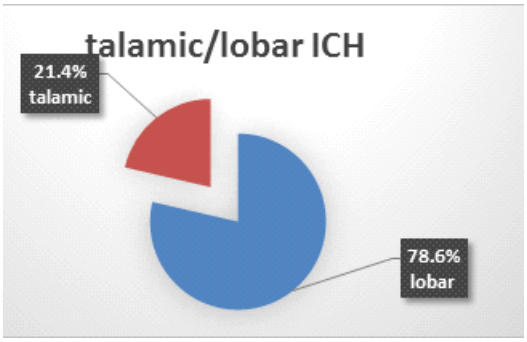

Fig. 3. Distribution of patients according to localization of hematoma

Epileptic seizures had 8.2% of the analyzed patients with ICH. In the first 7 days of the acute, spontaneous ICH 17 patients had epileptic seizure, and after the first week 8 patients. Thirteen patients had SGPS, four of them had CPS and SPS, and four patients had generalized seizure.

In most of the patients who had an epileptic seizure, ICH waslocalized in the frontal lobe (44%), which is $p<0.05$ (Figure 4).

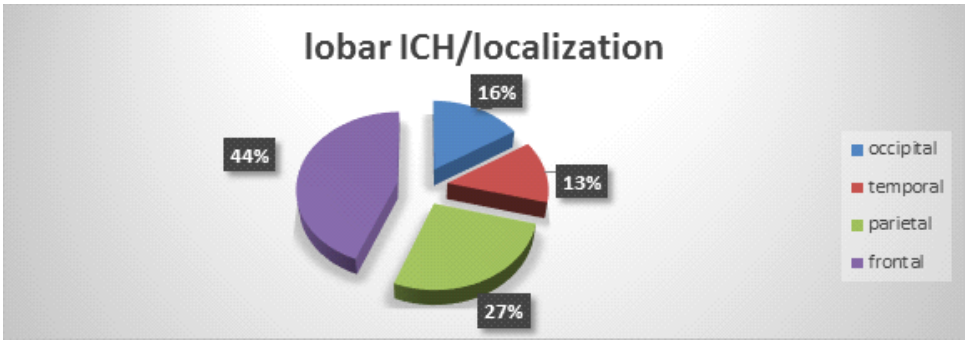

Fig. 4. Distribution of epileptic seizures according to localization of hematoma

Discussion

According to localization lobar ICH was divided into four groups: frontal, temporal, parietal and occipital. Statistically significant (for $p<0.05$), frontal lobar ICH were highly epileptogenic compared to occipital, temporal and parietal ICH. The frontal lobar ICH are second in frequency of symptomatic epilepsies (after temporal), but in our study they proved to be highly epileptogenic. This probably is due to the extensive cortical involvement of ICH [17,18]. According to the type of seizure most patients had PSS and PCS. The frontal lobe epilepsy, which was predominant in patients with ICH and seizures, was characterized mostly as PSS (without involvement of consciousness and memory) and PCS (stakeholder awareness or memory before, during and after the seizures [19,20]. In majority of patients we registered seizures in the first 7 days, patients with frontal and parietal localization of the hematoma, with extensive area of bleeding and direct compression cortical involvement. Similar results were registered in previous studies [21,22].

Conclusion

Our study suggest that large intracerebral hemorrhage, with cortical involvement, is an important factor in the occurrence of seizures, especially in the first days of brain bleeding, but also after 7 days of ICH. Most epileptogenic are frontally and temporally localized brain hematoma.

Conflict of interest statement. None declared.

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Original article

REACTIVE STROMA IN PROSTATIC CARCINOMA AND CORRELATION WITH TUMOR GRADE AND TUMOR STAGE

РЕАКТИВНА СТРОМА КАЈ ПРОСТАТИЧЕН КАРЦИНОМ И КОРЕЛАЦИЈА СО ГРАДУС И СТАДИУМ НА ТУМОР

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Abstract

Introduction. Reactive stroma co-evolves with prostatic carcinoma. The aim of this study is wasto establish stromal changes in the prostatic cancer tissue and to quantify those changes.
Methods. Samples from 70 patients treated with radical prostatectomy due to prostatic cancer were used for this analysis. Stromal changes in prostatic cancer tissue were analyzed using histochemical stain Trichrome Masson and immunohistochemical stains Vimentin and Desmin and those changes were compared to the stromal composition in the surrounding benign prostatic hyperplasia. These changes were quantified as follows: for the histochemical stain Trichrome Masson we measured the intensity of the stain and for the immunohistochemical stains Vimentin and Desmin we used the "stromal index" that combines the frequency and intensity of the signal. The received datawere correlated between themselves and with tumor grade and tumor stage using the Spearman's rank correlation test.
Results. There was a significant correlation between Trichrome Masson staining intensity and tumor grade (R=0,27 p=0,023) and tumor stage (R=0,24 p=0,049), between Vimentin expression and tumor grade (R=0,35 p=0,003) and tumor stage (R=0,28 p=0,019) and between Desmin expression and tumor grade (R=-0,25 p=0,035).
Conclusion. Analyses of the stromal composition and the expression of stromal markers in prostatic carcinoma and their quantification could serve as an additional tool in evaluation of tumor aggressiveness and tumor extension.

Keywords: prostatic carcinoma, stroma, immunohistochemistry

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Апстракт

Вовед. Реактивна строма коеволуира со простатичен карцином. Целата на студијата е да се утвдат стромални промени во простатичното канцерско ткиво и да се квантифицираат тие промени.
Методи. За оваа анализа се користеа примероци од 70 пациенти третирани со радикална простатектомија поради простатичен карцином. Стромалните промени кај простатичниот карцином беа анализирани користејќи го хистохемиското боење Trichrome Masson и имунохистохемиските боења: Vimentin и Desmin и овие промени беа споредени со околни подрачја на бенигна простатична хиперплазија. Промените беа квантифицирани на следниов начин: кај хистохемиското боење Trichrome Masson се одреди интензитетот на пребојувањето на стромата додека кај имунохистохемиските боења Vimentin и Desmin се употреби "индекс на пребојување" кој ги комбинира фрефкфенцијата на сигналот со интензитетот на сигналот. Добиените податоци се корелираа меѓусебно и со градус и стадиум на тумор користејќи Spearman-ов тест за корелација.
Резултати. Се покажа сигнификантна корелација помеѓу Trichrome Masson боењето со градусот на туморот (R=0,27 p=0,023) и со стадиумот на болеста (R=0,24 p=0,049), помеѓу експресијата на антителото Vimentin со градусот на туморот (R=0,35 p=0,003) и стадиумот на болеста (R=0,28 p=0,019) и помеѓу експресијата на антителото Desmin и градусот на туморот (R=-0,25 p=0,035).
Заклучок. Анализи на составот на стромата и експресија на стромални маркери кај простатичен карцином и нивна квантификација може да служи како дополнителна алатка во евалуација на агресивноста и проширеноста на простатичниот карцином.

Клучни зборови: простатичен карцином, строма, имунохистохемија.

Introduction

Stroma represents tissue component made up of extracellular matrix components and several cell types: fibroblasts, endothelial cells, smooth muscle cells, macrophages, mast cells and a number of cells that pass through the microenvironment via blood and lymph vessels. Smooth muscle cells predominate in prostatic tissue and they are derived from the mesenchyme of urogenital sinus. These cells are the most important cell type regarding prostate development, maintenance and homeostasis. Changes in smooth muscle cells could be important in evolution of prostatic carcinogenesis. The differentiation of prostatic smooth muscle cells occurs in a highly orderly manner with sequential expression of characteristic markers including vimentin, actin, desmin and vinculin. The process of dedifferentiation following castration is associated with rapid regression of prostatic epithelium combined with ordered loss of expression of these markers in opposite direction [1].

Changes occurring in the surrounding connective tissue stroma serve to enhance the malignant potential of the nearby epithelium [2]. Epigenetic influences derived from stromal cells may be crucial in determining whether a tumor will assume slowly growing or invasive phenotype [3-4]. Genetic mutation in the prostatic epithelium could alter the signaling to nearby smooth muscle cells and may trigger stromal dedifferentiation toward fibroblast phenotype. This transformation may yield a change in the local microenvironment, from promotion of epithelial homeostasis, toward epithelial mitogenesis and this may enhance the invasive potential of genetically altered epithelial cells [1]. This altered so called reactive stroma, surrounding epithelial carcinoma cells is not yet fully defined [5]. There are similarities of cancer stroma with the stroma involved in wound repair. A special cell type called myofibroblast is found in sites of pathologic tissue repair. In wound repair, myofibroblastsare derived from granulation tissue fibroblasts and in cancer carcinoma cells induce fibroblasts to the reactive myofibroblast phenotype [6]. Authors have suggested the term carcinoma associated fibroblasts for these cells. Some characteristics of these cells are established. They do not form tumors when grown in absence of epithelium, stimulate progression of genetically altered non tumorogenic prostate epithelium toward carcinomatous phenotype, and are unable to stimulate initiation of genetically normal prostatic epithelium [1,5].

Material and Methods

A retrospective analysis was performed using archive paraffin blocks from 70 consecutive patients that underwent radical prostatectomy due to previously diagnosed prostatic cancer on needle core biopsy. All cases presented with localized disease or locally advanced disease which means there were no metastatic deposits in the regional lymph nodes and no distant metastases according to the previous radiology imaging analyses. Adequate samples were chosen that contained almost equal amounts of prostatic cancer tissue and surrounding benign prostatic tissue.

First the sections were stined with Trichrome Masson histochemical stain, following a standard procedure. Normal prostatic smooth muscle cells stained red and reactive stroma surrounding prostatic carcinoma stained blue. Under low magnification (x40) an area of the most intense blue stain was chosen and then on high magnification (x400) five consecutive areas were analyzed. The amount of reactive stroma was graded semi quantitatively as follows: 0=no blue staining; 1=weak blue staining; 2=moderate blue staining; and 3=strong blue staining.

Then additional sections were taken for the immunohistochemical analysis of the stroma. For this analysis the following antibodies were used: Vimentin, clone V9, IgG1 class (DAKO), dilution 1:50 and Desmin, clone D33, IgG1 class (DAKO), dilution 1:50. Immunohistochemical staining was performed with the technique of Avidin-Biotin Immunoperoxydase Complex, Using LSAB and En-Vision kit for visualization of the antigen-antibody complex. Immunohistochemically, smooth muscle cells of normal prostatic stroma are Vimentin negative and Desmin positive, while carcinoma associated fibroblasts are Vimentin positive and Desmin negative.

In order to determine the intensity of stromal changes in prostatic carcinoma the percentage of stromal cells positive for Vimentin and Desmin the following procedures were taken: first, an area with the most intense blue staining on Trichrome Masson histochemical stain was identified, and then, on high magnification (x400), the same area was analyzed on five consecutive fields. Scoring scale was established for the analysis of frequency of positive cells from 0 to 3:0=0% positive stromal cells; 1=1-33% positive stromal cells: 2=34-66% positive stromal cells; and 3=67-100% positive stromal cells. Then on the same fields the intensity of the signal was analyzed using the following scale: 0=no signal; 1=weak signal detected on high magnification (x400); 2= moderate signal detected onmedium magnification (x100); and 3=strong signal detected on low magnification (x40). At the end the percentage of positive cells was added to the intensity of the signal to reach the "staining index": 0=no signal; 1-2 low staining index (1); 3-4=moderate staining index (2); and 6-9=high staining index (3) [5,7-8].

This counting method was repeated in the surrounding areas of benign prostatic tissue and the initial field chosen for analysis was the field with the most intense red color in the histochemical stain Trichrome Masson. Normal fibro muscular stroma of the prostate stains red, which means there is no reactive stroma that stains blue and the staining score is 0.

The results between the prostatic cancer stroma and stroma of the surrounding benign prostatic tissue were correlated. Also, additional pathological parameters like tumor grade (Gleason grade) and tumor extension or tumor stage (pT category) that were retrieved from the patohistology reports were correlated with the stromal changes in the prostatic carcinoma areas.

Statistical analysis was performed using chi square test and, for correlation between parameters Spearman's coefficient rank correlation test was used. The levels of statistical significance were set at $p<0.05$.

Results

Trichrome Masson histochemical stain showed the most frequent staining intensity score 2 in the stroma of the prostatic cancer (44.28%) and the most frequent staining intensity score 1 in the stroma of the surrounding benign prostatic hyperplasia (70%). The tested difference in the staining intensity between the stromal cells of prostatic carcinoma and benign prostatic hyperplasia is statistically significant (Chi-square=37.71 df=1 p<0.001) (Table 1).

Table 1. Staining intensity of Trichrome Masson in stromal cells of prostatic carcinoma and benign prostatic hyperplasia

Staining intensity	Trichome-carcinoma N %	Trichrome-BPH N %
0	0	0
1	11(15.71%)	49(70.0%)
2	31(44.28%)	20(28.57%)
3	28(40.0%)	1(1.43%)
1 and 2 – low	42 (59.99%)	69 (98.57%)
3 – moderate	28(40.0%)	1(1.43%)
Tested differences	Chi-square = 31.71 df=1 p<0.001	

Vimentin antibody showed most frequent staining index of 3 in the stroma of the prostatic carcinoma (48.57%) and in the surrounding benign prostatic tissue the most frequent staining index was 1(67.14%). Vimentin antibody showed significantly (Chi-square=45.55 df=1 p<0.001) greater expression in the stroma of the prostatic carcinoma compared to the stroma of benign prostatic hyperplasia (Table 2).

Table 2. Stainng index of Vimentin antibody in stromal cells of prostatic carcinoma and stromal cells of benign prostatic hyperplasia

Staining index	Vimentin-carcinoma (N%)	Vimentin-BPH N(%)
0	0	0
1	8(11.43%)	47(67.14%)
2	28(40.0%)	22(31.43%)
3	34(48.57%)	1(1.43%)
1 and 2 – low	36(51.43%)	69(98.57%)
3 – moderate	34(48.57%)	1(1.43%)
Tested differences	Chi-square = 45.55 df=1 p<0.001	

Desmin antibody in the stroma of prostatic cancer showed most frequent staining index of 2 (60%) while in the stroma of the surrounding benign prostatic hyperplasia all the cases showed staining index of 3(100%). The differences in staining index between the prostatic cancer stromal calls and stromal cells of the surrounding benign prostatic tissue is significant (Chi square=117.89 df=1 p<0.001) (Table 3).

Table 3. Staining index of Desmin antibody in stromal cells of prostatic carcinoma and stromal cells of benign prostatic hyperplasia

Staining index	Desmin-carcinoma N %	Desmin-BPH N %
0	0	0
1	22(31.43%)	0
2	42(60.0%)	0
3	6(8.57%)	70(100%)
1 and 2	64(91.43%)	0
3	6(8.57%)	70(100%)
Tested differences	Chi-square=117.89 df=1 p<0.001	

Trichrome Masson stain showed positive correlation with Vimentin expression (R=0.68 p<0.001), Gleason score (R=0.27 p=0.023) and tumor stage (R=0.24 p=0.049) and inverse correlation with Desmin expression (R=-0.28 p=0.023). This means that the intensity of blue staining grows with the intensity of Vimentin expression and the increase of tumor grade and tumor stage (Table 4).

Table 4. Correlations of Trichrome Masson, Vimentin and Desmin in stromal cells of prostatic carcinoma with each other and with tumor grade and tumor stage

Trichrome with	**Spearman Rank R**	**p-value**
Vimentin	R = 0.68	t = 7.67 p<0.001**
Desmin	R = -0.28	t = 2.39 p=0.02*
Tumor grade (Gleason)	R = 0.27	t = 2.32 p=0.023*
Tumor stage (T category)	R = 0.24	t = 1.99 p=0.049
Vimentin with	**Spearman Rank R**	**p-value**
Trichrome	R = 0.68	t = 7.67 p<0.001**
Desmin	R = -0.15	t = 1.28 p=0.2 NS
Tumor grade (Gleason)	R = 0.35	t = 3.03 p=0.003**
Tumor stage (T category)	R = 0.28	t = 2.4 p=0.019*
Desmin with	**Spearman Rank R**	**p-value**
Trichrome	R = -0.28	t = 2.39 p=0.02*
Vimentin	R = 0.15	t = 1.28 p=0.2 NS
Tumor grade (Gleason)	R = -0.25	t = 2.14 p=0.035*
Tumor stage (T category)	R = -0.2	t = 1.7 p=0.095 NS

*p<0.05 **p<0.01 NS-not significant

Vimentin expression in stromal cells of prostatic carcinoma showed significant correlation with Trichome Masson staining intensity (R=0.68 p<0.001), Gleason score (R=0.35 p=0.003) and tumor stage (R=0.28 p=0.019). It shows that Vimentin expression increases in stromal cells of prostatic carcinoma together with the increase of tumor grade and tumor stage (Table 4).
Desmin expression showed significant inverse correlation with Trichrome Masson staining intensity (R=-0.28 p=0.02) and Gleason score (R=-0.25 p=0.035). The correlation of Desmin expression with tumor stage was not significant (Table 4).

Discussion

The somatic theory states that genetic mutations are the basis of the process of carcinogenesis. Mutations are a direct cause of sporadic cancers that encompass 95% of human malignant neoplasms. However novel ideas question this theory [9-12]. In spite of aggressive attempts in laboratories worldwide this theory of somatic mutations can not be firmly established. Growing evidence support the role of tissue interactions in carcinogenesis [13-15]. The role of oncogene/suppressor gene concept as last incarnation of somatic theory has beenquestioned many times [13-14]. Tissue related concepts were introduced as corrections in the current theory of somatic mutations rather than discarding completely this somatic theory [16-17]. As a complement to mutations, the final resolution of malignant neoplastic phenotype had to accommodate the role of stromal-epithelial interaction, and a new hybrid theory for carcinogenesis emerged, that incorporated elements of theory of somatic mutations and the role of stromal-epithelial interactions in the process of carcinogenesis [18]. This hybrid theory is the epigenetic theory of carcinogenesis that implies tissue based phenomena in modifications of epigenetic gene expression. Alternative theories to somatic mutation emerged, and they state carcinogenesis to bea problem of normal histogenesis and tissue repair [15]. This new approach assumes that proliferation is the basic state of cells [19]. This view is diametrically opposite to the theory of somatic mutations where quiescence is the basic state of cells in multicellular organisms. This alternative theory, that incorporates the tissues as target of carcinogenesis, and proliferation as the basic state of cells is called tissue organization field theory [20].
In practice, stromal changes are currently thoroughly investigated in order to relate changes in tumor grade and tumor stage. Authors design various methods of quantification of these stromal changes [5,7-8]. These studies have shown that grading stromal changes can predict tumor aggressiveness and tumor recurrence. The value of the well established Gleason grading system, which analyzes the morphology of the epithelial malignant cells, is unquestionable.However assessment of stromal changes as well, could serve as valuable complement to Gleason grading system. When comparing patients with identical Gleason grade the intensity of Vimentin expression could identify patients with higher risk of disease recurrence [7]. Also Trichrome Masson histochemical stain can be used in everyday practice in interpretation of difficult cases of prostatic carcinoma in needle core biopsies when diagnostic epithelial malignant cells are few in number to render a correct diagnosis [8].
Our study showed a significant correlation of the intensity of Trichrome Masson stain with tumor grade (Gleason grade) that measures tumor aggressiveness and tumor stage (T category) that measures tumor extent, tumor volume or tumor spread. Also, there was a significant correlation of the expression of Vimentin antibody with tumor grade and tumor stage. Desmin expression showed a significant inverse correlation only with tumor grade. Our study analyzed specimens from radical prostatectomies where the whole prostate was sampled but other authors used the same methods on needle core biopsies [7,21-22]. This field of research is relatively new and additional studies like this are required to resolve several issues concerning the interpretation of the findings, Several methods of quantification of stromal changes have been proposed and a unifying concept has to emerge, concerning the issue of tumor heterogeneity, tumor volume, finding of adequate fields of assessment of stromal changes and so on.

Conclusion

Assessment of stromal changes in prostatic carcinoma, in the future, might serve as an additional diagnostic and prognostic tool in everyday practice. Further basic research studies might elucidate the changes on molecular level, concerning stromal cells in malignant prostatic carcinoma, and mutation of stromal cells could be target for novel monoclonal gene therapy.

Conflict of interest statement. None declared.

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ММР

Case report

ЕПИДУРАЛНА АНЕСТЕЗИЈА ЗА ЦАРСКИ РЕЗ И ПОЈАВАТА НА ХОРНЕРОВ СИНДРОМ

EPIDURAL ANESTHESIA FOR CAESAREAN SECTION AND OCCURRENCE OF HORNER'S SYNDROME

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Abstract

Recently, specifically in the last decade, at the University Clinic of Gynecology and Obstetrics, the number of patients treated with epidural analgesia for painless childbirth, which in some percentage ends in Caesarian section (35%), has increased. The increased use of the epidural anesthesia and analgesia is due to the fact that it is one of the most popular ways of childbirth today. This situation is a result of the benefits that epidural anesthesia has for the patient, which consist of allowing the pregnant woman to be conscious during childbirth and to feel and see her child coming into the world, accompanied with smaller intensity of intraoperative and postoperative pain. However, the results or the effects in practice have shown that in certain insignificant percentage patients can have negative consequences from the received analgesia (anesthesia) such as: headache, cases of durra puncture, epidural abscess or hematoma, neurological outbursts etc. But, the subject of this analysis or the aim of this study is the appearance of Horner's syndrome, as one of the negative effects of the epidural anesthesia, which even though rarely (only in 1% of the cases) can appear as a result of the epidural anesthesia. In the case study using the historic, comparative and empirical method we will try through a specific case to determine the causes for the occurrence of the Horner's syndrome, how it should be treated and what are the consequences for the patient.

Keywords: epidural analgesia, Horner's syndrome, anesthesia, C-section

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Апстракт

На Клиниката за гинекологија и акушерство, во последно време, поконкретно, во последната деценија е регистрирано зголемување на бројот на пациентки кои се третирани со епидурална аналгезија за безболно породување, која во одреден процент завршува со царски рез (35%).

Интензитетот на се почестата употреба на епидурална анестезија и аналгезија се должи на фактот што таа денес е меѓу најпопуларните методи за породување. Таквата ситуација е резултат на придобивките кои ги има епидуралната анестезија за пациентката, а кои пред сè, се однесуваат на тоа што на бремената жена и овозможува во текот на породувањето да биде свесна и да го почувствува и да го види своето дете кога доаѓа на свет, и тоа со намален интензитет на интраоперативна и постоперативна болка.

Но, она што може да се воочи од резултатите или од ефектите коишто се остварени во практиката, е дека во одреден незначителен процент, за пациентките може да се почувствуваат и негативни последици од примената аналгезија (анестезија), како што се: главоболки, случаи на пункција на дура, епидурални апцеси или хематом, невролошки испади и сл. Но, предмет на анализа или цел на истражувањето во овој труд ќе биде појавата на Хорнеров синдром, како еден од негативните ефекти, кој иако многу ретко, само во 1% од случаите може да се јави како резултат на епидурална анестезија.

За таа цел, во трудот преку примена на историскиот, компаративниот и емпириският метод ќе се обидеме преку приказ на конкретен случај да ги утврдиме причините за појава на хорнеровиот синдром, како истиот натаму треба да се третира и кои се последиците за пациентката.

Клучни зборови: епидурална аналгезија, хорнеров синдром, анестезија, царски рез.

Case report

A patient with initials GA, 28-year-old, on her first childbirth, in the 39th week of pregnancy with Dg. Graviditas ML X was hospitalized at the University Clinic of Gynecology and Obstetrics in Skopje. After the admission in the birthing room the first investigations were made: samples for laboratory were taken, her height

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and weight was measured and an ultrasound and vaginal exam were performed (Table 1). In addition, it was concluded by the gynecologist on duty that there were conditions for placing epidural catheter because the patient was with dilation of 4 cm, and at the same time the epidural was requested from the patient. Epidural anesthesia was performed by an anesthesiologist on duty who after cleaning the area, gave a local anesthetic 2% lidocaine 2 ml for pain relief in the area of the next puncture. After inspecting the results from the lab, especially the data concerning the number of the platelets and favorable medical history obtained from the patient, the anesthesiologist estimated that an epidural catheter can be placed. Area of puncture on level L3-L4 was cleaned and through a Touchy needle the epidural catheter on depth of 9 cm under the skin was placed in (Figure 1). Immediately after the setting of epidural catheter a test dose of 0.25% Marcaine 2 ml was administered. Thirty minutes later, revealing that the test was negative, a continuous administration of 0.125% Marcaine in combination with 0.05 mg fentanyl was given. After 45 minutes from the beginning of analgesia, the CTG registered fetal distress, what was the reason for switching to surgical treatment (Caesarean section). Analgesia was immediately deepened to epidural anesthesia (0.5% Marcain 5+3 ml). After 15 minutes from the beginning of the Caesarean section the patient began to complain on redness and weight on the left eye. The anesthesiologist also noticed this change; despite the stable hemodynamic state of the patient was. Blood pressure was 115/70 mmHg, heart rate 85 per minute and respiratory rate was 15 breaths per minute with 100% SaO_2. The anesthesiologist concluded the existence of ptosis or partially lowering the eyelid (Figure 1), miosis (narrowing of the pupil of the left eye), enophthalmos (indentation of the eye in the eye cavity) and anhidrosis (termination of sweating of the patient), and it was registered on only one side of the face. After noticing the symptoms the anesthesiologist stopped the continuous epidural anesthetic, which resulted in a spontaneous withdrawal of all symptoms after one hour. In the meantime the patient gave birth to a healthy baby boy with good Apgar score.

Table 1. Laboratory and clinical data

Parameter	Values during diagnosis/ before treatment
Age (years)	28
Weight (kg)	82
Height (cm)	169
Hemoglobin g/L	125
Leukocytes 10^9/L	7.9
Thrombocytes 10^9/L	215

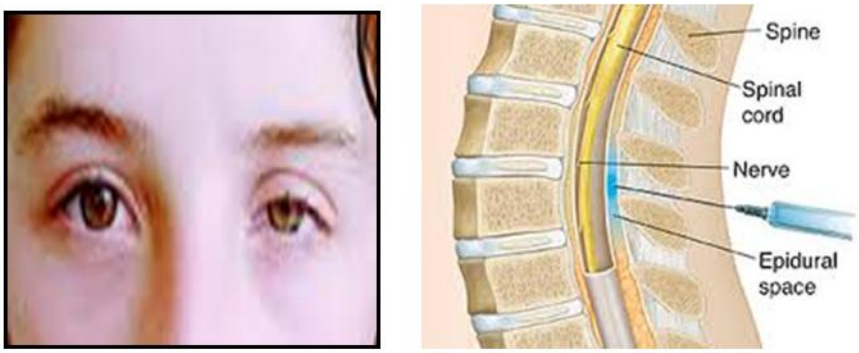

Fig. 1. Is taken from www.med-health.net%2FHorner%27s-Syndrome

Discussion

Horner's syndrome is a disorder which occurs as a result of unilateral interception of the sympathetic innervations of the eye and features classical tetrad of symptoms: miosis (contraction of the pupil) enolphthalmos (indented eye or increased ocular cheekbones), partial ptosis (lowered eyelid) and decreased or complete cessation of sweating (anhidrosis) and at the same time followed by pronounced redness [1]. The name of this syndrome comes from the name of the Swiss ophthalmologist Johann Friedrich Horner, who was the first to describe this syndrome in 1869. Even though it is believed that this syndrome is hereditary, it can occur with changes which happen in the sympathetic nervous system, and most often as a result of lesions in the neck area of the sympathetic nervous system. Thus, analyzing the etiology of this syndrome raises the question in which way and under which consequences does the epidural analgesia influence on the effects this syndrome has on the patient. This was the goal of the analysis of this specific case, from which few conclusions can be derived regarding the occurrence, effects and treatment of this syndrome. The conducted comparative analysis and analysis of past practice can not determine the precise reasons for its occurrence, particularly in pregnant women. However, in our opinion this phenomenon in pregnant women occurs more often because anatomic changes occur during pregnancy [2]. The epidural space has smaller volume and the intraabdominal pressure is increased because of the gravid uterus, moreover the epidural pressure is increased during the contractions that can contribute to the cephalic spread of the anesthetic [3,4].

Conclusion

During epidural analgesia the appearance of Horner's syndrome is very rare. In the future to make specific proposals for taking certain measures or giving appropriate treatment it is necessary to evaluate more such patients. They will provide essential data to more adequate selection of patients who will be given epidural analgesia.

Conflict of interest statement. None declared.

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ММР

Case report

CASE REPORT OF FEMINIZING GENITAL RECONSTRUCTION IN A FEMALE WITH CONGENITAL ADRENAL HYPERPLASIA

ПРИКАЗ НА СЛУЧАЈ НА ФЕМИНИЗИРАЧКА ГЕНИТАЛНА РЕКОНСТРУКЦИЈА КАЈ ЖЕНА СО КОНГЕНИТАЛНА АДРЕНАЛНА ХИПЕРПЛАЗИЈА

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Abstract

Introduction. Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders of adrenal steroidogenesis. In approximately 90-95% of the CAH cases, it is a deficiency of the enzyme steroid 21-hydroxylase. The degree of enzyme insufficiency determines the severity of the disease. In the simple virilizing type of CAH dominant symptoms are virilization in girls and precocious puberty in boys. Virilizing type of CAH is the most common etiology of ambiguous genitalia in women. There are several options for surgical reconstruction of such anomalies, which must always be optimized to the patient's anatomy, to achieve a good esthetic and functional result.

Detailed presentation of the case. The paper presents the case of a 36-year old woman with delayed pediatric diagnosis of simple virilizing type of CAH, due to deficiency of 21-hydroxylase, pronounced phenotypic virilization, clitoromegaly, hyperpigmentation of the external genitalia, vaginal hypoplasia and existence of low confluence of the urethra with the vagina in so called low type of urogenital sinus andbilateral micromastia, also called mammary hypoplasia. The patient underwent augmention mammoplasty, clitoroplasty, reduction of clitoral hood and proximal labioplasty.

Discussion. CAH is a continuum of disorders, affecting patients throughout the life. Feminizing genitoplasty includes three parts: clitoroplasty, labioplasty and vaginoplasty. Clitorectomy in modern times is unacceptable option.

Conclusion. Surgical management and reconstruction in women with simple virilizing type CAH and ambiguous genitalia remains still controversial and emotionally laden area in reconstructive surgical activity and requires a team approach.

Keywords: congenital adrenal hyperplasia-CAH, simple virilizing type CAH, feminizing genital surgery, feminizing genitoplasty, genital ambiguity

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Абстракт

Вовед. Конгениталната Адренална Хиперплазија (КАХ) е група на автозомно рецесивни нарушувања на адреналната стероидогенеза.Во приближно 90-95% од случаите на КАХ, се работи за дефицит на ензимот стероид 21-хидроксилаза. Степенот на инсуфициенција на ензимот ја одредува тежината на заболувањето. Кај едноставната виризилирачка форма на КАХ доминантни симптоми се вирилизацијата кај девојчињата и прераниот пубертет кај момчињата. Вирилизирачката форма на КАХ е најчестата етиологија на двосмислени гениталии кај жени. Постојат неколку опции за хируршка реконструкција на ваквите аномалии, кои мора секогаш да се оптимализирани кон анатомијата на пациентот за да се постигне добар функционален и естетски исход.

Приказ на случај. Во трудот претставуваме случај на 36-годишна жена со ненавремена педијатриска дијагноза на едноставна вирилизирачка форма на КАХ поради дефициенција на 21-хидроксилаза, нагласена фенотипска вирилизација, клиторомегалија, хиперпигментација на надворешните гениталии, вагинална хипоплазија со постоење на ниска конфлуенција на уретрата со вагината во т.н. низок тип на урогенитален синус, и билатерална микромастија т.е. мамарна хипоплазија. На пациентката и беше извршена аугментациона мамопластика, клиторопластика, редукција на клиторалниот препуциум и проксимална лабиопластика.

Дискусија. КАХ е континуум на нарушувања, кои ги афектираат пациентите во текот на целиот живот. Феминизирачката генитопластика опфаќа три дела: клиторопластика, лабиопластика и вагинопластика. Клиторектомија во модерно време е неприфатлива опција.

Заклучок. Менаџментот и хируршката реконструкција кај жените со вирилизирачка КАХ и двосмислени гениталии останува сè уште контроверзна и емо-

ционално оптоварена ареа во хируршката реконструктивна дејност и побарува тимски пристап.

Клучни зборови: конгенитална адренална хиперплазија-КАХ, едноставна вирилизирачка форма на КАХ, феминизирачка генитална хирургија, феминизирачка генитопластика, генитална двосмисленост

Introduction

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders of adrenal steroidogenesis with an incidence of 1/10 000 to 1/15 000 live births. It results from an inherited defect in one of the five enzymatic steps in the biosynthesis of cortisol from cholesterol. This is manifested in patients with varying degrees of virilization, which in turn is caused by over production of cortisol precursors and androgens of the adrenal gland, which consecutive hyperplasia is due to hypersecretion of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). In approximately 90-95% of the CAH cases, it is a deficiency of the enzyme steroid 21-hydroxylase (also known as CYP21A2 or P450c21B) localized in the endoplasmic reticulum, and responsible for catalyzing the conversion of 17α-hydroxyprogesterone in 11-deoxycortisol, which is a precursor of cortisol and progesterone in 11-deoxycorticosterone, which is a precursor of aldosterone. Affected enzyme can be completely or partially defective. Four other less frequent forms of the disease are due to deficiency of the following enzymes: 11β-hydroxylase (5%), 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase and steroid-desmolase 20-22 (or cholesterol side-chain cleavage enzyme). The degree of enzyme insufficiency determines theseverity of the disease. The main characteristic of CAH is inadequate synthesis of glucocorticoids i.e. cortisol, so glucocorticoids precursors are accumulated and converted to androgen steroids responsible for masculinisation in female patients. Mineralocorticoids synthesis is also impaired, resulting in electrolyte imbalance and hypotension. Depending on the extent and severity of the genetic defect of the enzyme, the disease is defined as a classical (severe) form and nonclassical (adult, mild) form, with the classical (severe) form further divided in salt-waiting type (75% because of disrupted aldosterone synthesis) and simple vizilizing type (25%).In the simple virilizing type of CAH dominant symptoms are virilization in girls and precocious puberty in boys. Virilizing type of CAH is the most common etiology of ambiguous genitalia in women, which is defined as external genitalia that do not have typical anatomical appearance. Female patients due to high levels of systemic adrenal androgens prenatally exposed from the 7th gestational weekare characterized by virilized external genitalia in the form of clitoromegaly (synonyms are macroclitoris and clitoral hypertrophy), labial fusion and their “scrotalisation” with hyperpigmentation, merging of the vagina and urethra and their opening in common urogenital sinus, various degrees of vaginal hypoplasia, micromastia i.e. mammary hypoplasia, premature mineralization and closure of the epiphyseal plates and subsequent short stature, hirsutism i.e. excessive growth of hair with specific pattern as in men, acne, oligomenorrhoa or amenorrhoa, polycystic ovary syndrome, infertility in 13% of cases, insulin resistance and generalized virilization in a form of masculinization with increased muscle mass, loss of the contours of the female body, deepening of the voice, temporofrontal hair loss and androgen flare in the form of a plethora of face, neck and upper chest. In the older medical literature this phenotype is defined as female intersex or female pseudohermaphroditism, i.e. when individual genetically female (46, XX) is exposed in utero to high doses of endogenous or exogenous androgens. With respect to sensitivity of patients to the term pseudohermaphrodite, which is a pejorative, today masculinized 46, XX individuals with two ovaries and congenital anatomical atypical female genitalia are marked as disorders in sexual development, 46, XX. Diagnosis is established usually in the neonatal period, through clinical presentation, determination of hormonal status, genital examination, abdominal and pelvic ultrasonography and demonstration of genetic defect of the corresponding enzyme. [1-4]. Very few fields in surgical reconstruction are so challenging and controversial as genital reconstruction in virilized patients. In these patients, it is necessary to make feminizing genital surgery, which aims at reconstruction of the female external genitalia, because these patients have the potential for normal sexual function and fertility. There are several options for surgical reconstruction of such anomalies, which must always be optimized to the patient's anatomy, to achieve a good esthetic and functional result. The main purpose of feminizing genital surgery is to create external genitalia with female appearance, which will be compatible with female sex, to allow the psychosexual development of normal sexual and reproductive function, to create a functional vagina, which will enable sexual activity and menstruation and to create unobstructed urinary function without the occurrence of urinary incontinence and infections and intra- and postoperatively to preserve glansclitoris with its innervation, sensitivity and blood supply [5-6].

Case report

The aim of this paper is to present the case of an adult woman with a simple viriliziring form of CAH, with genital ambiguity and emphasized virilization of external genitalia and the overall habitat, and feminizing reconstructive genitoplasty, which aimed to achieve a more natural physical, psychological and sexual development that was tailored to individual anatomical finding in the

patient. The paper presents the case of a 36-year old woman with delayed pediatric diagnosis of simple virilizing type of CAH, due to deficiency of 21-hydroxylase, pronounced phenotypic virilization, clitoromegaly, hyperpigmentation of the external genitalia, vaginal hypoplasia and existence of lowconfluence of the urethra with the vagina in so called low type of urogenital sinus and bilateral micromastia, also called mammary hypoplasia (Figure 1 and 2).

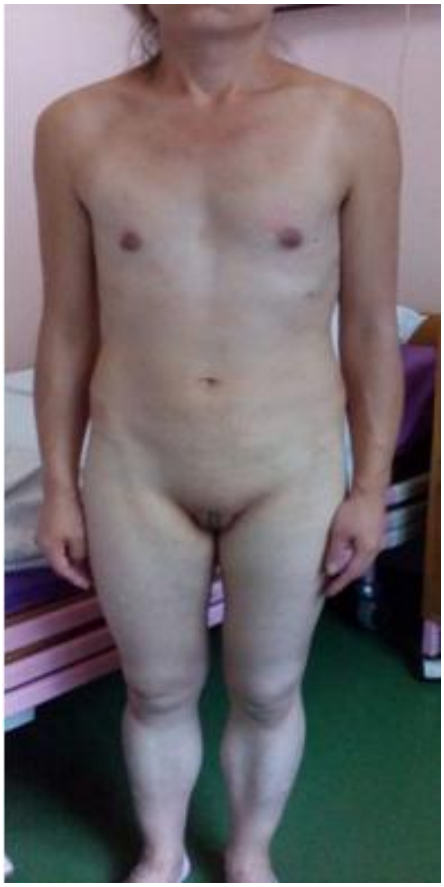

Fig. 1. Virilized habitus

The patient had no medical history of prior corticosteroid therapy, existence of abdominal tumors or previous crises with loss of salt and dehydration. The patient did not give information about any other medical conditions or surgical diseases. Her menarche was at 17 years of age and since then she had oligomenorhheic irregular cycles that lasted 2-4 days every 2 to 3 months without dysmenorrhoa, on average around 6-8 menstrual cycles throughout the year. Upon physical examination, she was 155 centimeters high, heavy 56 kilograms with body mass index (BMI) of 23.3.According to the classification of Tanner, the patient belongs to the group Tanner II for breasts, Tanner IV of pubic hair, and virilizing genitalia with hypertrophied clitoris, low urogenital sinus with covered vaginal and urethral ostia and appointed hyperpigmented and "scrotalized" labial skin and partial fusion, thereof, was ranked according to the classification

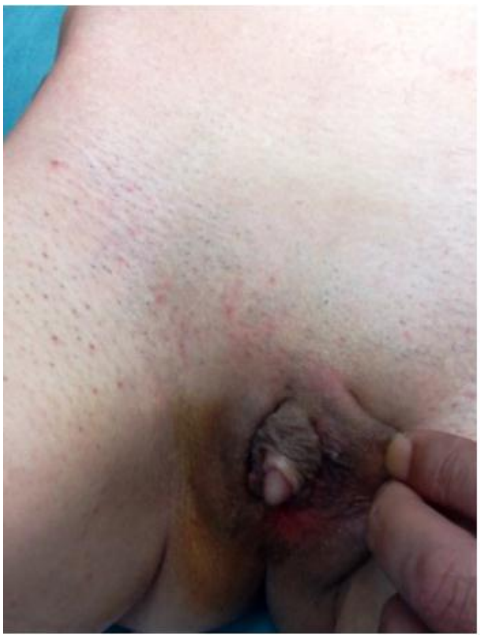

Fig. 2. Hypertrophy of the clitoris

of Prader for virilization as second degree. Her modified Ferriman-Gallwey score of hirsutism was 9. Clitoral hypertrophy was a length of 6 centimeters (it typically has a length of 1 to 2.5 centimeters and a width of 3-10 mm). Abdominopelvic ultrasonography showed normal configuration of the remaining internal genital organs, adrenal hypertrophy and absence of ectopic testicular tissue. Laboratory findings showed normal electrolytes, increased 17α-hydroxyprogesterone, free testosterone and dehydroepiandrosterone sulfate and lowbasal levels of cortisol. Advised by a gynecological endocrinologist, the patient was previously on a three-month treatment with drospirenone and ethinyl estradiol. The patient was monitored and controlled during the period July 2016 to December 2016. It is important to emphasize that it is essential to obtain perioperatively a good endocrinological control, with an application of appropriate stress doses of corticosteroids at a dose of 2 mg / day, then using 1000 milliliters of 0.9% saline and 500 milliliters solution of 5% glucose for good rehydration and adequate antibiotics. The patient was placed intraoperatively in supinational "frog-legged" position with bend knees, due to simultaneous augmentational mammoplasty, with circumferential prepping and isolation of the operative fields from the neck to tights and sterile compresses placed under gluteal regions. The first intervention was submuscular augmentational mammoplasty with periareolar approach where after the formation of muscle pocket under the large pectoral muscle, silicone implants were placed with a volume of 225 cubic centimeters in order to achieve full coverage of the implant with muscle tissue. The second surgical segment consisted of feminizing genitoplasty, which in this case included clitoroplasty with preserving the dorsal neurovascular pedicle, partial reduction of the prepuce of the

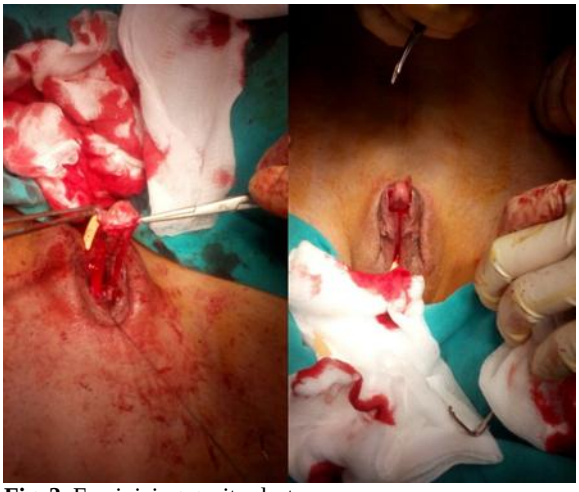

Fig. 3. Feminizing genitoplasty

clitoris and proximal labioplasty of the labia minora (Figure 3).

Initially 14 F Foley catheter was placed and it was removed the fifth postoperative day. The operation started with the release of redundant prepuce of the clitoris from glans clitoris, with its partial reduction, and setting a traction suture on the glans clitoris, then almost circumferent incision under glans clitoris from ventral to dorsolateral. This was followed by the full release of the body of the clitoris, firstdorsolateral preserving the dorsal neurovascular pedicle, and then ventral, which separated the body of the clitoris from distally positioned part of the urogenital sinus. Thus,the now free cavernous bodies of the clitoris were dissected proximal to their bifurcation under the pubic symphysis, and with ventral longitudinal incisions on their tunica albuginea, two ventral longitudinal partial corporectomies were made. After performing the hemostasis, closure and plication of the tunica albuginea ventrally by fixing the clitoris to the periosteal and perichondral tissue under the pubic symphysis, with the rest of the prepuce ofthe clitoris and surrounding adipose tissue, it was approached to establishing an appropriate mons pubis proximal, "coronal" sulcus of the prepuce with the glans clitoris distally, and proximal reconstruction of the rudimented labia minora, laterally. Thus were preserved the dorsally positioned nerve endings that are responsible for the sensitive innervation of the glans, and its blood supply. Postoperative analgesia was initiated immediately to control pain, and application of an antibiotic for the entire period of urinary catheterization. The duration of surgery was 180 minutes. Excellent aesthetic result without postoperative infection, dehiscence, loss of glans clitoris or other complication was achieved,also without involvement of the urinary control (Figure 4).

Follow-up of thepatient was 6 months. In assessing the esthetic outcome criteria the following parameters were taken: genital proportions and symmetry, shape and size ofclitoral prepuce, form and size of the glans

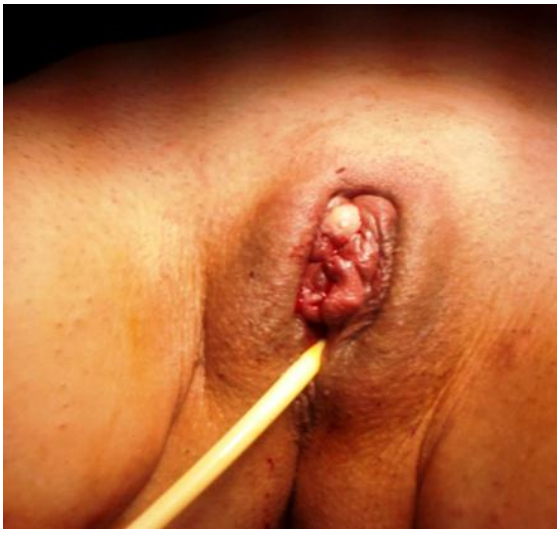

Fig. 4. Postoperative appearance of external genitals

clitoris, position, size, symmetry and proportions of the labia minora, position of the new vaginal introitus and its anatomic appearance and quality of the genital skin in general. Functional outcome was assessed by the position of the external urethral orifice and urinary continence and discharging. The patient was advised to abstain from physical and sexual activity in the next 6-8 weeks, and she was advised to make a consultation with internist-endocrinologist or gynecologist, and to consider consultation for possible vaginoplasty (Figure 5).

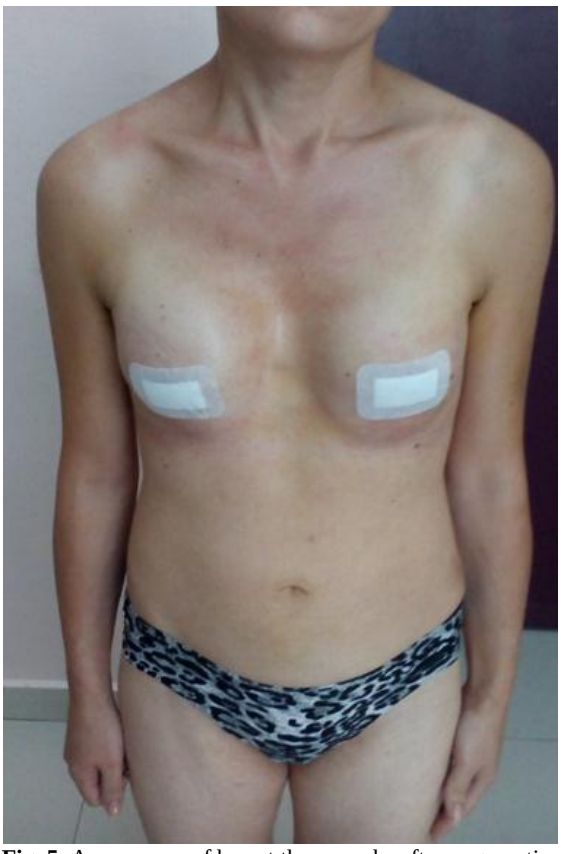

Fig. 5. Appearance of breast three weeks after augmention mammoplasty

Discussion

CAH is a continuum of disorders affecting patients throughout life. Feminizing genitoplasty for gender reassignment infemales should take into account factors such as: initial genital appearance, prenatal exposure to androgens, surgical options, the need for lifelong hormone therapy, the fertility potential, personal and family needs and expectations and social circumstances. Nowadays, there is a prenatal screening for CAH, which diagnosis can be set even prenatally and therefore to start early treatment. Treatment consists of using glucocorticoid and/or mineralocorticoid and early feminizing genitoplasty. In adults the recommended dose of the long-acting dexamethasone is 0.25-0.5 mg once daily.Treatment with oral contraceptives is sufficient to reduce menstrual problems, acne and hirsutism. No clear guidance for dosing mineralocorticoids exists, but current recommendations are the use of 0.05-0.1 milligrams fludrocortisonefor adults. Patients with CAH in cases of moderate to major stress, such as fever, trauma, surgery and general anesthesia need a stress dose of steroids. With proper treatment fertility in women with CAH is between 60-90% [1-4]. There are several types of surgery for genital reconstruction, which is always modified according to the individual anatomy of the patient. Nowdays, generally it is recommended to perform genital reconstruction within the period of 3 to 6 months of age, preferably in a single act.Feminizing genitoplasty includes three parts: clitoroplasty, labioplasty and vaginoplasty. Clitorectomy in modern times is unacceptable option. Clitoroplasty must respect innervation and vascularity, not only the appearance and function of the clitoris. There are 4 basic types of vaginoplasty: "cut-back" technique, neovaginoplasty with skin or intestine, posterior omega skin flap and "pull-through" technique.Only the latter two techniques are applied to CAH, given the fact that the first may be used only in labial fusion and the second in the case of vaginal atresia or agenesis that does not occur in CAH.Posterior omega skin flap is used in low urogenital sinus and "pull-through" technique in middle and high urogenital sinus. Complications are stenoses of the vagina, which require surgical reintervention [3-6].

Conclusion

Surgical management and reconstruction in women with simple virilizing type of CAH and ambiguous genitalia remains still controversial and emotionally laden area in reconstructive surgical activity and requires a team approach. Different specialists and subspecialists, such as a pediatrician, an endocrinologist, a gynecologist, a psychiatrist and a reconstructive surgeon for pediatric surgery, urologists or plastic surgeon should work as a team to ensure normal physiological, emotional, psychosocial and sexual development.The surgeon must be thoroughly and intimatelyfamiliar with the anatomy of the person and therefore use the reconstructive techniques that are appropriate in a given case. More importantly, long-term monitoring of patients will provide insight whether current techniques provide not just good esthetic outcome, but functional outcome too.

Conflict of interest statement. None declared.

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Case report

TETHERED CORD SYNDROME IN CHILDREN – REPORT OF TWO CASES

СИНДРОМ НА ВРЗАН ‘РБЕТЕН МОЗОК- ПРИКАЗ НА ДВА СЛУЧАИ

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Abstract

Tethered spinal cord syndrome is a neurological disorder caused by tissue attachments that limit the movement of the spinal cord within the spinal column. Attachments may occur congenitally at the base of the spinal cord (medullary cone) or they may develop near the site of an injury to the spinal cord. These attachments cause an abnormal stretching of the spinal cord. The course of the disorder is progressive.
We present two patients that were diagnosed at age of three months and three years, respectively. Final diagnosis was made by magnetic resonance imaging, and both patients were referred to University Clinic of Neurosurgery for further treatment.
Our aim is to illustrate the advantages of the early diagnostics of this progressive condition, to present diagnostic methods that are age-dependent and to illustrate the early clinical indicators for its existence.

Keywords: tethered cord, magnetic resonance, ultrasound, dysraphism, neural tube defects

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Апстракт

Синдром на врзан рбетен мозок е невролошко пореметување, предизвикано од ткивни додатоци, кои го ограничуваат движењето на рбетниот мозок, во рамки на рбетниот столб. Додатоците може конгенитално да се развијат во основата на рбетниот мозок (медуларниот конус) или тие може да се развијат во близина на местото на повредата на рбетниот мозок. Овие додатоци предизвикуваат абнормално растегнување на рбетниот мозок. Текот на болеста е прогресивен.
Ви презентираме двајца пациенти, кои соодветно биле дијагностицирани на возраст од три месеци и три години. Конечната дијагноза беше направена со помош на магнетна резонанца, и двајцата пациенти беа препратени за натамошен третман на клиниката за неврохирургија.
Наша цел е да ги илустрираме предностите на раното дијагностицирање на оваа прогресивна состојба, да ги презентираме дијагностичките методи, кои се зависни од возраста и да ги илустрираме раните клинички индикатори за негово постоење.

Клучни зборови: врзан рбетен мозок, магнетна резонанца, улгразвук, дизрафизам, дефицити на невралната туба

Introduction

The group of neurological disorders that involves malformations of the spinal cord includes tethered cord syndrome (TCS) or occult spinal dysraphism sequence [1]. TSC is usually identified in childhood and is defined as a stretch-induced functional disorder of the spinal cord with its caudal part anchored by an inelastic structure [1,2]. This disorder is usually associated with spinal defects such as myelomeningocele, diastematomyelia, lipomyelomeningocele, thickened filum terminale, and intradural lipoma [3].
The cause of TCS is spinal cord traction, which leads to anatomic and metabolic disorders that are responsible for the clinical presentation [4].
Neural tube formation is the essential process of neurulation. Developmental errors during neurulation can lead to the formation of a myelomeningocele, meningocele, intraspinal lipoma, lipomyelomeningocele, dermal sinus tract, or SCM [5-7].
The proposed normal functions of the terminal filum are to fixate, stabilize, and buffer the distal cord from normal and abnormal cephalic and caudal traction. The filum is a viscoelastic band that usually allows the conus medullaris to move slightly during flexion and extension of the spine. It is believed that, if this viscoelasticity of the filum is lost or compromised by either fatty infiltration [8] or abnormal thickening, then caudal tension and traction may cause undue stress upon the conus, resulting in TCS. It is believed that this abnormal inelastic filum interferes with normal cord ascension

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and results in a low-lying conus medullaris (that is, a conus below the L1-2 interspace). This is classically believed to be the hallmark of the TCS, but there are published data that demonstrate that TCS can exist when the conus is positioned normally [9-12].

Patients with symptomatic TCS can present with a wide variety of signs and symptoms in combination with cutaneous, orthopedic, spinal, anorectal, and urological abnormalities, as well as pain [13]. The common clinical presentations include the presence of cutaneous signatures associated with OSD (59%), neurogenic bladder with the development of primary or secondary incontinence or urinary tract infection (18%), leg or foot weakness, numbness and/or spasticity (12%), leg or foot length discrepancy (6%), foot deformity (for example, pes cavus, claw toes), spinal deformities, and nondermatomal back and leg pain (6%) [14]. Although pain is a major presenting symptom in the adults with TCS, it is less common and more difficult to identify in the pediatric population because pain often manifests simply as irritability, especially in younger children. Cutaneous signatures associated with OSD include lumbosacral hypertrichosis, cutaneous capillary hemangiomas (nevus), dermal sinus tracts, midline subcutaneous lipomas, lumbosacral skin appendages, and so-called cigarette burns or atreticmeningocele. Cutaneous signatures can be seen in 59% of patients with TCS, and the literature suggests that cutaneous anomalies are present in as many as 70% of patients with OSD [13,15]. Only about 3% of healthy neonates will have such lesions. Patients with TCS often exhibit multiple skin lesions when examined carefully [15].

Urological abnormalities range from obvious incontinence to subtle, subclinical findings seen on urodynamic testing. In the pediatric population, urological abnormalities usually do not become obvious until the child grows out of his/her infant years. They also tend to be more subtle than other clinical findings [16]. The urological presentation can include incontinence, urgency, increased/abnormal frequency, and recurrent urinary tract infections.

The neurological dysfunction in TCS is unusual, frequently having elements of both upper and lower motor dysfunction. Motor weakness is more prevalent than sensory deficits. Such motor dysfunction is usually asymmetrical. Children can present with delayed gait development, spasticity, hyperreflexia, hyporeflexia, and muscular atrophy.

In infants muscular atrophy can be hidden by subcutaneous fat. Sensory deficits, when present, are usually in the feet or perineum. Children can sometimes present with painless ulcerations of the foot or leg [17]. Orthopedic manifestations include foot deformities (most common), limb-length discrepancies, leg malformations, gluteal asymmetry, and vertebral abnormalities (for example, laminar defects, bifid vertebrae, hemivertebrae, SCM, sacral agenesis, segmentation errors, and scoliosis) [7]. Orthopedic deformities of one form or another are found in more than 90% of patients with TCS, [18, 7,11] and scoliosis is seen in up to 25% [16]. It is now well recognized that TCS is often seen with other congenital syndromes. The two most common associations are caudal agenesis (a spectrum of caudal regression abnormalities) [19,20] and anorectal atresia syndromes (OEIS [omphalocele, exstrophy, imperforate anus, spinal defect] syndrome, VATER [vertebrae, anus, trachea, esophagus, and renal] syndrome, and Currarino triad) [5,21-24]. Patients with these syndromes should be screened for OSD and TCS [25].

Diagnostic procedure

Neuroimaging is used to confirm the clinical suspicion of OSD and/or TCS. Ultrasonography can be a useful toolin young infants. The advantages are the ability to obtaina dynamic view without having to submit a young child toirradiation or sedation. The disadvantages are that imagescan be difficult to interpret and the quality is often operator-dependent. Identifying the level of the conus medullarisis not difficult in the very young child, but searching forfat or the thickness of the terminal filum can be challenging. Magnetic resonance imaging is the modality of choice in visualizing the level of the conus medullaris and for identifying a thickened and/or fatty filum. Sagittal T1- and T2-weighted images are best for localizing the level of the conus, whereas T1-weighted axial MR images are better for identifying fat within the terminal filum and for measuring the diameter of the filum.

Surgical intervention remains the only reliable treatment in TCS. Its main goals are to improve the neurologic deficits in the symptomatic patientand to prevent future deficits in theasymptomatic patient [25].

These two goals are predicted on the fact that sectioning of the terminal filum can be conducted safely with a minimal risk and a very low rate of morbidity. The reported complications of surgery are cerebrospinal fluid leakage (most common), wound infection, meningitis, bladder dysfunction, and neurological injury [25].

We present two children with TSC from different age groups, who exhibited different symptoms of the disorder, which highlights the significance of the early diagnosis of TSC

Case report

Case 1.

The first patient was referred to the Neurology department of the University Children's Hospital from the University Clinic of Gynecology and Obstetrics at the age of one month due to a big protuberance in the lumbosacral region which extended laterally.The child had no focal neurological signs or any other deformities. An

ultrasound examination of the mass was performed and it showed a medullary cone with normal location and lipoma out of the central line. The ultrasound was repeated at the age of three months because signs of a tethered cord appeared. Clinically there were no focal neurological signs. MRI was performed and the diagnosis was confirmed (Figure 1). The child was referred to the University Clinic of Neurosurgery for surgical treatment.

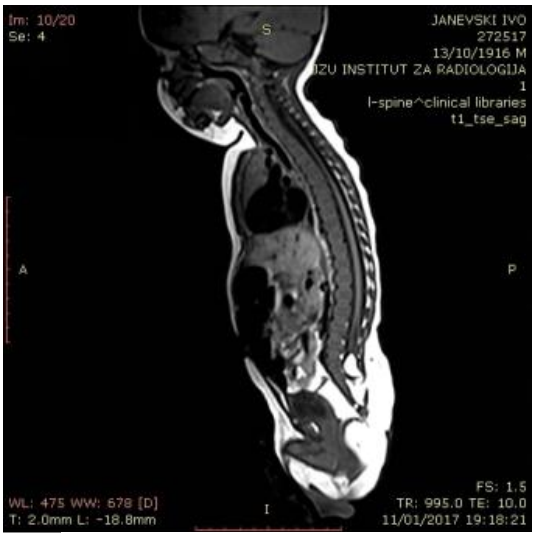

Fig. 1. MRI of the patient which shows tethering of the cord

Case 2.

The second patient was a three-year-old girl, who was hospitalized at the Neurology department due to the occurrence of focal neurological signs: flaccid paresis with slight spasticity of the right arm, tendon reflexes were normal, also spasticity of the left leg with increased tendon reflexes and slight deformity of the foot. The child experienced pain and was therefore with limited movements of the neck and the limbs. The skin on the spinal and sacral region was intact.

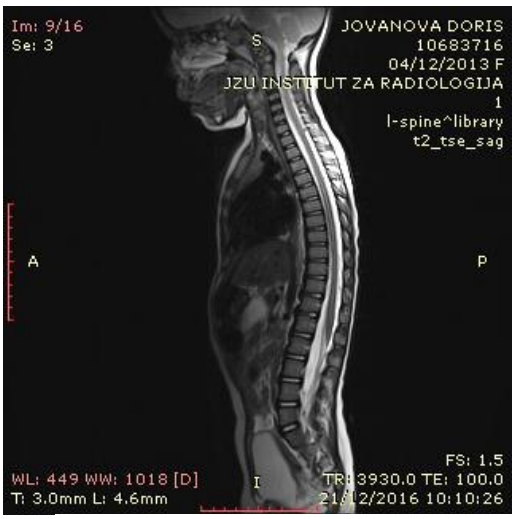

Fig. 2. MRI of the patient which shows tethering of the cord

All the biologic markers were normal, the MR of the brain confirmed TCS (Figure 2). Due to the recent flu infection the child had, our first probable diagnosis was spinal acute disseminated encephalomyelitis, also the location of the lesion indicated high spinal involvement. After a short treatment with nonsteroid anti-inflammatory drugs, cessation of the pain was achieved but the focal neurological signs persisted.

Results

MR was the main diagnostic tool for the tethered cord in both cases. Pictures 1 and 2 present the MR findings of the first patient and the second patient.

Discussion

The first patient reported in this case report has had a prompt diagnosis, before any clinical signs developed. The diagnosis was based on the existing lipoma. The first ultrasound of the spinal cord was not correctly interpreted; after a short period of time it was repeated and the second ultrasound showed progression of the spinal cord tethering. The ultrasound is an excellent imaging tool for examination of infants, especially in the first months of life, which offers great details in the spinal cord and spinal channel morphology [26].
There are reports in the literature that spinal ultrasound in neonates and magnetic resonance imaging (MRI) in older children allow diagnosis of TCS and almost always give the cause of the disease [27,28].
The second reported patient was diagnosed later in life, after the occurrence of neurological symptoms. The pitfall was that there were no guiding signs as lipoma, meningomyelocele, discoloration of the skin in the sacral area, etc. Atypical paresis with early onset accompanied by foot deformities should be a warning for spinal cord involvement. The clinical episode with pain was probably provoked by the physical activity, growth of the child and the preceding infection.
Definitive diagnosis in both children was achieved by MRI.

Conclusion

Whenever there is dysraphism as lipomyelomeningocele, myelomeningocele, dermal sinus, diastematomyelia, thick terminal filum, meningocele, awareness of the existence of TCS is warranted. The prompt diagnosis, before neurological signs occur, is of utmost importance.
MR of the spine is a superior diagnostic method and should be performed whenever there is suspicion of TCS.
Neonatal ultrasound is a very useful method and should be used as an initial screening modality.
Clinical examination is important; the presence of neurological signs as paresis or deformities of the extremities, asymmetric atrophies and neurogenic bladder are indicators of late diagnosis.

Surgery is the only treatment, relatively simple and safe and even when it is performed later in life enables reversal of the clinical signs.

In the second presented case we can say that the diagnosis has been delayed, and there have been grave consequences. The patient was without early warning signs and the diagnosis was suspected only after the occurrence of severe neurological symptoms. The admonition here is that tethered cord can occur at any age with atypical signs and that we should think of its existence at any age. In the first case the diagnosis was prompt and surgical treatment was effectuated soon after, which shows that the outcome of TCS is far more preferable when the condition is diagnosed and treated early.

Conflict of interest statement. None declared.

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ММР

Case report

IATROGENIC ADRENAL FAILURE DUE TO CORTICOSTEROID-TREATED PSORIASIS: PEDIATRIC CASE REPORT

ЈАТРОГЕНА АДРЕНАЛНА ИНСУФИЦИЕНЦИЈА ПРЕДИЗВИКАНА ОД КОРТИКОСТЕРОИДЕН ТРЕТМАН НА ПСОРИЈАЗА – ПЕДИЈАТРИСКИ ПРИКАЗ НА СЛУЧАЈ

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Abstract

Plethora of pediatric autoimmune, dermatological, neurological and atopic disease require chronic administration of steroid medication. Long-term use of corticosterioids can result in both local (atrophy of the skin, hypertrichosis, and telangiectasia) and systemic side effects (hypothalamic-pituitary-adrenal (HPA) axis disturbance, risk of infections). We report a case of 3.5-year-old boy, who developed Cushing syndrome and secondary adrenal insufficiency after corticosteroid cream maltreatment of his psoriasis. After initial hospitalization and recovery, physiological doses of hydrocortisone were used to normalize the HPA axis. In order to prevent Cushing syndrome development, adrenal insufficiencies, and secondary infections, precaution in use of steroid therapy in early childhood must be exercised.

Keywords: psoriasis, pediatric, case report, adrenal failure, iatrogenic

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Апстракт

Голем број педијатриски, автоимуни, дерматолошки, невролошки и атопични болести налагаат долготрајна употреба на стероидни лекови. Долгорочното користење кортикостероиди може да доведе до локални контраиндикации (атрофија на кожа, хипертрикозија и телангиектазија), како и до системски контраиндикации (нарушување на оскатата хипоталамус-хипофиза-надбубрежни жлезди-ХХН и ризик од инфекции).

Имаме случај на машко дете од 3,5 години, кое поради злоупотреба на кортикостероиден крем за псоријаза, развило Кушингов синдром и секундарна надбубрежна инсуфициенција.

По првичната хоспитализација и закрепнување, користени се физиолошки дози на кортикостероиди за нормализирање на оската ХХН. Затоа, за време на раното детство треба да се биде претпазлив при употреба на стероидна терапија, со цел спречување на развојот на Кушингов синдром, надбубрежни инсуфициенции и секундарни инфекции.

Клучни зборови: псоријаза, детска, приказ на случај, адренална инсуфициенција, јатроген.

Introduction

Hypothalamic-pituitary-adrenal (HPA) axis suppression due to short-term use of exogenous topical corticosteroids is fairly uncommon [1]. Supraphysiological doses of corticosteroids, when applied in longer time periods cause secretory inhibition of stimulatory hormones derived from the pituitary gland. Therefore, any sudden treatment cessation would not be answered with sufficient endogenous steroid production and produce adrenal crisis. It has been proposed that the most common cause of secondary adrenal insufficiency is a result of glucocorticoid withdrawal, however, due to its transient course it remains unnoticed [2]. We report a pediatric case who developed clinical characteristics of iatrogenic Cushing syndrome in concurrence of adrenal insufficiency due to unrestricted misuse of topical steroid cream.

Case description

On presentation, 3.5-year-old boy with his parents complained of scaly changes on the skin combined with areas of thinning. There was a positive family history of the skin disease with the father being affected. The

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symptoms first appeared 2 years ago and persisted despite continuous use of prescribed clobetasol steroid cream. The cream had been applied to the whole body for a period of one year. The patient displayed somatic aspect typical of Cushing syndrome ("moon face") and diffuse skin changes resembling psoriasis (exfoliations with erythematous base) (Figure 2).

Due to suspected adrenal failure/possibility of adrenal crisis and steroid-induced HPA dysregulation, the patient was admitted and full clinical examination was performed. His blood pressure was 80/60mmHg. His height was 98.5 cm (50^{th}percentile, standard deviation (SD):+0.5), weight 18.5 kg (90^{th}percentile, SD:+1.5). Based on the height and weight the BMI is 19.1, placing the BMI-for-age above the 99th percentile. Additionally, the x-ray revealed osteopenia and glycemia and HbA_1C t levels were normal.

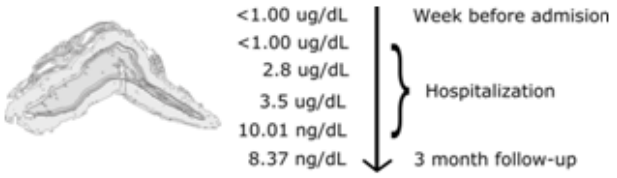

Fig. 1. Cortisol hormone dynamics over admission, hospitalization and follow-up period

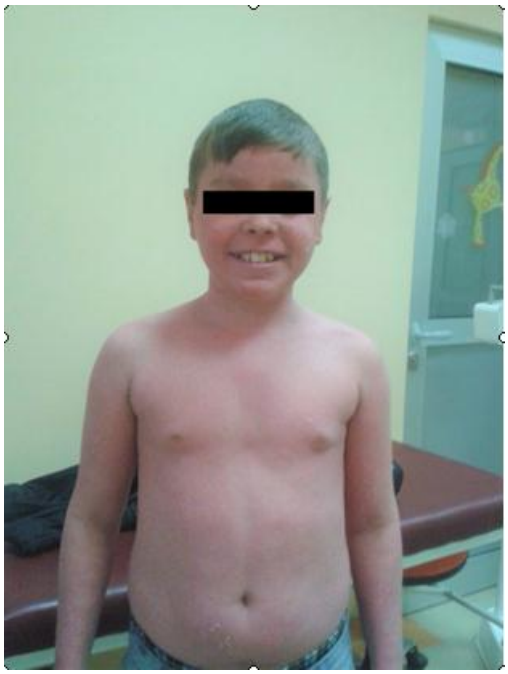

Fig. 2. A 5-year-old boy with normal cortisol levels but with still apparent psoriatic skin changes. (after the tretament)

The temporal change of cortisol over the hospitalization period is shown in Figure 1. Effectively, the corticosteroid therapy inhibited the pituitary gland with LH hormone level of 0.18mIU/ml at admission. His cortisol levels were low at <1 ug/dl (normal reference range 8-20.0 μg/dl). After performing the high-dose ACTH test, lack of cortisol response confirmed the adrenal insuffi- ciency. Since hospitalization, the patient was initiated on increasing doses of Hydrocortisone, Cefaclor, Ceftriaxone, and Acretin. Within few days, the cortisol levels returned within the normal range (2.8ug/dL and 3.5ug/dL, 2^{nd} and 3^{rd} day from hospitalization, respectively). Continuous regimen of hydrocortisone tapering was initiated during the hospitalization. Echosonography of the adrenal glands showed bilateral enlargement (11.7x20.2 and 14.4x2.3, right and left, respectively). The parenchyma was homo- geneous with no focal changes. In addition to the bilateral adrenal glands finding, during the complete battery of testing, the echo sonography revealed mitral valve prolapse and mitral regurgitation.

Additionally, histopathological examination of the skin was acquired. The biopsy confirmed the suspected diagnosis of chronic dermatitis within the spectrum of psoriasis vulgaris. Continuation of the tapering regimen was prescribed and follow-up was scheduled in the outpatient clinic.

Discussion

Only 3 years after the introduction of corticosteroid therapy in dermatologic disorders, reports of adverse effects started to emerge [3]. Adverse effects from misuse of corticosteroids can usually produce both local and systemic events [4]. Atrophic changes, skin infections, delayed wound healing, striae, acne, rosacea, hyperpigmentation, hirsutism and telangiectasia are among many local consequences reported [5]. In the casereport described earlier, our patient experienced systemic adverse effects of Cushing Syndrome and suppression of HPA axis [6]. It has been previously shown that even small doses as two days of 2g of clobetasol (0.05% cream) can cause decrease ofcortisol levels [7]. Even though guidelines for topical steroid use in adults are established, their use in the pediatric population is based on obscure recommendations [8]. Even controlled clinical trials in pediatric dermatology use vague descriptions on the amount used as in terms of "thin layers on the skin" and "finger-tip amount of cream". Therefore, several studies were set to quantify steroid application ensuring optimal treatment effect and ideal skin coverage. Nelson *et al.* used body surface area (BSA) and the amount of medication required to cover that unit of area. They have shown that it is possible to calculate recommended amount of topical corticosteroids to cover the body area in question [9].

Intermittent use of topical steroids has excellent risk-benefit ratio and it is commonly prescribed in various conditions. However, repeated continuous use of potent steroids may tip the scale towards more unwanted side effects. Measures like education for correct corticosteroid use of both the physicians and the patients will further increase the safety profile of this beneficial medication [10]. Use of intermediate and low-potent corticosteroids,

altering schedule and morning application are shown to improve clinical and patient outcomes [11].
In future, use of selective glucocorticoid receptor ligands will show the anti-inflammatory activity comparable to other potent steroids, in addition toremarkably superior side-effect profile [12].

Conclusion

Long-term use of topical corticosteroid creams carry inherited risk of broad local and system adverse effects. In addition, standardized treatment prescription, especially in the fragile pediatric population, is warranted. Continuous monitoring, vigilance in prescribing and patient education will advance the quality of life.

Acknowledgments. We thank the patient and his family for participation in this study. In addition, we thank all the medical personal involved in treatment and care of this patient.

Conflict of interest statement. None declared.

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Case report

BILATERAL SEROUS RETINAL DETACHMENT IN PREECLAMPSIA: CASE REPORT

БИЛАТЕРАЛНА СЕРОЗНА АБЛАЦИЈА КАЈ ПРЕЕКЛАМПСИЈА (ПРИКАЗ НА СЛУЧАЈ)

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Abstract

Introduction. Preeclampsia presents a medical condition in pregnancy that is manifested with increased blood pressure and protein urine. Ocular involvement is rare. Retinal detachment in preeclampsia is a rare complication; it only occurs in 1-2% of severe preeclampsia but in 10% of those with eclamptic seizures.
Case report. A pregnant patientG1P0 visited the outpatient clinic of the University Clinic for Ophthalmology complaining onvisual disturbances. Thechief complaint was blurred vision and headaches. She was in 31 week of gestation and complained that she had increased blood pressure overthe last month. After initial assessment she was suspected ofcentral serous retinal ablation (CSCR). Ocular ultrasound and posterior segment OCT (optical coherence tomography) confirmed the diagnosis.
Treatment and outcome. Obstetric examination confirmed high blood (TA180/130) pressure with dipstick urine showing(+++). Unfortunately, the ultrasound showed an eutrophic pregnancy in 31 g.w. with fetus mortus inutero. The patient was administered to the intensive care unit. She had an ophthalmologic check-upat 2 weeks and one month post-partum that showed regression and visual acuity was getting better. The final check-upafter 6 months revealed that retina was in place with no subretinal substantial fluid and no macular edema.
Conclusion. Serous retinal detachment is a rare complication of preeclampsia. In most case it resolves spontaneously few weeks post delivery.

Keywords: serous retinal detachment, preeclampsia, OCT

Апстракт

Вовед. Прееклампсија е заболување во бременоста, кое се манифесттира со зголемен крвен притисок и протеинурија. Како мултисистемско заболување, очите се ретко засегнати. Одлепување на ретината е ретка компликација кај тешки прееклампсии и се сретну- ва во 1-2%, до 10% во случај на еклампtичен напад.
Случај. 31 трудница Г1П0 се јавила на клиника за очни болести, заради проблеми со видот. Пациентката се жалела на тешки главоболки, била во 31 г.н со покачен притисок во последниот месец од бременоста. По првичниот офталмолошки прегед поставено е сомнение за билатерална серозна одлепување на ретината. Со помош на Уз и ОСТ (оптичка кохерентна томографија) дијагнозата беше потврдена.
Третман и исход. Акушерскиот преглед покажа зголемен крвен притисок ТА 180/30 и квантитативно +++ протеини во урината. За жал, контролата покажа и еутрофичен плод без срцева акција.Трудницата веднаш беше примена во единицата за интензивна нега. Контролните офталмолошки преглед беше направен по две недели, каде се забележа регресија на промените и подобрување на видот. На наредната контрола по шест месеци ретината беше на место, без субретинална течност и без макуларен едем.
Заклучок. Серозно одлепување на ретината е ретка компликација на прееклампсија.Во најголем дел од случаитенастапува спонтана регресија на промените за неколку недели.

Клучни зборови: серозно одлепување, ретина, прееклампсија , ОСТ

Introduction

A mother's body undergoes many changes throughout the course of a pregnancy. Every system in the body is affected including the eyes. The conditions of pregnancy that affect the retina may be broken in two categories: preexisting conditions worsened by pregnancy and pathological changes caused by pregnancy. Preeclampsia presents a medical condition in pregnancy that is manifested with increased blood pressure and protein urine.

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It occurs in 5-8% of pregnancies [1]. Preeclampsia is a pregnancy-related disorder that involves increased blood pressure >140/90mmHgand increased amount of urine protein >0.3 gr/l [2]. Preeclampsia usually develops in the last third of pregnancy. With advancing pregnancy preeclampsia gets more difficult [3]. In more severe cases of the disorder it is possible to see decreased number of platelets, erythrocytes breakdown, liver and kidney failure, swellings, pulmonary edema and even death [4]. A severe form of preeclampsia can lead to an eclamptic seizure. Additional risk factors for preeclampsia include: obesity, previous hypertension, older age and diabetes. It is more common in the first pregnancy and in twin pregnancies. The eyes are affected in 30 to 100% in patients with preeclampsia [5].

Retinal detachment in preeclampsia is a rare complication; it only occurs in 1-2% of severe preeclampsia but in 10% of those with eclamptic seizures [6].

The majority of patients with clinical management have a complete recovery in the case of serous retinal detachment. Complete recovery is expected in a couple of weeks [7]. There is no need for any surgical intervention [8].

The serous retinal detachment in preeclampsia is unusual cause of visual loss and is produced by the involvement of the choroidal vascularization [9].

Long-term visual changes may occur due to retinal pigment epithelium changes or optic atrophy.

Case report

A pregnant patient(G1P0) visited the outpatient clinic of the University Clinic for Ophthalmology complaining onvisual disturbances. The chief complaint was blurred vision and headaches. She was in 31 week of gestation and complained that she had increased blood pressure overthe last month. She was previously placed on antihypertensive therapy with Methydopa 3x 250 mg. On the first check-up visual acuity on the right eye was VOD: counting fingers in front of her on 5m distance, and on the left VOS: counting fingers on 4m distance. Intraocular pressure was measured normal and there were no changes on the anterior eye segment. According to the initial assessment she was suspected ofcentral serous retinal ablation (CSCR)

Both pupils were dilated and there was partial retinal elevation affecting the macula on the right eye with central serous choroid retinopathy on the left. Ocular ultrasound and posterior segment OCT (optical coherence tomography) confirmed the diagnosis. TA was 160/100. She was sent to the Department of Obstetrics for further check-ups. The obstetric examination confirmed high blood (TA180/130) pressure with dipstick urine showing (+++). Unfortunately, the ultrasound also showed an eutrophic pregnancy in 31 g.w. with fetus mortus inutero. She was admitted to the intensive care unit. The next day she delivered, her blood pressure returned to normal and in 3 days post-deliveryshe was released from hospital.

The patient had an ophthalmologic check-upat 2 weeks and one month post-partum that showed regression and visual acuity was getting better. The final check-upafter 6 months revealed that retina was in place with no subretinal substantial fluid and no macular edema. The final examination showed the best corrected visual acuity on the right eye-0.8cc and on the left eye-1.0cc. Fundus findings showed nothing but changes on the RPE (retinal pigment epithelium), and slightly reduced fovea reflection. Control OCT was preformed and the diagnosis was confirmed.

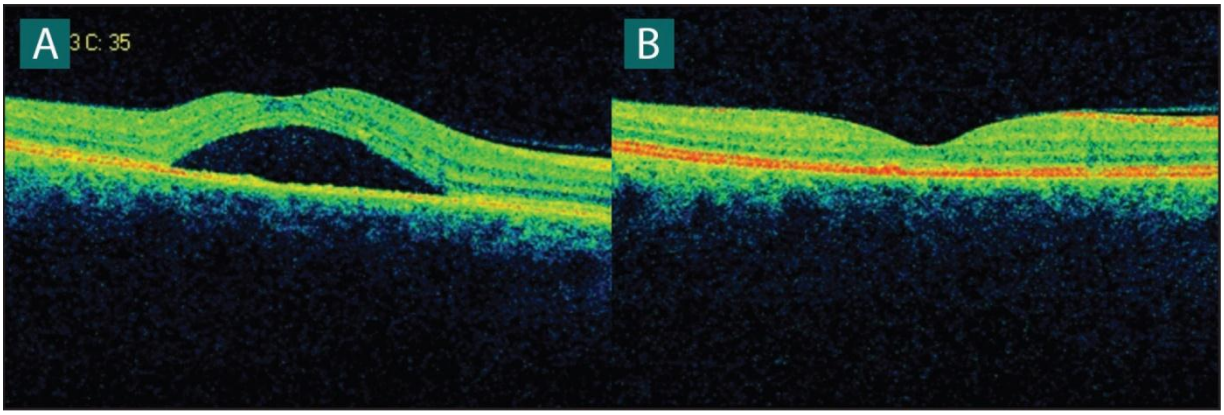

Fig. 1. A-OCT/Macula showing subretinal exudation with central serous retinal ablation, B-6 months later OCT/Macula showing reattached retina with minor subsequent RPE (retinal pigment epithelium) changes

Discussion

Preeclampsia is a serious condition that affects pregnancy. It can be divided in early or late preeclampsia. Early preeclampsia occurs before the 34 g.w. and has more severe effects on both, the mother and the baby. The exact pathogenesis of preeclampsia is unknown; several theories exist. The case that we present is just one of many who seem to be badly managed. The patient had lacked the proper controls and therapy so that early signs of preeclampsia were missed.

In severe cases of preeclampsia ocular involvement occurs in 30-100% The most common symptom is blurred vision; other signs include: photophobia,visual spots and diplopia. These symptoms can be attributed to posterior cerebral artery vasospasm with ischemia or to cerebral edema in the occipital area. Less common complications with preeclampsia may include involvement of the choroid, conjunctive, the optical nerve and visual cortex [10].

Retinal detachment may happen before or after delivery [11]. There is no clear consensus whether the presence of serous retinal detachment in the mother has some kind of prognostic implication to the fetus, however most believe that maternal and fetal prognosis is worse with fundoscopic alterations [12]. The exact pathophysiology of serous retinal detachment in preeclampsia is unknown. The retinal pigment epithelium (RPE) is capable of pumping a great amount of fluid and other metabolites out of the neuroepithelium. RPE is greatly influenced by the choroidal circulation [13]. Preeclampsia is a known condition that can lead to vasoconstriction and hemorheological changes that decrease blood flow which can lead to choroidal ischemia [14]. Due to pregnancy there are some limitations to which evaluation methods can be used. The use of fluorescein angiographic studies has been limited due to the fear of teratogenicity effects on the fetus; however some results show that retinal detachments in preeclampsia are due to alterations of the choroid vasculature [15]. Posterior segment OCT seems to be a logical choice in pregnancy, especially in breast feeding mother. It is non-invasive technique; it is save, superior diagnostic method to fluorescein angiography in evaluation and monitoring of serous retinal detachment inpregnancy [16].

Conclusion

Serous retinal detachment is a rare complication of preeclampsia. In most case it resolves spontaneously a few weeks post-delivery. It should be noted that in cases of severe preeclampsia or an eclamptic seizure ocular changes occur. A multidisciplinary approach is needed and better cooperation between ophthalmologists and obstetricians. In our case despite thebad outcome, a year laterthe women remained pregnant again. She was monitored for high blood pressure and treated. She delivered a healthy baby.

Conflict of interest statement. None declared.

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In memoriam

Проф. д-р Ѓорѓи Ставриќ
(1933-2017)

Медицински факултет-Св. „Кирил и Методиј„ во Скопје, Република Македонија

Проф. д-р Ѓорѓи Ставриќ е роден на 4.1.1933 година во Скопје, каде го завршил основното и средното образование. Во 1951 година се запишува на Медицинскиот факултет во Скопје, кој го завршува во 1958 година. За време на апсолвентскиот стаж бил вработен на Институтот за патологија во својство на лаборант-демонстратор за работа со студентите, и тоа за времето од апсолвирањето до дипломирањето. Во 1963 година се вработува на Институтот за радиологија и онкологија на Медицинскиот факултет во Скопје и во истата година ја започнува специјализацијата по патолошка анатомија. Специјализацијата ја обавува на Институтот за патологија во Скопје, а за време на специјализацијата студиски престојува во Заводот за патологија на Клиничката болница „Др. Младен Стојановиќ“ во Загреб и во Лабораторијата за онколошка цитологија во Љубљана.

Веднаш по завршувањето на специјализацијата во 1968 година, проф. д-р Ѓорѓи Ставриќ бил на шестомесечен студиски престој во Заводот за патологија на Онколошкиот институт „Марија Склодовска-Кири“ во Варшава, Полска.

Неговата академска кариера започнува во 1969 година со изборот во звањето хонорарен асистент по предметот патолошка анатомија на Медицинскиот факултет во Скопје. Понатаму следат избори за асистент во 1973 година, доцент во 1977 година, вонреден професор во 1983 година, редовен професор во 1990 година.

Проф.д-р Ѓорѓи Ставриќ ја организирал првата Лабораторија за клиничка цитологија во РМ, во рамките на Институтот за радиологија и онкологија во кој беше вработен. Во 1971 година ја организирал Лабораторијата за гинеколошка цитологија при Градска болница во Скопје, како и Лабораторијата за гинеколошка цитологија на Клиниката за гинекологија и акушерство во Скопје. Покрај едукацијата на кадрите за овие лаборатории, во истите го супервизираше програмот за цитолошки скрининг на женското население на град Скопје.

Во 1972 година бил на едномесечен стручен престој во Одделот за клиничка цитологија на Каролинска Хоспитал во Стокхолм, Шведска, во врска со истражувањата на цитодијагностиката на штитната и простатната жлезда, а во 1983 година на Институтот за патологија во Келн, Германија заради проучување на патологијата на лимфните жлезди и малигните лимфоми.

Во лабораторијата што ја раководел, се вршеле хистопатолошки и цитопатолошки анализи, а сиот материјал се систематизирал по SNOP и бил компјутерски обработен по разни обележја и во вид на „Кумулативен преглед на хистопатолошки и цитопатолошки анализи“.

Во 1974 година бил избран за член на Интернационалната Академија за цитологија (MIAC). Во 1975 година Здружението на гастроентеролозите на Југославија му доделиле диплома за гастроентеролог-патолог за успешно и долгогодишно соработување, а во 1981 година Здружението на нефролозите на Југославија за нефролог-патолог. Преку изнесувањето на сопствените резултати од стручната и научната работа учествувал во бројни интернационални и југословенски конгреси по онкологија, патологија и цитологија.

Активно партиципирал во едукацијата на стручниот и научен подмладок.

Проф. д-р Ѓорѓи Ставриќ зборувал на повеќе странски јазици меѓу кои и англиски, француски и руски јазик.

Во почетокот на својата научна активност ги проучувал можностите за контрола на цервикалниот канцер со помош на масовен цитолошки скрининг. Резултатите од таа активност се сумирани во неговиот труд: „Евалуација на можностите за ерадикација

на carcinoma planucellulare cervicis uteri во цитолошки протектирана популација“.

Покрај тоа, предмет на негово научно интересирање било испитувањето на можностите за рано откривање и дијагностицирање на ракот на дојката. Првите резултати од ова испитување во нашата средина се публикувани во 1973 година и денеска се цитираат како изворни трудови во оваа област на медицината. Исто така специјален интерес бил посветен на испитувањето на можностите за детекција на локализираните и диференцирани облици на тироидната неоплазија во популација со струма. Покрај овие проекти партиципирал во истражувачките проекти водени од другите институции на Медицинскиот факултет. Партиципирал и во проектот за проучувањето на неоплазмите на црниот дроб, а го водел и проектот за одредувањето на маркерите на површината на лимфоцитите во инфламаторните и неопластични лимфаденопатии.

Проф. д-р Ѓорѓи Ставриќ активно учествувал во работата на стручните професионални здруженија. Член бил на Управниот одбор на здружението на клиничките цитолози на Југославија, од нивното основање. Во периодот од 1980 до 1984 година бил генерален секретар на Здружението на патолозите на Југославија, а од 1983 година до 1987 година бил претседател на Здружението на клиничките цитолози на Југославија.

Активно учествувал и во работата на самоуправните органи на Институтот, Факултетот и Универзитетскиот сенат. Од 1986 до 1989 година бил претседател на Колегијалниот работоводен орган на Институтот за радиотерапија и онкологија.

По повод 40 годишнината од постоењето на Медицинскиот факултет во Скопје доделена му е Јубилејна златна плакета. Во 1989 година во знак на признание за посебен придонес во основањето, развојот и извршувањето на задачите на Универзитетот му била доделена плакета од Универзитетот „Св. Кирил и Методиј“ во Скопје. Исто така добитник е на плакета и од страна на Сојузот на здруженијата на лекарите на СР Македонија. Носител бил на орденот на труд со златен венец.

Проф.д-р Ѓорѓи Ставриќ има публикувано бројни стручни и научни трудови.

Медицинскиот факултет засегогаш ќе му остане благодарен за се што твореше и се што направил преку својата самопрегорна работа и посветеност на факултетот преку студентите, специјализантите, магистрите и докторантите.

Тешко е да се признае фактот дека го нема повеќе меѓу нас и дека ќе продолжи да живее во нас преку спомените, преку љубовта и сеќавањата кои ги носиме во нас за нашиот сакан почитуван професор, човек, сопруг, родител, колега, пријател.

Медицински факултет
Св. „Кирил и Методиј„ во Скопје,
Република Македонија

Мак Мед Прегледˉ 2017; 71(2): 148-149

ММР

In memoriam

Проф. д-р Ѓорѓи Ставриќ
(1933-2017)

Проф. др. Кирил Трпков

Универзитетот во Калгари, Канада и директор на Одделот за Патологија и Лабораториска медицина

ЗБОГУМ ПРОФЕСОРЕ, УЧИТЕЛЕ НА УМОТ И ДУХОТ

Ако микроскопот ти е основниот алат, тогаш ти си патолог. Тоа значи да научиш да гледаш остро и прецизно, да мислиш критички и широко, но со мир и мекост во душата. За ниедна нејзина турбуленција да не ти ја помати мислата и резонот. Да бидеш систематичен, скромен, страсен, но и да се помириш со тоа дека (најчесто) ќе бидеш невидлив за пациентот. Само така ќе бидеш добар патолог. Зашто кога треба да се постави точна дијагноза, никогаш не се работи за лекарот-патолог, а само за пациентот и неговото здравје. Лекарот тука не е битен, и неважно е што тој лично чувствува. Или мисли. Патологот е невидливиот режисер на медицинската судбина на пациентот. Да, на сцената на еден важен животен миг излегуваат на сцена пациентот и лекарот/клиничар што него го лекува, но патологот ја режира таа претстава и го пишува нејзиниот синопсис. Зашто без точна медицинска дијагноза, нема ни пат до лек и лекување. И не попусто е кажано, патологијата е огледало на медицината на една средина!

Во ова мајско попладне разбрав дека проф. Ставриќ починал. Каква гордост и чест за мене е да кажам дека сум бил негов ученик! Кога се наоѓаш далеку од некое место или настан со кој те поврзуваат нишки на умот и душата, само солзата во окото, како леќа од двоглед, телескоп или микроскоп ти го доближува тоа место, луѓето и настаните што те врзуваат за него.

Ѓорѓи Ставриќ беше не само патолог, учител, педагог, професор, врвен дијагностичар и стручњак. Тој беше еден од втемелувачите на модерната југословенска и македонска патологија и цитологија. Еден од ретките луѓе што имав гордост, привилегија и чест да ги сретнам во животот, да работам со нив, да ги запознаам одблиску. Всушност, заради него станав патолог. Тој ми беше професионален татко во патологијата, мој прв учител и единствен професионален ментор. За време на студиите не сретнав похаризматичен и поостроумен професор и човек. Едноставно, сакав да бидам како него, тој ми беше рол модел. Неговиот збор и дијагноза тежеа. Затоа што во него луѓето гледаа врвен стручњак и дијагностичар, но и спасител, човек со огромна чест и доблест, лидер со храброст и морал, но и човек што знае извонредно да слуша и луцидно да мисли, дури и за дијагностицирање на работите на светот и душата. Човек на кого му се верува. Човек што знае да сослуша, посоветува, упати, помогне. Човек што функционира со "оптимизам и присуство на дух". Човек кој кога ќе ти го каже и она што не сакаш да го чуеш - ќе бидеш среќен дека ти ја кажал вистината, без ракавици. Човек што храбро и со доблест секогаш ја зборува и се бори за вистината, вредности што бликаат и од животниот пат на неговото потесно семејство. Човек на рид качен, што гледа повеќе од тие под ридот. Човек што ја има онаа недопирлива способност да биде магионичар на умот и на душата!

Се сретнавме на еден обичен студентски испит што го полагав кај него. Неколку години потоа, кога дојдов да прашам дали има место за мене во неговата лабораторија, тој ме пречека како да ме знаел и чекал со години. Како секој отворен и љубопитен млад човек го прашав: Зошто сте станале патолог? Заради точната дијагноза, ми одговори, таа медицинска вистина, што бара да биде откриена, зашто таа е водилката во патологијата, онаа кон која секогаш се стремиме и онаа заради која секој ден чувствуваме сатисфакција. Ако сакаш да лекуваш пациени и да глумиш Господ, ова не е за тебе! Но ако сакаш да бидеш како Шерлок Холмс, да! Зарем не сте размислувале да заминете надвор професоре, прашав? Како не сум размислувал, ама проклето не можам без ова Водно, Скопска Црна Гора, Шара…некој може, некој не-ми одговори искрено и без двоумење.

Кога ќе се пожалевме дека немаме ова или она, и затоа не можеме, ќе речеше "hic Rhodus, hic salta" - покажи што можеш овде и сега (и не наоѓај оправдувања). И, "на муци се познају јунаци"! Беше учител што секогаш сакаше да го извлече максимумот од оние околу него, од неговите ученици, соработници, до техничарите во лабораторијата и дактилографките. Ајде сега, време е за фрлање од стена...имаше обичај да каже кога се соочувавме со некој нов, сериозен предизвик. За себе скромно кажуваше, јас сум удрен во крило, со сета во гласот опишувајќи ја личната посветеност и љубов кон професијата, во која, да се сознае, да

се научи, да се усоврши, да се разбере, е исто што и да се дише и да се постои.

Нашите утрински состаноци во лабораторијата на Институтот за Онкологија и Радиотерапија, во едно турбулентно време на почетокот на 90-те, беа и лекции по живот, морал, професионалност, по наука. Честопати ќе скршневме во разговорот и кон уметност или филм. Во овие разговори учествуваше и прерано починатиот др. Ѓорѓи Зографски, уште еден од интелектуалните синови на проф. Ставриќ и мој учител, блескав ум. Конверзациите со проф. Ставриќ понекогаш се претвораа во поетски дијалози - тој настапуваше со Његош и Вук Караџиќ, јас со Конески и Прличев. При нашата разделба во далечната 1993 година ми рече: "Путуј игумане, за манастир не брини!", и ме посоветува "како и да решиш, едно каење ти претстои", тешејќи ме, но и охрабрувајќи ме да го следам патот на професионалната и животна судбина. Останавме во контакт и во овие 25 години откако го "напуштив манастирот", а и се среќававме често и за време на моите посети на Македонија, разговарајќи за "чашата мед и чашата жолч" од кои се состои животот.

Неговата работна етика и долг кон пациентите беа легендарни. Дневната клиника за цитолошка дијагноза ја водеа тој и д-р Зографски и прегледуваа и по 30 до 40 пациенти дневно, а ние, помладите лекари асистиравме. Тие самите вршеа тенкоиглени биопсиии и препаратите ги читаа истиот ден, за пациентите да имаат готов резултат и наод следниот ден. Тоа беше вистински пример за тоа како треба да фунционира една клиника. Тој и од погреб на најблиски се враќаше на работа, за да ги прочита сите препарати, за пациентите на време да го добијат резултатот. Зашто, секогаш за нив се работеше, за пациентите! Илјадниците наоди и дијагнози што ги правевме тој упорно инсистираше да ги кодираме и организираме по светска системска класификација, создавајќи уште тогаш компјутерски преглед-пресек на она што го наоѓавме кај нас како патологија. Тој беше пионер на цитологијата во Југославија и на Балканот, и ја внесе и разви оваа метода по престојот на врвните институции во Шведска и Америка во 70те години од минатиот век. Неговиот труд за рана цитолошка дијагноза и детекција на тироидна неоплазија, испечатен во престижниот Cancer во 1980 година, беше еден од оние трудови што остануваат како темелници на нашето научно наследство. Со гордост се сеќавав на него и на овој труд, кога по многу години ми излегоа два труда таму. Знам дека и тој се гордееше исто колку и јас.

И ден денеска чувствувам дека ги следам неговите стапки, ги слушам неговите зборови, се однесувам во професијата и во животот така како што сум научил од него, зашто тоа е всадено во моето кредо. И сеуште сум горд дека заради него - како човек и професионалец - сум го одбрал овој пат. Неговото семејство, најблиските, и ние што сме биле среќни да делиме барем дел од професионалниот пат со него, ќе го чуваме споменот за човекот со остро око, критички ум и мека душа!

Нека ти е вечна слава и спомен професоре, учителе на умот и духот!

Проф. д-р Кирил Трпков,
Универзитетот во Калгари, Канада и
директор на Одделот за Патологија и
Лабораториска медицина

Мак Мед Прегled 2017; 71(2): 150-150

ММР

In memoriam

Проф. д-р Цвета Толевска
(1945-2017)

Медицински факултет-Св. „Кирил и Методиј„ во Скопје, Република Македонија

Проф. д-р Цвета Толевска е родена на 29.5.1945 година во с. Љубојно-Преспа. Основно училиште и гимназија завршила во Битола. Во 1964 година се запишала на Медицинскиот факултет во Скопје, а дипломирала во 1970 година со среден успех 8.

Во 1972 година се врботила во Институтот за радиотерапија и онкологија, при Медицинскиот факултет во Скопје. Во 1978 година го положила специјалистичкиот испит по радиологија.

Во 1977 година била избрана за помлад асистент по предметот радиологија. Во 1982 година е избрана за асистент по истиот предмет, а во 1986 и 1991 година е реизбрана во истото звање.

Во 1984 година била на едногодишно стручно усовршување во САД, Henry Ford Hospital, Детроид, каде се запознава со целокупната технологија на работа во одделот за радиотерапевтска онкологија и со сите новини од таа област. При овој престој изработила научна студија за третманот на карциномите на белите дробови со интраоперативна, интерстицијална радиотерапија, која била презентирана на симпозиум за карцином на белите дробови во истата болница, во април 1985 година.

Проф. д-р Цвета Толевска во 1988 година била избрана за шеф на Одделот за тумори на централниот нервен систем и скелетот.

Во текот на својата работа проф. д-р Цвета Толевска учествувала со свои трудови на повеќе научни и стручни конгреси, симпозиуми и интерсекциски состаноци на просторот на некогашна Југославија и Македонија, како и на повеќе европски и светски конгреси.

Проф. д-р Цвета Толевска учествувала на три едукативни курсеви во организација на Европската школа за радиотерапевтска онкологија (ESTRO).

Во ноември 1991 година одбранила докторска дисертација на тема: „Хиперфракционирана радиотерапија и хемотерапија со BCNU кај малигните супратенторијални астроцитоми“.

Во септември 1992 година била избрана за научен соработник по предметот онкологија со радиотерапија, во Мај 1995 година за доцент, во октомври 1997 година за вонреден професор, а во 2002 година била избрана за редовен професор по предметот онкологија со радиотерапија.

Проф.д-р Цвета Толевска беше врвен лекар во својата специјалност, совесна и трудољубива. Перманентно ги освежувала и дополнувала своите знаења со следење на стручна литература. Новите сознанија ги аплицирала во секојдневната практична работа.

Бројните стручни и научни публикации, како и докторската дисертација на проф. д-р Цвета Толевска претставуваат научен придонес во областа на радиотерапијата и хемотерапијата на малигните заболувања во нашата земја.

Проф. д-р Цвета Толевска беше докажан педагог во областа на радиотерапијата и онкологијата. Нејзините предавања биле јасни и лесно разбирливи за студентите. Таа покажува еднаков ентузијазам и при едукацијата на специјализантите.

Проф.д-р Цвета Толевска е коавтор на учебникот „Радиотераписка онкологија“ издадена во 2002 година како заеднички труд на наставниот кадар при катедрата по онкологија со радиотерапија, а има публикувано и бројни стручни и научни трудови.

Медицинскиот факултет засегогаш ќе и остане благодарен за се што твореше и се што направи преку својата самопрегорна работа и посветеност на факултетот преку студентите, специјализантите, магистрантите и докторантите.

Тешко е да се признае фактот дека ја нема повеќе меѓу нас и дека ќе продолжи да живее во нас преку спомените, преку љубовта и сеќавањата кои ги носиме во нас за нашата сакана почитувана професорка, човек, сопруга, родител, колега, пријател.

Медицински факултет
Св. „Кирил и Методиј„ во Скопје,
Република Македонија

Мак Мед Преѓлед 2017; 71(2): 151-152

ММР

In memoriam

Проф. д-р Јелка Масин Спасовска
(1964-2017)

Медицински факултет-Св. „Кирил и Методиј„ во Скопје, Република Македонија

Проф. д-р Јелка Масин Спасовска е родена на 7 март 1964 година, во Охрид. Средно образование и гимназија завршила во Скопје, а високо образование завршила на Медицинскиот факултет при Универзитетот „Св. Кирил и Методиј“ во Скопје во 1991 година со просечен успех 9,1.

Во 1992 година се запишала на магистерски студии на Медицинскиот факултет во Скопје и ги завршила со просечен успех 9,6, а во Мај 1999 година го одбранила магистерскиот труд на тема: „Динамика на промените на плазма-вискозноста и фибронектинот кај хипертензија индуцирана со гравидитет“.

Докторската дисертација ја пријавила на 31.10.2002 година на Медицинскиот факултет во Скопје на тема: Раните исхемиско-реперфузиски имунолошки оштетувања на графтот и нивната предиктивна важност врз појавата, клиничкиот тек и исходот на реналната дисфункција кај болните со пресадерн бубрег“, а ја одбранила на 9 јануари 2009 година, и со тоа се стекнала со научен степен доктор на медицински науки.

На Медицинскиот факултет во Скопје во јуни 1994 година е избрана во звањето помлад асистент по предметот интерна медицина, а во Септември 1997 година е реизбрана во истото звање. Од јуни 2000 година е избрана во звањето асистент од областа интерна медицина, а во април 2004 е реизбрана во истото звање. Во Мај 2010 година е избрана во звањето научен соработник од областа интерна медицина. За виш научен соработник е избрана на 02.03.2015 година, и за вонреден професор е избрана на 22 декември 2015 година.

Проф. д-р Јелка Масин Спасовска изведувала настава на студиските програми од прв и втор циклус студии, учествувала во континуирана обука за лекари за водење на акутна и хронична дијализа, лекари-стажанти и лекари од примарното здравство. Активно била вклучена како ментор и едукатор на специјализантите по интерна медицина.

Проф. д-р Јелка Масин Спасовска има објавено 74 научни труда од нефролошката трансплантациска област, од кои 33 печатени трудови, 10 научни труда во научни списанија со импакт-фактор, 20 труда во меѓународни научни списанија, 1 труд во меѓународна научна публикација, 2 труда со оригинални научни резултати објавени во научно/стручно списание и 41 труд во зборници од научни собири.

Проф. д-р Јелка Масин Спасовска учествувала и во изработка на 4 научни проекти (1 национален и 3 меѓународни). Дел од проектите во кои партицирала се финансирани од FP-7 програмата од Комисијата за наука на ЕУ. Учествувала во настава на бројни работилници, школи, конгреси, теоретски и практични курсеви за континуирана медицинска едукација во повеќе европски земји, со секциски и пленарни предавања.

Проф. д-р Јелка Масин Спасовска активно била вклучена во стручно-апликативната работа на Универзитетската клиника за нефрологија во Скопје како лекар во Одделот за трансплантација, Одделот за ехосонографија и амбулантата на Клиниката за нефрологија.

Стручно усовршување во странство остварила со студиски престои во:

- Нинберг, Клиника „Др. Ерлер“ во склоп на Ерланген Универзитетот, Германија во 1993 г. (3 месеци - Проф. Стерцел (перитонеална дијализа),
- Клиника за нефрологија, во склоп на Универзитетот во Болоња, Италија. во 1996 г. - 3 месеци, и
- во Болницата „Ребро“, Клиниката за нефрологија и Министерството за здравство-Центар за национална координација за кадаверична трансплантација, Загреб, Хрватска (25.11-1.12.2012).

Била член на повеќе национални, балкански, европски и интернационални здруженија: Македонско здружение за нефрологија, дијализа, трансплантација и вештачки органи, Македонско лекарско друштво, Лекарска комора на РМакедонија, BANTAO, International Transplantation Society, International

Society of Nephrology (ISN), European Society for Artificial Organs.

Соработник и коавтор е на поглавје на книгата **Organ Transplantation: Ethical, Legal and Psychosocial Aspects.** од авторот **Weimar *и сор*.** 2012 година. Има направено превод на: Препораки за евалуација на дарители и приматели на бубрег и нивна перипоративна нега, објавен во Македонски медицински преглед во 2014 година.

Проф.д-р Јелка Масин Спасовска била член на уредувачкиот одбор на научно-стручното списание Bantao Journal, рецензент на Македонски медицински преглед, и член на управниот одбор на Македонско здружение за нефрологија, дијализа, трансплантација и вештачки органи.

Била член на организационен одбор и секретар на Третиот Конгрес по нефрологија во Р. Македонија со меѓународно учество, модератор на Четвртиот конгрес по нефрологија во Р. Македонија со меѓународно учество, Член на Научниот комитет на Единаесетиот конгрес на БАНТАО (Балканска нефролошка асоцијација) во Романија; Член на Научниот комитет на Четвртиот конгрес на SouthFast European Medical Forum во Порторож, Словенија; модератор на сесија на Меѓународни нефролошки денови во чест на 75 години од раѓањето и 50 години научна работа на акад. проф. д-р Момир Поленаковиќ и многу други.

Медицинскиот факултет засегогаш ќе и остане благодарен на проф. д-р Јелка Масин Спасовска за огромниот придонес и белег што го остави како наставник, научник и стручњак за успешна реализација на дејностите на Факултетот, манифестирана преку нејзината самопрегорност и посветеност на факултетот преку студентите, специјализантите, магистрите и докторантите.

Медицински факултет
Св. ,,Кирил и Методиј,, во Скопје,
Република Македонија

УПАТСТВО ЗА ПРИЈАВА НА ТРУД ОД СОРАБОТНИЦИТЕ НА ММП

"Македонски медицински преглед"(ММП) е стручно списание на Македонското лекарско друштво, првенствено наменето на лекарите од општа практика, специјалистите од одделните медицински дисциплини и истражувачите во областа на базичните медицински и други сродни науки.
Списанието ги има следниве рубрики и категории на трудови:

- **Изворни трудови**
- **Соопштувања за клинички и лабораториски искуства**
- **Прикази на случаи**
- **Од практика за практика**
- **Едукативни статии**
- **Вариае (**писма од редакцијата, општествена хроника**,** прикази на книги, извештаи од конгреси, симпозиуми и други стручни собири, рубриката „Во сеќавање„ и др).

Изворните трудови имаат белези на научни трудови, додека трудовите категоризирани во рубриките 2-5 имаат белези на стручни трудови.
Во ММП се објавуваат трудови на членовите на МЛД или на членови на други стручни здруженија. Авторите се одговорни за почитувањето на етичките начела при медицинските истражувања, а изнесените ставови, изведени од анализата на сопствените резултати, не се нужно и ставови на Редакцијата на ММП.
Редакцијата ги испраќа ракописите на стручна рецензија; рецензентот (ите) и Редакцијата ја определуваат дефинитивната категоризација на ракописот кој е прифатен за печатење. Редакцијата го задржува правото ракописите да ги печати според рецензираниот приоритет.
Упатството за соработниците на ММП е во согласност со Ванкуверските правила за изедначени барања за ракописите кои се праќаат до биомедицинските списанија.

- **ТЕКСТ НА РАКОПИСОТ**

Сите ракописи се испраќаат во електронска форма на електронската адреса (е-маил) на МЛД-ММП, со двоен проред и најмногу 28 редови на страница. Трудот се поднесува на англиски јазик латиничен фонт Times New Roman големина 12 и апстракт на македонски јазик. Лево, горе и долу треба да се остави слободна маргина од најмалку 3 см, а десно од 2,5 см.. Редниот број на страниците се пишува во десниот горен агол.
Ракописот на трудот треба да е придружен со писмо на првиот автор, со изјава дека истиот текст не е веќе објавен или поднесен/прифатен за печатење во друго списание или стручна публикација и со потврда дека ракописот е прегледан и одобрен од сите коавтори, односно со придружна декларација за евентуален конфликт на интереси со некој од авторите.

Насловната страна треба да има: наслов на македонски и англиски, имиња и презимиња на авторите, како и институциите на кои им припаѓаат, имињата на авторите и насловот на установата се поврзуваат со арапски бројки; автор за кореспондеција со сите детали (тел. е-маил); категорија на трудот; краток наслов (до 65 карактери заедно со празниот простор); како и информација за придонесот за трудот на секој коавтор (идеја, дизајн, собирање на податоци, статистистичка обработка, пишување на трудот).

Насловот треба концизно да ја изрази содржината на трудот. Се препорачува да се избегнува употреба на кратенки во насловот.

Изворните трудови и **соопштувањата** го имаат следниов формален редослед: насловна страна, извадок на македонски јазик (вовед, методи, резултати, заклучок) со клучни зборови, извадок на македонски јазик со клучни зборови, вовед, материјал и методи, резултати, дискусија и заклучоци, литература и прилози (табели, графици и слики) и легенди за прилозите во еден фајл.

Приказите на случаи треба да содржат вовед, детален приказ на случајот, дискусија со заклучок и литература со прилози.

Извадокот на македонски јазик треба да содржи најмногу 250 зборови и да биде структуриран со сите битни чинители изнесени во трудот: вовед со целта на трудот, методот, резултати (со нумерички податоци) и заклучоци. Заедно со извадокот, треба да се достават и до 5 клучни, индексни зборови.

Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик. Клучните зборови треба да се во согласност со MeSH (Medical Sibject Headings) листата на Index Medicus.

Воведот треба да претставува краток и јасен приказ на испитуваниот проблем и целите на истражувањето, со наведување на етичкиот комитет односно институцијата која го одобрила испитувањето (клиничка студија која се работи според принципите на Хелсиншката декларација за пациентите и нивните права).

Методите треба да бидат точно назначени, за да се овозможи повторување на прикажаното истражување. Особено е важно да се прецизираат критериумите за селекција на опсервираните случаи, воведените модификации на веќе познатите методи, како и идентификација на употребените лекови според генеричното име, дозите и начинот на администрација.

Резултатите треба да се прикажат јасно, по логичен редослед. Резултатите се изнесуваат во стандардните СИ единици. Во текстот треба да се назначи оптималното место каде ќе се вметнат табелите и илустрациите, за да се избегне непотребното повторување на изнесените податоци. Значајноста на резултатите треба да се обработи статистички, со детален опис на употребените статистички методи на крајот на делот *методи*.

Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем.

Заклучоците треба да не бидат подолги од 150 зборови.

- ***ПРИЛОЗИ***

Како прилог-документација на трудовите предложени за печатење, може да се достават до 5 прилога (табели, фигури,/слики - илустрации).

Табелите се доставуваат на крајот на трудот во истиот фајл. Секоја табела треба да има свој наслов и реден број кој ја поврзува со текстот. Хоризонтални и вертикални линии на табелата не се дозволени; ознаките на колоните во табелата се пишуваат скратено или со симбол, а нивното објаснување се пишува на дното на табелата, во вид на легенда.

Илустрациите се доставуваат со реден број како слика во црно-бела техника, а секоја слика треба да е придружена со легенда (опис).

Микрофотографиите може да содржат посебни ознаки во вид на стрелки или симболи. Покрај описот на сликата, мора да се наведе и зголемувањето и видот на боењето на препаратот (ако тоа веќе не е направено во секцијата *материјал и методи*).
Сите ознаки на фотографиите мора да бидат доволно големи, за да може јасно да се распознаат и по смалувањето во печатницата, при нивното вклучување во печатената страница на списанието.

 ЛИТЕРАТУРА

Цитираната литература се пишува на крајот на трудот по заклучоците, со редни броеви според редоследот на појавувањето на цитатот на текстот на трудот ставени во средни загради и без простор меѓу нив (ако се последователни треба да се поврзани со цртичка, на пр. [3-6]).
Литературата се цитира на следниов начин (кратенките за насловите на списанијата треба да се според листата прифатени во Index Medicus):

 статија во списание (се наведуваат сите автори, ако ги има до 4 или помалку; ако ги има повеќе од 4 се наведуваат првите 3 автори и се додава: *и сор*.) Neglia JP Meadows AT, Robison LL *et al*. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325:1330-6.

 заеднички автор

GIVIO (Interdisciplinary group for cancer care evaluation). Reducing diagnostic delay in breast cancer. Possible therapeutic implications. *Cancer* 1986; 58: 1756-61.

в) *без автор* - анонимно. Breast screening: new evidence. (*Editoriall Lancet* 1984; i :1217-8).

г) *поглавје во книга или монографија*

Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. Vo: Sodeman WA Jr, Sodeman WA, Ed. Pathogenic physiology: mechanisms of disease. Philadelphia; W B Saunders, 1974: 457-72.

Првите отпечатоци на трудовите им се праќаат на авторите за корекција: авторите се должни коригираниот отпечаток да и го вратат на Редакцијата на ММП во рок од 2 дена.

Уплата за испечатен труд во списанието ММП изнесува 3.000, 00 денари и се уплаќаат на жиро сметката на: Македонско лекарско друштво
300000000211884 – Комерцијална банка
со цел на дознака: уплата за стучен труд

Адресата на Редакцијата
Даме Груев бр. 3
Градски ѕид блок II,
1000 Скопје,
Тел.: ++ 389 02 3162 577

Електронска адреса (Е-маил): mld@unet.com.mk

Известување за рецензентите за ММП

Во склад со правилникот на УКИМ рецензентите што навремено и одговорно ќе ја одработат рецензијата ќе добијат 0.4 бода кои се собираат за унапредување во академските звања. Бодовите можат да се добијат и ретроградно преку побарување во МЛД – 3162 557.