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Original scientific paper

Profesional paper

Review

Case report

Medical Journal

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

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

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

The Oath of Hippocrates

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

My colleagues will be my brothers.

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

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EFFECTIVENESS OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR IN CYSTIC FIBROSIS PATIENTS WITH COMPLEX CFTR ALLELES INVOLVING P.{LEU467PHE;PHE508 DEL}

LJ.Proeska Stojanovski[1], T.Jakjovska[1,2]

[1]University clinic for respiratory diseases in children-Kozle, CF center
[2]Medical Faculty, UKIM

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ABSTRACT

Background: Cystic fibrosis (CF) arises from pathogenic variants within the CFTR gene.Complex alleles defined by two or more variants arraged in cis -may modify disease severity and therapeutic responsiveness.The coexistence of p.Leu467Phe(L467F) with p.Phe508del(F508del) has been reported to exert an additive pathogenic effect,potentially altering the response to the CFTR modulator combination Elexacaftor/Tezacaftor/Ivacaftor (ETI)Aims:To determine the frequency of the complex allele p.{Leu467Phe;Phe508 del} among patients with CF (PwCF) in North Macedonia, who carry at least one F508del variant, and to evaluate its impact on clinical course and treatment response to ETI.Methods:In a cohort of 76 pWCF with ≥1 F508 del allele, full CFTR coding region sequencing and polymorphic marker analysis were used to identify complex alleles. Clinical variables included disease severity, exacerbation frequency, and therapy use. Comparisons were made between patients with homozygous F508 del and compound heterozygous p.{Leu467Phe;Phe508 del}Results:The complex allele [L467F;F508del] was detected in 8 patients (10.5%).3 patients (4%) were homozygous for this complex allele.No statistically significant differences were observed between patients with homozygous F508del and those with [L467F;F508del] in terms of disease severity, exacerbation rate, or treatment use.However, the presence of L467F in cis with F508del leads to a reduction in CFTR protein activity due to a maturation defect, resulting in decreased ETI effectiveness.Conclusions:Complex alleles involving F508del were identified in 10.5% of CF patients in North Macedonia. This finding emphasizes the importance of genetic characterization when selecting optimal CFTR modulator therapy, as the [L467F;F508del] allele may negatively influence the therapeutic response to ETI.

INTRODUCTION

Cystic fibrosis is an autosomal recessive multisystem disease caused by mutations in the CFTR gene with over 2000 variants described. The most common pathogenic variant is p.Phe508 del(F508del), presented in approximately 70-90% of individuals of European descent. In recent years, the development of CFTR modulators, including the highly effective triple therapy Elexacaftor/Tezacaftor/Ivacaftor (ETI), has profoundly altered disease prognosis for many PwCF.

However, genetic complexity within CFTR continues to challenge therapeutic stratification. Complex alleles-defined as two or more variants located in cis on the same chromosome-can modify the functional consequences of individual mutations. The complex allele p.{Leu467Phe;Phe508 del}(L467F;f508del) has been described as contributing additional structural instability and impairing CFTR maturation beyond that caused by F508del alone.

Because modulator therapy efficacy relies on specific conformational rescue of CFTR, complex alleles may influence therapeutic responsiveness. Previous in vitro studies suggest that the presence of L467F may limit the corrective capacity of ETI for F508del-containing CFTR protein. However, real world evidence remains scarce.

This study aimed to determine the prevalence of p.{L467F;F508del} among PWCF on North Macedonia, and to explore whether this complex allele is associated with differences in clinical severity or response to ETI therapy compared with classical F508del genotypes.

METHODS

Study population

The study included 76 PwCF followed at the national CF center in North Macedonia who possessed at least one F508 del allele. All patients had confirmed CF based on clinical phenotype and diagnostic criteria (sweat chloride ≥60 mmol/l and/or two CF -causing mutations) (table 1.)

Genotype	F508del_L467F/ F508del_L467F	F508del_L467F/G 542X	F508del_E474K/ F508del_L467F	F508del_L467F/ F508del_L467F2	F508del_L467F/ F508del	F508del_L467F/ G542X2	F508del_L467F/ F508del3	F508del_L467F/ F508del_L467F4
No.	1	2	3	4	5	6	7	8
Age at the time of the study, years	15	20	21	21	21	26	29	38
Gender (m/f)	f	m	f	m	m	m	m	m
tt 0	54	65	60	60	50	64	63	72
tt 6	54	64	61	60	50	63	63	72
FEV_1 [%], 0 months	48	70	72	79	58	82	54	40
FEV_1 [%], 6 months	42	81	83	92	60	87	66	59
FEV_1 [%], 12 months	55	90	81	90	56	80	60	56
Cl [mmol/l], 0 months	96	103	90	109	103	87	106	105
Cl [mmol/l], 6 months	103	92	107	102	105	83	87	96
Cl [mmol/l], 12 months	99	106	101	99	94	90	102	118
pa chr	1	0	1	1	1	0	1	0
mrsa	0	1	0	1	0	0	0	0
staf chr	1	1	0	0	0	1	1	0
diabet	1	0	0	1	0	0	1	1
egzacerb	2	1	1	2	2	2	2	1
asperg	0	1	0	1	0	1	0	0
ntm	0	1	0	0	0	1	0	0

Table 1. Parameters in pwCF with complex alleles in N.Macedonia

Genetic Testing

Genomic DNA was analyzed using:

Full sequencing of all CFTR coding regions and exon-intron boundaries

Polymorphic marker analysis to determine cis/trans configuration

Variant phasing to confirm presence of complex alleles

Patients were classified into three comparison groups:

1.Homozygous F508del

2.Compound heterozygous p.{L467F;F508del}

3.Homozygous p.{L467F;F508del}

Clinical Assesment

Clinical data collected included:

-Age, sex, pancreatic status

-Lung function (FEV1 % predicted)

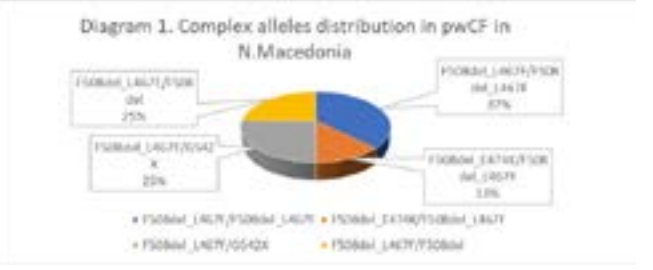
-exacerbation frequency over the previous year

-Chronic therapies and antibiotic usage

-Eligibility for and response to ETI therapy (when applicable)

Statistical Analysis

Descriptive statistics were used to compare groups. Given small sample size, nonparametric methods were applied. Significance was defined at $p < 0,05$. Due to the limited number of patients with complex allele, the study was exploratory in nature and not powered for hypothesis testing



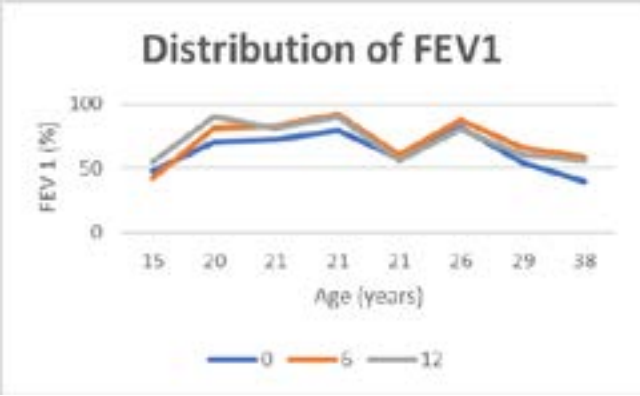
Results

Frequency of the complex allele

- p.{Leu467Phe;Phe508 del} was 8 of 76 patients (10,5%)

- Three patients (4%) were homozygous for the complex allele.

- The remaining 5 were compound heterozygotes (one complex allele+another pathogenic CFTR variant)

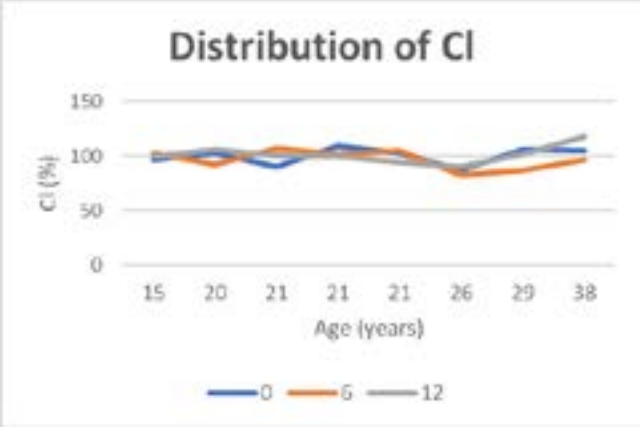


Clinical Characteristics

No statistically significant differences were observed between:

Homozygous F508 del patients,and patients carrying p.{Leu467Phe;Phe508 del}

Across the following domains:



Baseline FEV1

Exacerbation frequency

Chronic therapy requirements

Nutritional status

Implications for ETI therapy

Although clinical metrics did not show significant differences, mechanistic data and patient level observations suggest:

-L467F in cis with F508del reduces CFTR protein maturation, resulting in decreased chloride transport

-This structural impairment may partially reduce the effectiveness of ETI compared to classic F508del genotypes.

-Individual therapeutic responses varied, reinforcing the importance of genotype informed treatment planning.

DISCUSSION

This study provides the first national assessment of the p.{Leu467Phe;Phe508 del}, complex allele in N. Macedonia, Identifying a prevalence of 10,5% among PwCF with at least one F508 del mutation. This rate is consistent with reports from European cohorts, where complex alleles occur in approximately 5-15% of individuals with F508 del.

While no significant clinical differences were documented between patients with the complex allele and those with typical F508del genotypes, the interpretation is limited by small sample size. Importantly, functional studies suggest that L467F reduced maturation efficiency and diminished trafficking to the cell surface.

Because ETI relies on improving the folding and stability of F508 del CFTR,additional structural impairment may hinder its effectiveness.Several reports describe attenuates in vitro and clinical responses in individuals with similar complex alleles.

Our finding emphasize the need for:

-Comprehensive genetic characterization,including phasing analysis

-Individualized assesment of modulator therapy response

-Further multicenter studies to quantify the specific impact of p.{Leu467Phe;Phe508 del} on ETI outcomes

CONCLUSION

Complex CFTR alleles involving F508del,specifically p.{Leu467Phe;Phe508 del},occur in 10,5% of pwCf in North Macedonia,.Altough overt clinical differences were not statistically significant in this cohort,biological evidence strongly suggest reduced responsiveness to ETI in patients with this allele.These findings support the integration of extended genetic testing into routine clinical care to optimize precison based CFTR modulator therapy selection.

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Original scientific paper

LIMITATIONS IN UTILIZATION OF SODIUM FLUORESCEIN AS A CONTRAST AGENT DURING BRAIN SURGERY

Ivchev L[1,2], Damjanovski S[3], Markovski V[1], Kostov M[1,3]

[1]Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia

[2]General City Hosptial – September the 8th - Skopje, Republic of North Macedonia

[3]Department of Neurosurgery. Private Clinic Hospital "Acibadem - Sistina" – Skopje, Republic of North Macedonia.

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APSTRACT

Introduction: Although today's neurosurgery worldwide accepts the use of sodium fluorescein as a useful intraoperative contrast agent, there are several limitations and disadvantages of its utilization. Human medicine requires continuous research and development. Thus we made a clinical study that will provide useful information about some specific details about the use of sodium fluorescein intraoperative for brain tumors. In advance, we are looking forward in improving the fluorescent surgery and overcoming these disadvantages. Sodium fluorescein has a great potential as an intraoperative contrast agent and overcoming these limitations will lead to a more successful outcome.

Material and methods: Specific information about sodium fluorescein's characteristics was gained from 39 patients operated with its utilization during surgery of brain tumors. All of these patients were injected intravenously sodium fluorescein at a dose of 5mg/kg prior to skin incision. During surgery, operative microscope Zeiss Kinevo 900 with "white" (daylight) and "yellow" (with 560nm filter) was used. The data was collected during a period of 3 years from year 2022 to 2025. Details were discussed during surgery and notes were taken weather tumor margins are clear or blur. Patients' neurological status was assessed after surgery. Imagine methods such as MRI and CT scans pre and post operatively were compared in order to assess the extent of tumor resection. Days of hospital stay were used as an indirect indicator of postoperative complications. All this data was helpful in estimating surgical success using sodium fluorescein intraoperative. However, the goal of this study is to emphasise the problems and disadvantages that we encountered utilizing sodium fluorescein. Thus, the analytical part is of greater value, than the numerical.

Conclusion: Sodium fluorescein is useful adjunct for brain tumor surgery. However, in some specific cases and situations it can guide the neurosurgeon in wrong direction and cause unwanted damage. Therefore, every neurosurgeon who utilizes sodium fluorescein for tumor resection need to receive thorough education for its characteristics first. In the hands of skilled and experienced neurosurgeon these limitations can be overwhelmed and sodium fluorescein guided surgery can contribute to greater overall surgical success.

INTRODUCTION

Today, in modern neurosurgery, the use of sodium fluorescein during brain tumor surgeries is widely accepted as justified. This has been confirmed by numerous studies, most of which focus on patients with malignant brain tumors. However, the fact that sodium fluorescein does not bind within malignant cells raises some doubts about its precision. In contrast to 5-ALA, which is metabolized in the cytoplasm of malignant cells, sodium fluorescein accumulates in tumor tissue due to disruption of the blood-brain barrier. Guided by this fact, the aim of this paper is to present the limitations

of sodium fluorescein use in various pathological brain processes. The affordable cost and easy availability of this contrast agent facilitate its application in everyday neurosurgical practice. Any institution equipped with a microscope featuring a 560 nm yellow filter can routinely perform brain tumor surgeries with intraoperative use of sodium fluorescein. In addition to malignant tumors, its application can also be extended to benign tumors (1), arteriovenous malformations, and cerebral aneurysms. This opens opportunities for numerous studies that could highlight both the advantages and disadvantages of sodium fluorescein. In this context, it is necessary to clearly define which tissues show a strong fluorescence and whether such tissue should actually be removed during surgery. Intracranial, there are physiological tissues that exhibit intense fluorescence, as well as tumor tissues that do not fluoresce under yellow light. This is due to the varying biological and pathological characteristics of intracranial processes, as well as individual patient differences. Our goal is to emphasize these specific features and to demonstrate situations in which the neurosurgeon should not rely solely on the tissue accumulation of sodium fluorescein. In the following sections, we will present and analyse specific clinical experiences and observations from our practice.

MATERIALS AND METHODS

To demonstrate the specific properties of sodium fluorescein, data were analyzed from both a prospective and retrospective study involving 39 patients aged between 9 and 86 years. All patients received an intravenous administration of 5 to 10 mg/kg of sodium fluorescein after induction of anesthesia and before the start of surgery. All surgical procedures were performed by the same operative team. The extent of tumor resection was assessed by comparing preoperative contrast-enhanced magnetic resonance imaging (MRI) with postoperative contrast-enhanced computed tomography (CT) scans. Although these are imaging modalities with different levels of precision, postoperative CT scans clearly display residual or recurrent tissue and can therefore serve as reliable evidence of the resection extent. The scans were performed within a short postoperative period of 2 to 5 days.The intracranial lesions included a variety of pathologies–both benign and malignant tumors with different grades of malignancy, as well as recurrent and metastatic tumors. Furthermore, the lesions were located in various intracranial regions, including the posterior cranial fossa, cerebral convexity, skull base, pontocerebellar area, parasagittal region, intralobar locations, and others. The wide range of tumor malignancy and anatomical diversity enabled us to obtain extensive data on the behaviour of sodium fluorescein under different conditions. All surgeries were performed using a Carl Zeiss Kinevo 900 microscope under both “white (standard)” and “yellow (560 nm filter)” light. The surgical procedures were video recorded, and additional images were captured, annotated, and presented in the following sections. Patients were monitored in the postoperative period, and their neurological status was evaluated. For simplicity, the outcomes were categorized into three groups: improved, unchanged, or worsened neurological status. However, the present study focuses on qualitative rather than quantitative data. The aim was to demonstrate the varying degrees of contrast agent accumulation within different intracranial tissues.

RESULTS

A total of 39 patients who underwent surgery for various types of brain tumors with intraoperative use of sodium fluorescein were evaluated. The statistical data obtained are presented in the table below (Table 1).

Table 1. Patients operated with the use of sodium fluorescein intraoperative.

Patient	Pathohistological diagnosis	Residual/recurrent tissue on postoperative CT or MRI with contrast	Hospital stay (days)	Neurological status	Demarcation
1	MS melanoma	+	27	Unchanged	Clear
2	Glioblastoma	-	8	improved	Clear
3	Meningeomaatypicumrecidivans	-	8	Unchanged	Unclear
4	MS colonis	+	90	Worsened Exituslethalis	Partial
5	Glioblastomarecidivans	+	7	Unchanged	Clear
6	Meningeoma	-	6	Worsened	Clear
7	Astrocytoma gr III	+	8	improved	Clear
8	Meningeoma	-	7	improved	Unclear
9	MS pulmo	-	7	improved	Clear
10	Glioblastoma	-	7	Unchanged	Unclear
11	Glioblastoma	-	7	Unchanged	Clear
12	Glioblastomarecidivans	-	12	improved	Unclear
13	Medulloblastoma	-	15	improved	Clear
14	Pylocitic astrocytoma	+	8	Unchanged	Partial
15	Sphenoid wing meningeoma	+	18	Worsened	Unclear
16	Ependymoma gr II	-	7	improved	Unclear
17	Astrocytoma gr IV	+	10	Unchanged	Partial
18	Glioblastoma	+	9	Worsened	Clear
19	Sagitalmeningeoma	-	8	improved	Partial
20	Meningeoma gr III	-	7	improved	Clear
21	Medulloblastoma	-	28	Worsened	Partial
22	MS	-	7	improved	Clear
23	Masson tumor	-	6	Unchanged	Partial
24	Glioblastoma	-	7	improved	Clear
25	Glioblastoma	-	6	Unchanged	Clear
26	Glioblastomarecidivans	-	9	Unchanged	Partial
27	Pylocitic astrocytoma	+	16	improved	Clear
28	Oligodendroglioma gr III recidivans	+	7	Unchanged	Clear
29	MS Pulmo	-	24	Worsened	Clear
30	Medulloblastoma	-	11	Unchanged	Clear
31	Pleomorphic xantoastrocytoma	-	6	improved	Unclear
32	Necrosis	-	11	Unchanged	Clear
33	MS melanoma	-	10	improved	Clear
34	Glioblastoma	-	21	Unchanged	Clear
35	MS melanoma	-	8	Unchanged	Partial
36	Astrocytoma gr III	-	11	Unchanged	Partial
37	Glioblastoma	-	6	improved	Partial
38	GBM recidivans	+	7	Unchanged	Partial
39	TuGlomusJugulare	-	8	Worsened	Partial

Legend

MS – Metastatic spread

+ – Presence of residual/recurrent tissue

– – No residual/recurrent tissue

Demarcation: Clear = distinct fluorescence boundary; Partial = partially visible boundary; Unclear = poor or absent boundary

Discussion

During the use of sodium fluorescein as a contrast agent in brain tumor surgeries, we encountered several situations that could potentially mislead the neurosurgeon during the operative course. These situations are discussed in the text below. Every neurosurgeon performing operations with the aid of sodium fluorescein should be aware of these details. When speaking about limitations, it generally refers to which tissues retain and which do not retain the contrast agent—that is, which structures exhibit strong fluorescence and which do not. According to the literature, several anatomical structures are known to accumulate sodium fluorescein and therefore produce strong fluorescence under the microscope's yellow light. The best-known such structure is the dura mater, which usually does not pose a significant problem due to its clear distinction from the surrounding tissue. However, in meningioma surgeries, confusion regarding the tumor–dura boundary can occasionally occur. In such cases, sodium fluorescein is not helpful, since there is no difference in fluorescence intensity under yellow-light illumination. Nevertheless, because it facilitates easier identification of tumor portions in less accessible regions, the use of sodium fluorescein remains justified even in surgeries of benign tumors.

In addition to the dura, it is important to note that arachnoid granulations (GA) also produce a strong fluorescence signal under yellow-light microscopy (Figure 1). These anatomical structures should be taken into consideration, particularly in parasagittal pathologies such as meningiomas, parietal glioblastomas, astrocytomas, and similar lesions. Although these structures can easily be identified without a microscope and under white light, during tumor resection under yellow-light illumination and from certain angles, they may create a false perception of tumorous tissue.

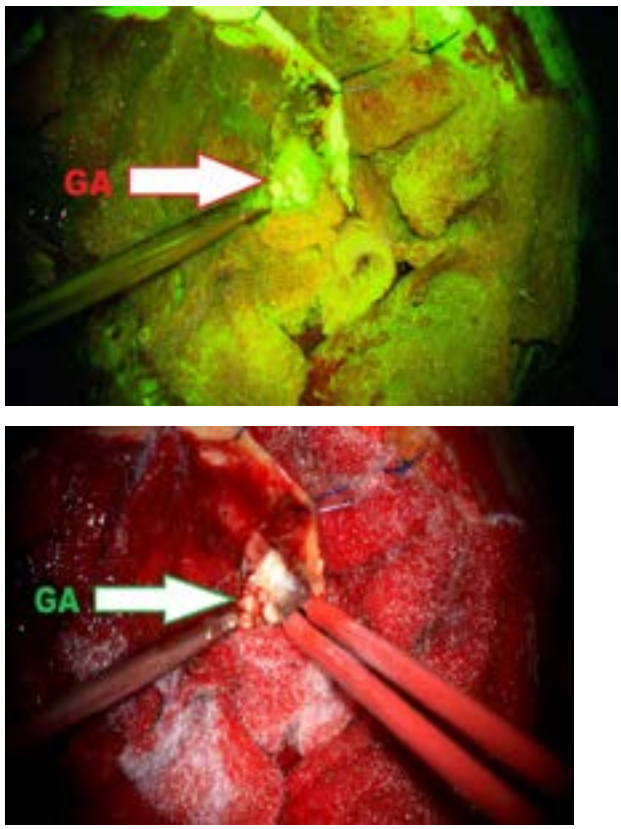
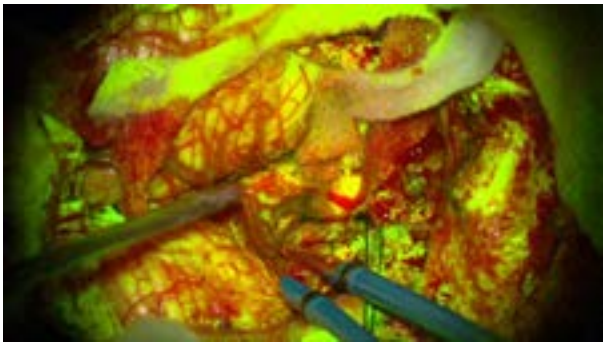
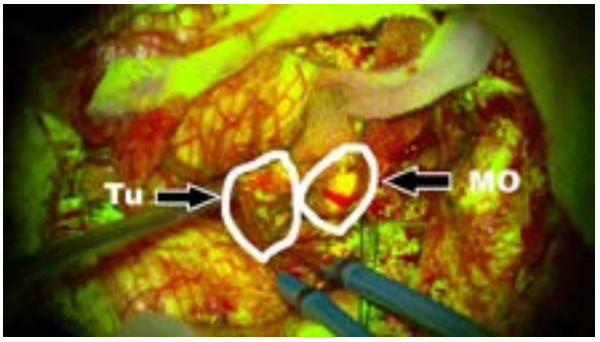
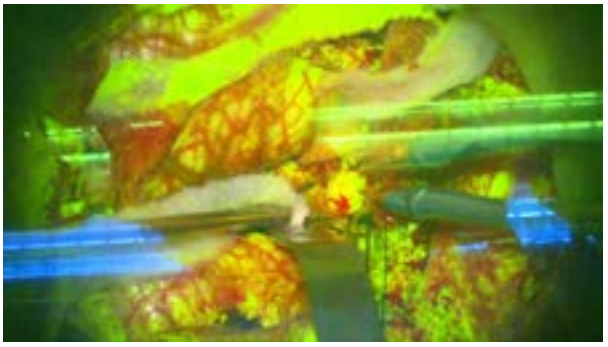


Figure 1. GA = Granulationes Arachnoidales.

The ependymal lining of the ventricular system accumulates a large amount of sodium fluorescein and exhibits fluorescence intensity comparable to that of the dura mater and tumorous tissue. This characteristic can, in certain situations, represent a disadvantage. Such examples include tumors located near or in communication with the ventricular system, such as intraventricular tumors, glioblastomas with ventricular infiltration, and lesions within the posterior cranial fossa.A particularly challenging situation arises due to the staining of the ependymal surface of the fourth ventricle, which covers the posterior wall of the brainstem during surgeries involving tumors in this region. After cerebrospinal fluid (CSF) drainage, both the tumor and the posterior aspect of the medulla oblongata may display nearly identical fluorescence (Figure 2). This may falsely guide the neurosurgeon and lead to inadvertent injury of the brainstem, which is especially vulnerable.Therefore, the use of sodium fluorescein in procedures involving the posterior cranial fossa should be approached with extreme caution and reserved for experienced neurosurgeons only.







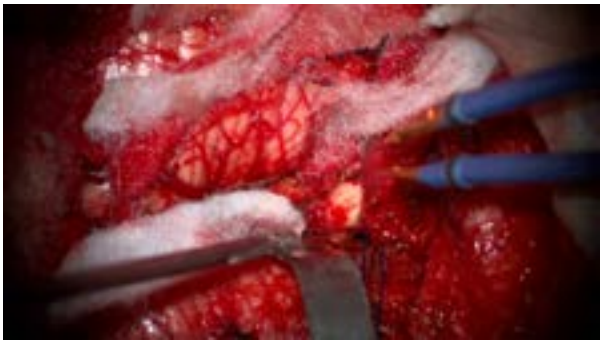


Figure 2.Tu = Tumor, MO = Medulla oblongata. The tumor and the brainstem may falsely give the impression of being in continuity, potentially misleading the neurosurgeon. The second image shows the marking of the tumorous tissue and the medulla oblongata for clearer differentiation. The third image demonstrates the strong fluorescence of the medulla oblongata under yellow light, while in the fourth image, it is clearly delineated from the surrounding structures.

Within the ventricular system, another structure exhibits strong contrast accumulation–the choroid plexus. Due to its rich capillary network, the plexus displays intense fluorescence under yellow light, similar to the previously mentioned arachnoid granulations and dura mater. This presents a potential problem when dealing with intraventricular tumors. Furthermore, the choroid plexus should be taken into consideration in cases where tumors are in close proximity to the ventricular system and where ventricular perforation occurs during tumor excision. After cerebrospinal fluid (CSF) drainage, the plexus may appear within the surgical field and falsely mimic tumorous tissue. Although the plexus is not as vulnerable as some other central nervous system structures, its injury can still result in undesirable postoperative consequences.

An especially important topic in contemporary neurosurgery is the accumulation of sodium fluorescein within peritumoral brain edema (Figure 3). Some authors argue that edematous tissue does not retain the contrast agent and therefore does not fluoresce, while others report the opposite. In our study, after completion of the resection, we frequently observed tissue that was partially stained with the contrast agent. The borders of this tissue could be clearly distinguished both from the tumor and from the surrounding healthy brain parenchyma. Based on its location, frequency of occurrence, and association with malignant (particularly metastatic) tumors, we believe this tissue represents peritumoral brain edema (Figure 4). From a pathophysiological standpoint, our interpretation appears consistent. In edematous tissue, a disruption of the blood–brain barrier and contrast agent attenuation are to be expected. This differentiates it from normal brain parenchyma, where the blood–brain barrier remains intact and contrast accumulation is absent. Conversely, the tumor causes far greater destruction of the blood–brain barrier, leading to higher contrast uptake. As a result, our conclusion is that peritumoraledema partially attenuates sodium fluorescein, producing weak fluorescence under yellow light. Nevertheless, further studies on this specific issue are necessary, since preservation and recovery of edematous brain tissue significantly contribute to better postoperative outcomes.

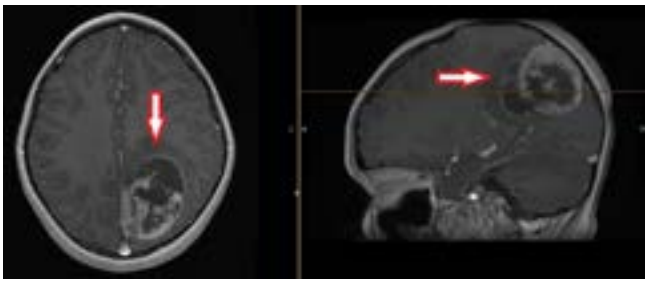


Figure 3.Perilesionaledema

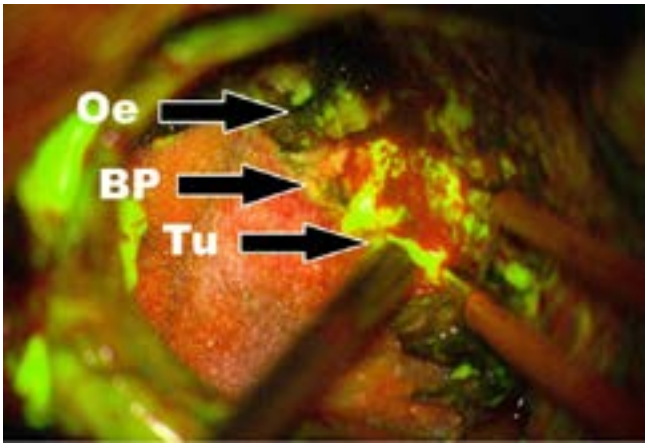


Figure 4.Oe = Edema, BP = Brain Parenchyma, Tu = Tumor. The tumorous tissue shows the strongest fluorescence, followed by the peritumoral brain edema, which demonstrates partial fluorescence. The healthy brain parenchyma does not retain the contrast agent and shows no fluorescence.

A particular challenge in neurosurgery is presented by operations on recurrent tumors. Adhesions, in addition to disrupting normal anatomy, also complicate the use and interpretation of sodium fluorescein. The literature contains very few references regarding the fluorescence characteristics of recurrent adhesions. From our experience, these adhesions exhibit a strong fluorescence under yellow light, comparable to that of the dura mater. This creates difficulties in identifying the true borders of the recurrent tumor. In our study, all five cases of recurrent tumors showed similar staining of both the tumor and the adhesions (Figure 5). This made it impossible to clearly determine the final tumor margins and to separate the lesion from the surrounding healthy brain parenchyma.

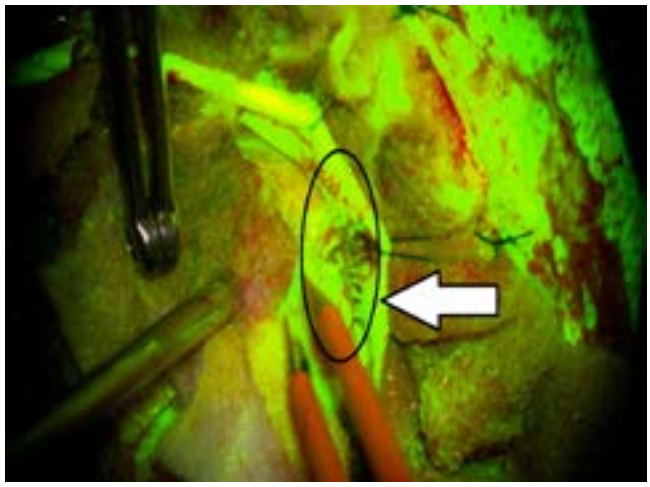


Figure 5. Adhesions strongly retain contrast and complicate the surgical process.

In addition to the undesired accumulation of sodium fluorescein in the anatomical structures mentioned above, a problem also arises from its absence in certain tumors. In our study, we encountered both malignant and benign tumors in which, despite the expected staining under yellow light, the tumor tissue did not fluoresce and appeared inert. Although it is generally accepted that glioblastomas accumulate contrast, in one case from our study, the tissue appeared grayish in color with a friable consistency, clearly demarcated from the surrounding healthy parenchyma (Figure 6). Histopathological analysis confirmed the diagnosis of glioblastoma, validating our intraoperative suspicion.This raises the question: why did sodium fluorescein fail to accumulate in this tumor tissue? This uncertainty prevents the surgeon from relying fully on the degree of contrast accumulation as a marker for tumor tissue. Upon further analysis, one possibility considered was that the tissue might be necrotic. However, whether the tissue represents tumor or radionecrosis, we would generally still expect strong fluorescence, since sodium fluorescein accumulates in tissues where the blood-brain barrier is disrupted. In the results described above, there is one example of a patient in whom histopathology confirmed necrosis. In this case, the necrotic tissue accumulated contrast and fluoresced similarly to tumor tissue. The distinction from healthy parenchyma was clear, and intraoperatively the process was treated as malignant, leading to an excellent postoperative outcome. Therefore, further studies with detailed explanations of such situations are necessary to increase understanding of the specific behavior of sodium fluorescein.

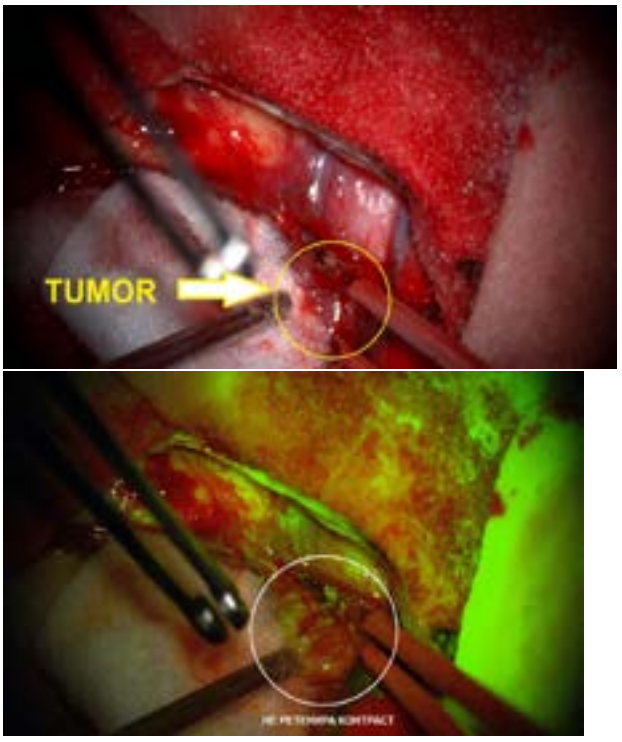


Figure 6.Tissue highly suspicious for glioblastoma, which does not fluoresce under yellow light in the microscope.

Tumors that did not accumulate sodium fluorescein have also been reported in the study by Christian Ott and colleagues, where three cases involving tumors in the posterior cranial fossa showed only weak fluorescence. Their study was compared with the study by Bat and collaborators, in which no contrast agent was used for tumor resection in the posterior cranial fossa, and it was concluded that the extent of resection was not significantly different. One contributing factor to this finding is the tendency of tumors in the posterior cranial fossa to infiltrate vital anatomical structures. Therefore, it is emphasized that microsurgical procedures under white light should remain the standard, while fluorescent-guided tumor resection can be used as a helpful adjunct. The diversity of tumors and patients in our study complicates classification and percentage-based presentation of results. Nevertheless, some conclusions can be drawn from detailed analyses. To provide a clearer overview, patients were grouped according to operative success into three categories (Table 2).

Excellent outcome: Patients with improved neurological status and no postoperative residual tumor or recurrence on imaging studies.

Good outcome: Patients in whom the surgical goal was achieved, and overall treatment was satisfactory, considering the circumstances and complex nature of the pathology.

Poor outcome: Patients who experienced postoperative deterioration, severe complications, incomplete tumor resection (voluntarily or involuntarily), and/or fatal outcomes.

Table 2. Tabular presentation of operative success in patients undergoing surgery with intraoperative use of sodium fluorescein.

Operative outcome	Number of patients
Excellent	18
Good	16
Poor	5

It is important to note that the numerical data in our study have limited statistical significance, as the primary goal is to highlight the characteristic properties of sodium fluorescein and present specific clinical situations related to its use. Gender and age were omitted from the table, as they are not relevant to the properties of sodium fluorescein. The purpose of classifying operative success is to provide a clearer picture of whether intraoperative use of sodium fluorescein is justified. From Table 2, it can be observed that undesirable outcomes occurred in only 5 out of 39 patients, indicating a generally solid operative success. Postoperative residual tumor or recurrence occurred in 28% of patients (11 out of 39). The mean length of hospitalization was 12.4 days. Postoperative neurological deterioration was recorded in 7 patients (18%). Based on these results, it can be concluded that, despite the aforementioned limitations, sodium fluorescein is of significant benefit in the surgical management of intracranial lesions.

CONCLUSION

Sodium fluorescein is a valuable tool in neurosurgery which, when used correctly, can contribute to safer, more precise, and successful surgical interventions. The aim of this study was to illustrate specific situations and dilemmas encountered during intraoperative use of sodium fluorescein, which may lead to misinterpretation by the surgeon. Therefore, comprehensive theoretical and practical training is essential before its clinical application. In conclusion, the intraoperative use of sodium fluorescein by a surgeon with adequate experience and knowledge of its properties contributes to overall improved operative success.

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Original scientific paper

THREE-YEAR SURVIVAL OF PATIENTS WITH MICROSATELLITE INSTABILITY (MSI) COMPARED TO MICROSATELLITE STABLE (MSS) COLON CANCER BY STAGE: A RETROSPECTIVE STUDY

Qemal Rushiti[1], Nikola Jankulovski[1], Rexhep Selmani[1], Svetozar Antovik[1], Fatjona Mislimi Ollomani[2]

[1]University Clinic of Digestive Surgery, Medical University, Skopje, R. North Macedonia;
[2]General City Hospital of Struga, Struga, R. North Macedonia;

Study period: 2020–2022
Location: University Clinic of Digestive Surgery, Medical University, Skopje, Republic of North Macedonia
Total patients: 490 (467 MSS, 23 MSI)
Outcome measure: 3-year survival by stage

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ABSTRACT

Background: Microsatellite instability (MSI) is a molecular subtype of colorectal cancer (CRC) resulting from mismatch repair deficiency. Its presence has been associated with better prognosis and specific therapeutic implications, yet data on real-world survival by clinical stage remain limited.

Objective: This study aimed to evaluate and compare three-year survival outcomes of patients with MSI and microsatellite stable (MSS) colon cancer by stage, based on patients surgically treated at a tertiary referral center in Skopje.

Methods: A retrospective review was performed on 490 patients who underwent surgery for colon cancer at the University Clinic of Digestive Surgery, Medical University, Skopje, Republic of North Macedonia between 2020 and 2022. Of these, 467 were MSS and 23 were MSI. MSI status was determined solely by PCR-based microsatellite testing. All patients were followed up clinically one year postoperatively with office visits, laboratory investigations, tumor marker testing, and computed tomography (CT). At three years post-surgery, survival status was confirmed via direct phone contact.

Results: Three-year survival among MSS patients was 65.9%, while MSI patients demonstrated a higher survival rate of 82.6%. Stage-wise comparison showed that MSI patients in Stage II and III disease had superior survival relative to MSS patients, while Stage I survival was equally excellent in both groups. No MSI cases were recorded in Stage IV.

Conclusion: MSI was associated with improved three-year survival, especially in intermediate disease stages. Routine PCR-based MSI testing should be integrated into clinical practice to optimize prognostic evaluation and therapeutic decision-making in colon cancer.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer-related death globally [1,2]. Its incidence continues to rise in developing regions, largely due to changing diets, sedentary lifestyles, and aging populations. Although early detection and advances in surgical and oncological care have improved outcomes, survival remains variable and influenced by both clinical stage and molecular characteristics [3].

Among these molecular features, microsatellite instability (MSI) represents a critical biomarker that reflects a distinct biological pathway of carcinogenesis. MSI arises due to inactivation of the DNA mismatch

repair (MMR) system [1,3], which normally corrects replication errors. Loss of this repair mechanism leads to the accumulation of mutations within repetitive DNA sequences known as microsatellites, causing widespread genomic instability. Tumors without such instability are termed microsatellite stable (MSS).

MSI occurs in approximately 12–15% of colorectal cancers [1,9], though prevalence varies geographically and by patient population. MSI is particularly common in tumors located in the proximal colon and in younger patients or those with a family history of cancer due to hereditary nonpolyposis colorectal cancer (Lynch syndrome) [6,11].

The clinical significance of MSI extends beyond its diagnostic role. It has been repeatedly associated with favorable prognosis, especially in early and intermediate stages of disease [4,5,9], and it serves as a predictive marker for response to immunotherapy in advanced settings [12]. By contrast, MSS tumors typically follow a chromosomal instability pathway and tend to have a higher likelihood of metastasis and poorer survival [7,8].

Despite the growing international literature, data from Southeastern Europe remain limited. Understanding the distribution and impact of MSI in local populations is crucial for adapting diagnostic and treatment strategies.

This study therefore evaluates three-year survival outcomes among patients with MSI and MSS colon cancer treated surgically at the University Clinic of Digestive Surgery, Medical University, Skopje, Republic of North Macedonia, stratified by stage, to clarify the prognostic importance of MSI status in a real-world clinical context.

MATERIALS AND METHODS

Study Design and Setting

This was a retrospective, single-center observational study conducted at the University Clinic of Digestive Surgery, Medical University, Skopje, Republic of North Macedonia, a tertiary referral institution that serves as the main center for colorectal surgical oncology in the region.

Study Period

The study included patients operated between January 2020 and December 2022.

Patient Selection

All patients who underwent elective or emergency surgery for histologically confirmed colon adenocarcinoma during the study period were included.

Inclusion criteria:

Histopathological diagnosis of colon adenocarcinoma.

Curative-intent surgical resection.

Availability of PCR-based MSI testing.

Complete follow-up data for at least three years postoperatively.

Exclusion criteria:

Rectal cancer (to avoid confounding by neoadjuvant therapy).

Recurrent or metastatic disease at presentation without surgery.

Missing molecular or survival data.

After exclusions, 490 patients met the inclusion criteria: 467 MSS and 23 MSI.

Molecular Testing

MSI status was determined solely by PCR-based analysis of microsatellite loci. Tumors exhibiting instability in ≥2 of the tested loci were classified as MSI, while tumors showing stable microsatellites at all loci were classified as MSS. No immunohistochemistry (IHC) was used in this study.

Follow-up Protocol

At 1 year post-surgery: All patients underwent clinical follow-up at the clinic, including:

Full clinical examination

Laboratory investigations (complete blood count, liver enzymes)

Tumor marker testing (CEA, CA 19-9)

Chest and abdominal CT scan for recurrence surveillance

Colonoscopy

At 3 years post-surgery: Survival status was confirmed through direct phone contact with patients or family members.

Outcome Measure

The primary endpoint was 3-year overall survival (OS), defined as the proportion of patients alive three years after surgery. Survival was analyzed by stage (I–IV) and compared between MSI and MSS groups.

Data Analysis

Data were summarized using descriptive statistics. Stage-specific survival proportions were calculated separately for each molecular subtype and presented in both table and narrative form.

RESULTS

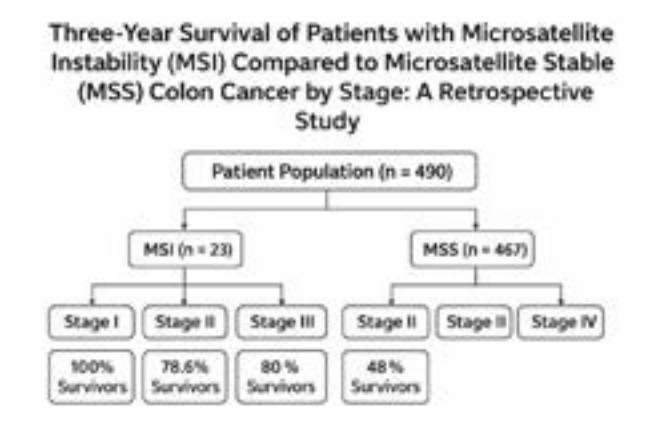
Patient Demographics

Among the 490 patients, 467 (95.3%) were MSS and 23 (4.7%) were MSI. The mean age at diagnosis was 64 years (range 32–85), with a slight male predominance (57%). Most cases were diagnosed in Stages II and III.

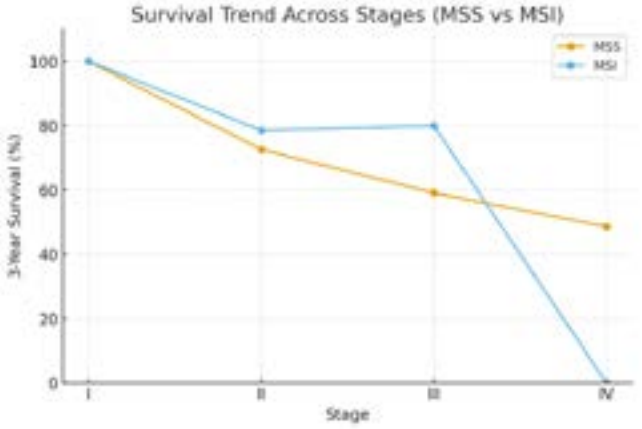
Three-Year Survival Outcomes

Stage	MSS Alive (n)	MSS Dead (n)	MSS Total	MSS Survival (%)	MSI Alive (n)	MSI Dead (n)	MSI Total	MSI Survival (%)
Stage I	41	0	41	100%	4	0	4	100%
Stage II	122	46	168	72.6%	11	3	14	78.6%
Stage III	110	76	186	59.1%	4	1	5	80.0%
Stage IV	35	37	72	48.6%	0	0	0	–
Total	308	159	467	65.9%	19	4	23	82.6%

A visual overview of the three-year survival distribution between MSI and MSS patients by stage is provided in Figure 1. This diagram graphically represents the proportion of survivors in each stage for both molecular subtypes, complementing the tabulated results and facilitating clearer comparison of survival patterns across stages.



Three-year survival trend across pathological stages (I–IV) comparing microsatellite stable (MSS) and microsatellite instability (MSI) colon cancers. The curve below demonstrates that both molecular subtypes exhibit excellent survival in Stage I, with 100% three-year survival. From Stage II onward, the trajectories diverge, with MSI tumors showing a consistently more favorable survival profile compared to MSS tumors. In Stage II, MSI cases achieve a 78.6% survival rate versus 72.6% in MSS, and this difference becomes more pronounced in Stage III, where MSI survival reaches 80.0% compared with 59.1% in MSS. No MSI cases were present in Stage IV within this cohort, whereas MSS tumors demonstrate a marked decline in survival at this stage (48.6%). Overall, the figure highlights the prognostic advantage associated with MSI status, particularly in intermediate disease stages, and underscores the importance of molecular classification in guiding clinical expectations and therapeutic decision-making.



Interpretation

Three-year survival declined progressively with higher stage in both groups. MSI tumors demonstrated superior survival in Stage II and III disease compared with MSS tumors. Importantly, there were no MSI cases in Stage IV, suggesting lower metastatic potential.

Overall survival:

MSS: 65.9%

MSI: 82.6%

DISCUSSION

This study provides valuable regional evidence on the survival outcomes of MSI and MSS colon cancer in a real-world cohort from the University Clinic of Digestive Surgery, Medical University, Skopje.

Our findings reaffirm the established observation that MSI-positive tumors are associated with improved survival, particularly in non-metastatic disease stages [4,5]. This is consistent with numerous international studies, including those by Sinicrope et al. (2011) and Domingo et al. (2010), which reported better outcomes for MSI-high tumors in Stage II and III disease [4,5].

Biological Basis

The enhanced prognosis in MSI tumors is largely explained by their hypermutated phenotype. Defective DNA mismatch repair leads to accumulation of mutations, creating neoantigens that stimulate strong anti-tumor immune responses [1,13]. Histologically, MSI tumors often contain dense lymphocytic infiltrates, reflecting this heightened immunogenicity [13].

These immune mechanisms contribute to limited metastatic spread and better surgical outcomes, which may explain the absence of Stage IV MSI tumors in our cohort [8].

Clinical Implications

From a therapeutic perspective, MSI testing provides crucial information:

Prognostic: MSI tumors generally have better outcomes independent of stage [4,9].

Predictive: MSI tumors show poor response to fluorouracil (5-FU) monotherapy [3] but are highly responsive to immune checkpoint inhibitors such as pembrolizumab and nivolumab [7,12].

Hereditary Insight: MSI may indicate Lynch syndrome, prompting family genetic counseling [6,11].

Our results reinforce these implications. The relatively higher survival in MSI Stage II and III suggests that aggressive chemotherapy may be unnecessary in some MSI cases, aligning with evidence that adjuvant 5-FU offers minimal benefit in MSI tumors [3]. Conversely, for MSS cancers—especially Stage III—adjuvant therapy remains vital due to their higher relapse rates [5,8].

Comparison with Literature

Previous studies have consistently demonstrated that MSI confers a 15–20% improvement in overall survival compared to MSS tumors [9]. For example, Sargent et al. (2010) found that MSI status predicted favorable prognosis and lack of benefit from 5-FU [3]. Similarly, Overman et al. (2017) emphasized the success of immunotherapy in metastatic MSI-high disease, which revolutionized treatment strategies [7].

Our regional data echo these trends and highlight the importance of implementing universal PCR-based MSI testing in diagnostic algorithms even in smaller or resource-limited institutions [1,8].

Public Health and Institutional Context

In North Macedonia, systematic MSI testing is increasingly adopted but not yet universal. This study underscores its necessity for guiding both patient management and long-term surveillance, particularly for families potentially affected by Lynch syndrome [6,11].

Furthermore, the University Clinic of Digestive Surgery functions as a national referral center, offering a comprehensive follow-up system—an aspect that strengthens the reliability of our survival data.

Limitations

The main limitation is the small number of MSI patients (n=23), reflecting the low natural prevalence of MSI [1,9].

The retrospective design may introduce bias in data collection and follow-up accuracy.

Stage IV MSI cases were absent, preventing direct comparison in advanced disease [7,12].

Nevertheless, these limitations do not undermine the observed survival patterns, which closely parallel international evidence.

Future Directions

Future multicentric prospective studies with larger MSI cohorts are recommended to further assess stage-specific outcomes and evaluate quality-of-life measures post-surgery. Integration of molecular testing into electronic health records could facilitate long-term outcome tracking [8,10].

CONCLUSION

In this single-center retrospective study from the University Clinic of Digestive Surgery, Medical University, Skopje, Republic of North Macedonia, microsatellite instability (MSI) was associated with significantly better

three-year survival than microsatellite stable (MSS) colon cancer, particularly in Stage II and III disease.

No MSI tumors were observed in Stage IV, reinforcing their reduced metastatic potential. These results support routine PCR-based MSI testing as a standard diagnostic and prognostic tool in colon cancer management, enabling personalized treatment approaches and optimized resource allocation.

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Original scientific paper

TRIGLYCERIDE/GLUCOSE INDEX AS A BIOMARKER FOR THE ASSESSMENT OF CARDIOVASCULAR DISEASE RISK

Luzana Shabani[1], Jehona Ali[2,3], Mimoza Bafqari-Bakiji[2,3], Sheqibe Beadini[2], Mije Reçi[1]

[1]Faculty of Mathematics and Natyral Science, Department of Biology – Biochemistry University of Tetova,,
[2]Faculty of Medical Sciences, University of Tetova,
[3]Clinical Hospital of Tetovo

E-mail of corresponding author: luzana.shabani@unite.edu.mk

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ABSTRACT

Cardiovascular diseases continue to be the foremost contributor to global mortality, with their incidence demonstrating a substantial upward trend in recent decades. Elevated fasting glucose and triglyceride levels are closely associated with the development of cardiometabolic disorders and constitute significant risk factors. The triglyceride-glucose (TyG) index has been shown to be positively correlated with several cardiometabolic factors, while its higher values are associated with an increased prevalence of coronary artery disease, metabolic syndrome, and type 2 diabetes. In this retrospective study, 568 patients with cardiovascular pathologies and a control group of 50 healthy individuals were included. Fasting glucose and triglyceride levels were measured in all participants, while the TyG index was calculated using the standard formula. The results showed that patients with cardiovascular diseases had significantly higher values of glucose, triglycerides, and the TyG index compared to the control group, with statistically significant differences. The mean TyG index was notably higher among patients with cardiovascular conditions, reflecting a strong association between this indicator and cardiometabolic risk. The findings support the use of the TyG index as a valuable, simple, and practical marker for identifying and predicting cardiovascular risk, as well as an auxiliary parameter in the early assessment of patients predisposed to these diseases.

Key words: Triglyceride-glucose index (TyG), glucose, triglycerides, cardiovascular diseases

INTRODUCTION

Globally, cardiovascular diseases represent the leading cause of mortality. The incidence of cardiovascular diseases has increased significantly from 1990 (estimated at 271 million cases) to 2019 (estimated at 523 million cases). Deaths due to cardiovascular diseases rose by nearly 50%, reaching 18.6 million in 2019 compared to 12.1 million in 1990. Ischemic heart disease remains the primary cause of cardiovascular-related mortality, accounting for almost 50% of these deaths.

The TyG index serves as a significant marker for evaluating the incidence of cardiovascular disorders (Kurniawan, 2024) and is associated with increased morbidity, including carotid atherosclerosis, coronary artery disease, metabolic syndrome, type 2 diabetes, and cardiovascular mortality (Lopez-Jaramillo et al., 2023). Metabolic syndrome and its components also represent significant risk factors for cardiovascular diseases (Jiang et al., 2022).

The triglyceride-glucose (TyG) index was first introduced in 2008 by Mendia and colleagues (Mendia et al., 2008). The formula for calculating the TyG index is: TyG index = Ln [fasting triglycerides (mg/dl) × fasting glucose (mg/dl)

/ 2], and it represents a composite marker derived from fasting triglyceride (TG) and fasting plasma glucose (FPG) levels, exhibiting high sensitivity and specificity (Sun et al., 2025). Mendía et al., 2008, demonstrated that the TyG index exhibits high sensitivity in identifying insulin resistance in both healthy individuals and the general population (Fang et al., 2025). The TyG index represents an important cardiometabolic marker, as it is positively associated with a wide range of risk factors, including arterial stiffness and hypertension, thereby reflecting its significant role in the development and prognosis of cardiovascular diseases (Ciu et al., 2023). Elevated values of this index are linked to a higher prevalence of coronary artery disease, including in asymptomatic patients (Nam et al., 2020; Araújo et al., 2022; da Silva et al., 2019; Park et al., 2020). Therefore, the aim of this study is to evaluate the association between the triglyceride-glucose (TyG) index and the presence of cardiovascular diseases in patients from the Tetovo region, as well as to determine the utility of this index as a marker of metabolic disturbances and cardiovascular risk.

MATERIALS AND METHODS

This retrospective study was conducted between May 2024 and January 2025 at the Biochemistry Laboratory of the Clinical Hospital of Tetovo. A total of 568 outpatient patients diagnosed with cardiovascular diseases and 50 healthy individuals, who served as the control group, were included in the study. Blood samples were collected from patients between 7:00 and 9:00 a.m., in a fasting state, after 12 hours from the last meal. The blood was collected in tubes to obtain serum.

Glucose and triglyceride levels were analyzed using spectrophotometric methods (Triglycerides- GPO-PAP, enzymatic methode; Glucose-Hexokinase, enzymatic methode). After obtaining the results, the TyG index was calculated using the formula: TyG index = ln[TG (mg/dl) × FBG (mg/dl) / 2]. The cut-off values for the TyG index were defined as < 8.73 for women and < 8.82 for men (Avagimyan et al., 2025).

For statistical analysis, the minimum and maximum values, mean, and standard deviation were determined using IBM SPSS software, version 20. A p-value < 0.05 was considered statistically significant.

RESULTS

Based on the results and statistical data, it was observed that during this period, 568 patients were diagnosed with cardiovascular diseases. The study included a total of 618 patients, of whom 398 were male and 220 were female.

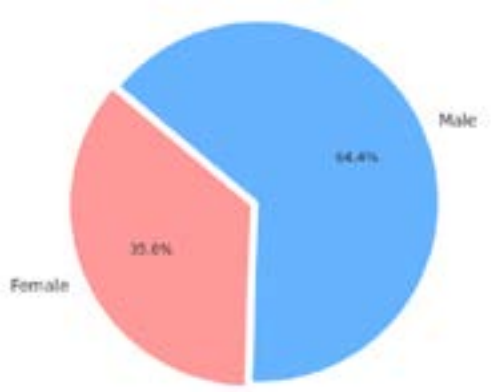

Figure 1. Gender distribution of study participants

The figure illustrates the percentage of male and female participants in the study. The data show that the majority of patients were male, accounting for 64.4% of the total, while females comprised 35.6%, indicating a predominance of the male group in the study.

Table 1. Mean age and distribution of participants in the control group and the cardiovascular disease group

	N	Range	Minimum	Maximum	Mean	Std. Deviation
C group age	50	50.00	34.00	84.00	53.5400	10.69276
CVD group age	568	68.00	19.00	87.00	58.9507	12.96846

Table 1 presents the age distribution of participants in the control group (CAge, N=50) and the cardiovascular disease group (CVDAge, N=568). In the control group, ages ranged from 34 to 84 years, with a mean of 53.54 years and a relatively low standard deviation (10.69), indicating a more homogeneous age distribution. In contrast, the cardiovascular disease group exhibited a considerably wider age range (19–87 years), with a higher mean age of 58.95 years and a larger standard deviation (12.97), reflecting substantial heterogeneity. These findings suggest that the control group is more age-restricted and uniform, whereas the cardiovascular disease group encompasses a broader and older age spectrum, consistent with the higher prevalence of cardiovascular conditions among older individuals.

Table 2. Descriptive statistics of metabolic parameters in the control group and the cardiovascular disease group

	N	Range	Minimum	Maximum	Mean	Std. Deviation
CGl	50	2.43	3.97	6.40	5.0870	.54647
CTgl	50	1.49	.72	2.21	1.4160	.45457
CIndex	50	1.16	8.07	9.23	8.6152	.31437
CVDGl	568	20.00	3.20	23.20	6.8932	2.81923
CVDTgl	568	8.81	.41	9.22	1.8643	1.10030
CVDIndex	568	4.59	7.40	11.99	9.0126	.64951

The descriptive statistics table provides a comparative overview of the control group (N=50) and the cardiovascular disease group (N=568). The control group exhibited a relatively homogeneous distribution of glucose and TyG index values, with low standard deviations, whereas triglyceride levels showed greater variability. In contrast, the cardiovascular disease group displayed marked heterogeneity, particularly in glucose (6.89 mmol/L) and triglyceride (1.86 mmol/L) levels, alongside a notably higher mean TyG index (9.01). Overall, the control group appears more uniform, whereas the cardiovascular disease group demonstrates substantial within-group variability, indicative of a strong association between metabolic disturbances and the presence of cardiovascular pathology.

Table 3. Comparison of metabolic parameters (TG, Glucose, TyG) between the control group and the cardiovascular disease group

Parameter	Control Group		CVD Group		p value
	Mean	SD	Mean	SD	
Ty	1.416	0.454	1.864	1.100	0.0044
Gl	5.087	0.546	6.893	2.819	0.0001
TyG	8.615	0.314	9.012	0.649	0.0001

Table 3 presents a comparison of the mean levels of triglycerides (TG), glucose (Gl), and the TyG index between the control group and the cardiovascular disease (CVD) group, along with standard deviations and p-values. In the control group, triglycerides had a mean of 1.416 mmol/L with an SD of 0.454, whereas in the CVD group, they increased to 1.864 mmol/L with an SD of 1.100; this difference was statistically significant ($p = 0.0044$). Similarly, glucose levels were markedly higher in CVD patients (mean 6.893 mmol/L, SD 2.819) compared to the control group (mean 5.087 mmol/L, SD 0.546), with a highly significant p-value ($p = 0.0001$), indicating a strong statistical difference. The TyG index, which integrates both parameters, was also higher in the CVD group (9.012 versus 8.615 in controls), with a statistically significant difference ($p = 0.0001$). These findings suggest that both triglycerides and glucose contribute to the elevation of the TyG index, making it a valuable marker for differentiating individuals at high risk for cardiovascular disease.

DISCUSSION

Understanding the complex mechanisms related to the pathology, physiology, and molecular biology of fasting glucose and triglycerides provides important insights into their role in the development of cardiovascular diseases and adverse cardiovascular events. Elevated fasting glucose and triglyceride levels lead to disruptions in metabolic pathways, causing a pro-inflammatory state in blood vessels and promoting endothelial dysfunction (Sena & Carrilho, 2018). Previous studies have demonstrated a strong association between the TyG index and the incidence of coronary heart disease (CHD), both in observational studies and meta-analyses conducted in the general population (Yang et al., 2025).

Da Silva et al. included patients who had experienced at least one cardiovascular disease (CVD) event over the past ten years and classified them into three groups: (a) asymptomatic, (b) symptomatic, and (c) treated for coronary artery disease (CAD). After calculating the TyG index for all patients, they found that a statistically significant difference appeared only in the symptomatic group (Group b), where patients with higher TyG index values had a greater prevalence of symptoms (Da Silva et al., 2019). The explanation for the higher number of symptomatic patients in the top tertile of the TyG index lies in the fact that they had uncontrolled diabetes and/or hyperlipidemia, which led to an increase in the TyG level, given its direct relationship with triglycerides and glucose (according to the TyG formula) (Alizargar et al., 2020).

A study conducted in a population cohort of 7,521 participants in Iran showed that a high TyG index was significantly associated with an increased risk of cardiovascular disease (CVD) and coronary artery disease (CAD) after a 3-year follow-up period (Barzegar et al., 2020). Furthermore, results from the Kailuan study in China demonstrated a correlation between the TyG index and myocardial infarction (MI). These findings suggest that the TyG index may serve as an indicator of cardiovascular disturbances, independent of established risk determinants in the general population (Liu et al., 2022).

The results of our study are consistent with the findings of Lopez-Jaramillo, where a significant association between the TyG index and increased cardiovascular risk was identified, highlighting the importance of the TyG index as a practical and easily applicable marker for the early identification of individuals at high risk for cardiovascular disturbances (Lopez-Jaramillo et al., 2023).

CONCLUSION

The results support the use of the TyG index as a valuable and practical marker for identifying and predicting cardiovascular risk. This index can serve as an auxiliary parameter in clinical practice for the early assessment of patients predisposed to cardiovascular diseases.

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Profesional paper

SYNCHRONOUS AND METACHRONOUS PRIMARY MALIGNANT NEOPLASM OF THE UROGENITAL ORGANS - OUR RECENT EXPERIENCE

Ivchev J12, Ivchev Lj12

1Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia
2General City Hospital "8th September", Skopje, North Macedonia

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INTRODUCTION

Synchronous malignant infections occur in two or more primary neoplasms that occur continuously or at different intervals in the same patient.

According to the time of occurrence, they can be divided into so-called simultaneous multiple so-called synchronous small neoplasms that occur within 6 months, and multiple hetero small neoplasms that occur at an interval of more than 6 months (1). According to the studies published so far, synchronous small neoplasms of different generation of origin can be considered the same between organs or controls of different or different organ systems. The most common reasons for their occurrence include: increasingly advanced screening diagnostic methods, genetic defects, reduced immunity due to receiving oncological therapy, the influence of one of the malignant processes, congenital or acquired diabetes, chronic renal failure, environmental influences, etc. (2). The prevalence rate of such two or more synchronous primary neoplasms is estimated at 4.5% to 11.7%. In most cases, over 75% of diagnosed patients belong to the population group older than 50 years. Men are more affected than women in terms of synchronous and metachronous neoplastic phenomena (3).

The treatment is most often multimodal, which simultaneously includes surgical, oncological and radiological treatment approaches.

MATERIAL AND METHODS

The study includes an analysis of 19 rare cases of surgically treated patients, in whom the presence of two or more histological different malignant tumors from the same or different organ system was diagnosed simultaneously or at different time intervals, at the urology department of the City General Hospital "8th September" - Skopje, in the last five years.

The data related to the type of malignant neoplasm, etiology, accompanying comorbidities, used diagnostic procedures and treatment methods, in the study are statistically processed and presented through percentage representation, mean value, tabular and graphical display.

OBJECTIVE OF THE STUDY

-Determination of the most common malignant neoplasm associated with malignant tumors of the urogenital organs in the studied group.

-Determination of the etiological relationship for the simultaneous occurrence of two different malignant entities in the same patient with other diseases or

conditions, as induction factors for the occurrence of malignant tumors.

-Determination of the most adequate approach in the treatment of synchronous malignant tumors, depending on the type of malignant process, the type of affected organs or tissues, the age and general health status of the patient, based on our clinical experience to date.

Results

Out of a total of 19 patients with pathohistologically verified primary neoplastic tumor, operated on at the urology department of the "8th September" General Hospital in Skopje, in the last 2,5 years, in 8 patients or 42.1%, simultaneous carcinoma of two organs of the urogenital tract (UGT) was diagnosed preoperatively (table no. 1). Primary neoplastic tumor of two different organs of the UGT, diagnosed and operated on in different time intervals, was determined in 5 patients or 26.31% (table no. 2).

Table No. 1 - Simultaneous finding of primary carcinomas of two organs of the urogenital tract, operated on in the last five years (Synchronous neoplasm).

Types of synchronous primary malignant neoplasms among organs of the urogenital tract in the last 2,5 years	Number of patients
Renal cell carcinoma (RCC) of both kidneys	1
RCC of the right kidney and Adrenocortical carcinoma of the left adrenal gland	1
Prostate adenocarcinoma and transitional cell carcinoma of the bladder	2
Adenocarcinoma of the prostate and Carcinoma of the penis	1
Sarcomatoid urothelial carcinoma of the bladder and adenocarcinoma of the prostate	1
Invasive (High Grade) Urothelial Bladder Cancer and Prostate Adenocarcinoma	2
Total	8

Table No. 2 - Finding of primary carcinoma of UGT organs and organs of other organ systems in different time intervals (heterochronous-metachronous neoplasm).

Types of metachronous (heterochronous) primary malignant neoplasms among organs of the urogenital tract in the last 2,5 years	Number of patients
Renal cell carcinoma of both kidneys	1
Prostate adenocarcinoma and transitional cell carcinoma of the bladder	3
Renal cell carcinoma of the right kidney and Adrenocortical carcinoma of the left adrenal gland	1
Total	5

In 4 patients or 21.05%, primary neoplasm of UGT organs were diagnosed simultaneously with organs of other organ systems (table no. 3), while in 2 patients or 10.52%, primary neoplasm between UGT organs and organs of other organ systems were diagnosed at different time intervals (heterochronous neoplasm) (table no. 4).

Table No. 3 - Patients with simultaneous malignant neoplasm of UGT organ and organ of another organ system, operated on in the last 2,5 years at the Urology Department of the "8th September" General Hospital - Skopje.

Synchronous primary malignant neoplasms of organs of the urogenital tract with organs of other organ systems, in the last five years	Number of patient
Prostate adenocarcinoma with high-grade gastric adenocarcinoma	1
Papillary renal cell carcinoma of the left kidney with basal cell carcinoma of the skin of the nose and face	1
Uroepithelial carcinoma of the bladder with basal cell carcinoma of the skin of the nose	1
Prostate adenocarcinoma with basal cell carcinoma of the skin of the nose	1
Total	4

Table No. 4 - Patients with malignant neoplasm of an organ of the UGT with an organ from another organ system diagnosed and operated on in different time intervals (Heterochronous neoplasm).

Metachronous (heterochronous) primary malignant neoplasms of urogenital organs with organs of other organ systems, in the last 2,5 years	Number of patients
Prostate adenocarcinoma and sigmoid carcinoma	1
Breast adenocarcinoma with ovarian adenocarcinoma and sigmoid adenocarcinoma	1
Total	2

Of total of 19 patients with synchronous and metachronous malignant neoplasm, 16 patients or 84.21% are men and only 2 (10.52%) are women. The average age of the patients is 67.46 years.

The analysis of biochemical parameters in patients with synchronous and heterochronous multiple primary malignant neoplasm (MPMN) in most cases showed elevated values of the hepatic enzymes SGOT (Aspartate Aminotransferase) SGPT (Alanine Aminotransferase), Creatine kinase SK, CRP (C-reactive protein), pancreatic enzymes Amylase and Lipase in patients with prostate cancer PSA (Prostate Specific Antigen) and moderately elevated blood glucose values. In contrast to these values in most cases, the blood analysis showed reduced values of urea and albumin (table no. 5).

Table 5. Characteristic changes in the biochemical analysis of blood in patients with multiple primary malignant neoplasm in the study group.

Biochemical blood parameters in patients with MPMN	Elevated values	Low values
SGOT (Aspartate Aminotransferase)	<91 U/L	
SGPT(Alanine Aminotransferase)	<118 U/L	
Creatin kinase CK	<174 U/L	
CRP (C-reactive protein)	28-72mg/l	
PSA (Prostate Specific Antigen) in patients with Prostate Cancer	>15,1 ng/ml	
Amylase	>114 U/L	
Lipase	>96 U/L	
Glucosis	<7,7 mmol/l	
Urea		< 2,3 mmol/L
Albumin	<32,4 g/l	

Characteristically for most patients with MPMN in the study group, urine analysis showed elevated values of erythrocytes, leukocytes, glucose and urobilinogen (table no. 6).

Table No. 6 - Elevated biochemical parameters in urine in patients with multiple primary malignant neoplasm in the study group.

Biochemical parameters in urine in patients with MPMN	Elevated values	Normal values
Erythrocytes	>25 Er/ml	
Leukocytes	>15 Le/ml	
Glucose	>5,5 mmol/l	
Urobilinogen	>16 umol/l	
Proteins		>0,3 g/l

DISCUSSION

Malignant primary multiple neoplasm (MPMN) represent the simultaneous presence of two or more primary malignant neoplasm in the same patient. If they are diagnosed at the same time, we are talking about the so-called synchronous malignant neoplasm, and if they are diagnosed at different time intervals, we are talking about the so-called heterochronous or metachronous malignant neoplasm.

The etiology of multiple cancers in the same patient is quite complex and still not sufficiently explained. In the published studies so far, the following etiological factors for their occurrence are included: genetic predisposition, environmental factors, reduced immunity due to an already present cancer, radiological and chemotherapy, autoimmune diseases or a combination of some of them (6,7,8).

-The genetic predisposition for the occurrence of MPMN, especially in some autosomal dominant hereditary syndromes such as Von Hippel-Lindau (VHL) syndrome, Lynch syndrome, Cowden syndrome, Bird Hogg Dube Syndrome and others is based on mutations in the gene located in chromosome 3, which is a tumor suppressor. When this gene mutates, tumors develop in various parts of the body as a result of the production of abnormal and non-functional proteins that lead to uncontrolled cell growth and the formation of tumors or cysts (8). Genetic hereditary syndromes such as: Von Hippel Lindau (VHL) syndrome and Birt Hogg Dube Syndrome, which are characterized by the diagnosis of a kidney tumor in combination with malignant tumors of the skin, lungs

or some gastrointestinal organ, were also diagnosed and treated in our study group.

- Environmental factors such as long-term exposure to carcinogenic agents (chemical agents, drugs containing acetaminophen), smoking and alcohol, can cause MPMN, especially involving the organs of the urogenital tract.

In the majority of studies published so far regarding MPMN, the most common cases described are the simultaneous occurrence of lung or breast cancer in combination with ovarian cancer, colon cancer or squamous cell carcinoma of the skin (9,10,11,12).

In this study, an attempt was made to determine the most common types of MPMN in which neoplasm is present in two or more urogenital organs or in a urogenital organ in combination with an organ from another organ system in the same patient. The latest published study shows that organs of the urogenital tract are represented in multiple primary malignant neoplasm in 0.9% of cases, and in relation to the total number of treated urological cancers, they are represented by about 9%. In this case, malignant urological tumors were most often combined with cancer of the stomach, small and large intestine and with tumors of the nervous system. 76% of all MPMN in which cancer of a urogenital organ is included belong to the so-called metachronous malignant neoplasm, with the second tumors being diagnosed within five years of the diagnosis of the first cancer (13,14).

In the period from 01.01.2023 to 15.08.2025 in the surgical departments of the General Hospital "8th September" in Skopje, out of a total of 1352 cases of malignant neoplasm operated on, 19 (1.4%) patients with multiple primary malignant neoplasm in which at least one urogenital organ was affected were operated on (diagram no. 1). In relation to the total number of 677 urological operations for malignant neoplasm for the same time period, the percentage of occurrence of synchronous and metachronous malignant tumors of two or more urogenital organs is 2.3% (diagram no. 2). In this, a total of 66 operations for kidney cancer were performed, and of these, two patients or 3.03% were diagnosed with renal cell carcinoma simultaneously in both kidneys. It is characteristic that in both cases, in addition to bilateral renal carcinoma, skin (fibrofolliculomatous) changes were also present, characteristic of Birt Hogg Dube syndrome.

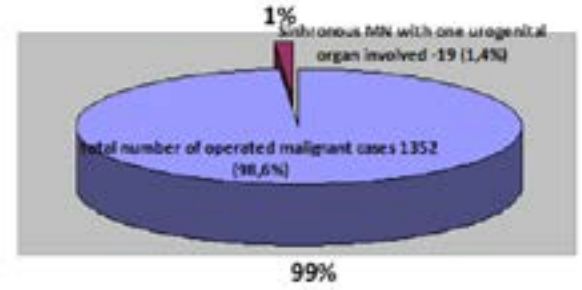


Diagram No. 1 - Percentage of Multiple Primary Malignant Neoplasm where at least one urogenital organ was affected, in relation to the total number of operated malignant diseases for a period of 2.5 years in the General Hospital "8th of September" - Skopje.

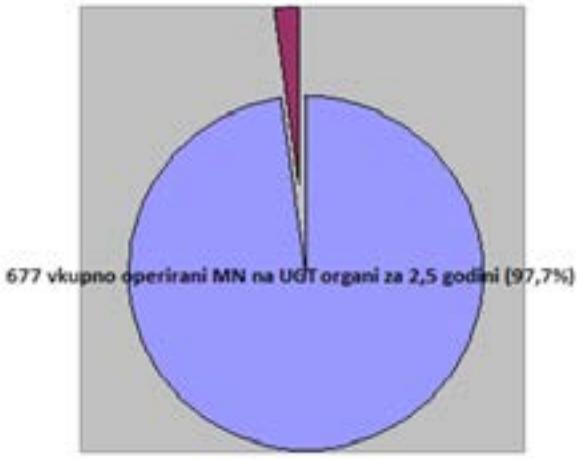


Diagram No. 2 - Percentage prevalence of synchronous and metachronous malignant tumors of two or more urogenital organs for a period of 2.5 years in the "8th of September" General Hospital - Skopje

The treatment of patients was based on the principle of an individual approach to treatment, taking into account: the type of malignant neoplasm, the stage of the disease, the patient's age, the present comorbidities and the expected five-year survival period of the patient (life expectancy).

Patients with multiple primary malignant neoplasm in which the urogenital organs were affected with organs of other systems (intestinal carcinomas, lung carcinoma, ovarian carcinoma and skin carcinoma), were treated multidisciplinary.

The patient with simultaneous diagnosis of renal cell carcinoma on both sides (by percutaneous biopsy), with frequent spontaneous pneumothorax due to cystic changes in the lungs and characteristic fibrofolliculomatous benign skin change on the neck (Birt Hogg Dube Syndrome), was surgically treated with radical

nephrectomy on the left side and a radical nephrectomy on the right side was proposed, due to the finding of three biopsy-confirmed tumorous malignant changes (RCC) in the same kidney (Figure 1).

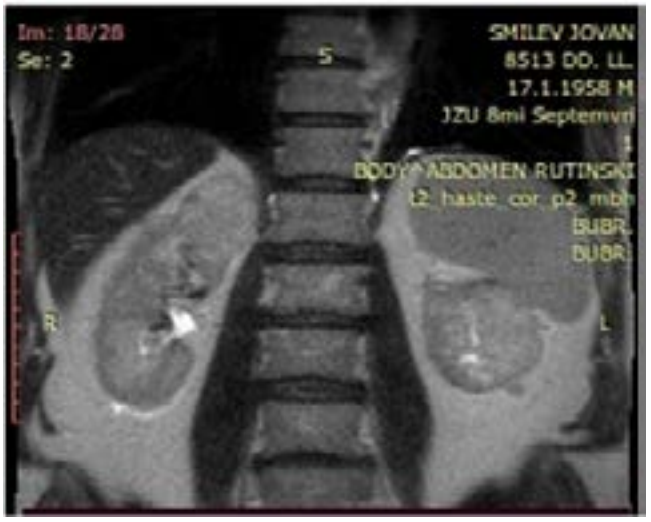


Figure 1. A 64-year-old patient with synchronous malignant neoplasm of both kidneys, frequent spontaneous pneumothorax due to cystic changes in the lungs and characteristic skin changes on the neck (Birt Hogg Dube Syndrome), operated on at the General Hospital "8 September" - Skopje, North Macedonia.

The patient was advised that after the right nephrectomy he would undergo chronic hemodialysis. Due to his refusal to undergo this, he was referred for oncological therapy.

In the second patient, cancer of the left kidney was diagnosed four years after a right nephrectomy, also performed due to massive renal cell carcinoma (Figure 2).

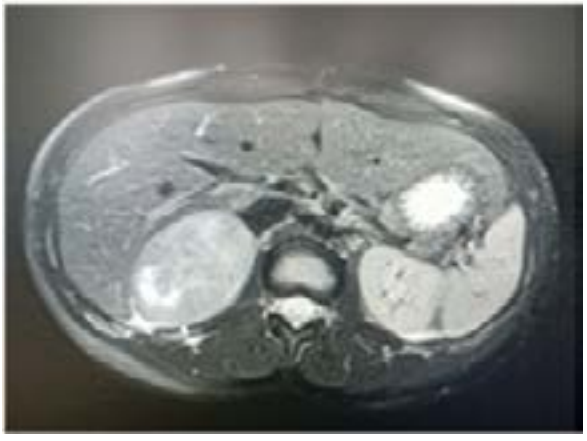
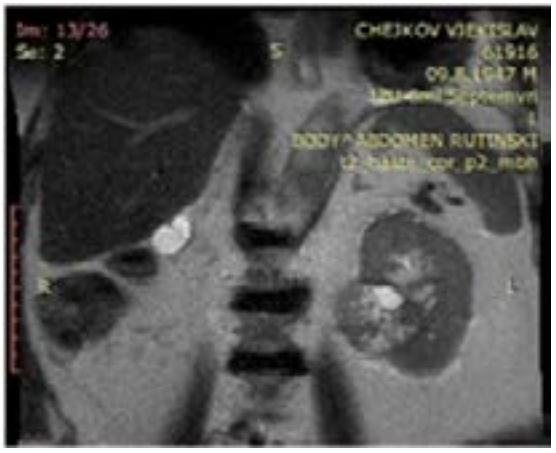


Figure 2. Patient 77 years old with diagnosed massive tumor (RCC) of the right kidney. Radical nephrectomy performed in GOB "8mi Septemvri", Skopje.

After four years, due to his age (81 years) and previous abdominal aortic aneurysm surgery and iliac blood vessel grafts, the patient did not agree to the proposed partial nephrectomy of the left kidney or oncological therapy and is undergoing active surveillance (Figure 3,4).



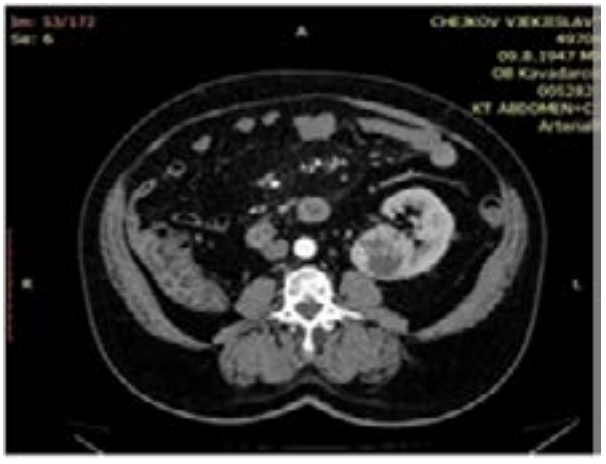


Figure 3.4. - Metachronous renal cell carcinoma, diagnosed four years after right nephrectomy performed due to massive carcinoma in an 81-year-old patient operated on at the "8th September" General Hospital - Skopje, North Macedonia.

CONCLUSION

Multiple primary malignant neoplasm represent a constant challenge in terms of timely diagnosis and adequate treatment. Out of a total of 1352 cases of malignant neoplasm operated on in the surgical departments of the General Hospital "8th September" in Skopje, in two and a half years, 19 or 1.4% were patients with multiple primary malignant neoplasm in which at least one urogenital organ was affected. In relation to the total number of 677 urological operations on malignant neoplasm for the same time period, the percentage of occurrence of synchronous and metachronous malignant

tumors of two or more urogenital organs is 2.3%. Out of a total of 66 operations on kidney cancer, two patients or 3.03% were diagnosed with renal cell carcinoma simultaneously in both kidneys. It is characteristic that in both cases, in addition to bilateral renal carcinoma, cystic changes in the lungs with frequent spontaneous pneumothorax and fibrofolliculomatous skin changes, characteristic of Birt Hogg Dube syndrome, were present.

The most common factors for the occurrence of synchronous and metachronous malignant neoplasm, in our practice so far, were determined to be: the familial factor, i.e. genetic predisposition, given that they were diagnosed in patients with autosomal hereditary genetic syndromes such as Von Hippel Lindau Syndrome and Birt Hogg Dube Syndrome, reduced immunity as a result of radiological or hematological therapy, and autoimmune diseases such as: Diabetes Mellitus, Myasthenia Gravis and Sclerosis multiplex.

The incidence of Multiple Primary Malignant Neoplasm in the studied group is significantly higher in men than in women in the ratio of 84.21% to 10.52%. Therefore, timely screening diagnostics in men over 50 years of age is the main prevention for their occurrence.

The analysis of each individual case in the studied group indicates the need for a so-called individual approach to the treatment of these patients, based on the principle of multimodal and multidisciplinary treatment, given that there is still no standard protocol for the treatment of synchronous and heterochronous primary malignant neoplasm.

Keywords: Synchronous primary malignancies, renal carcinoma, prostate carcinoma, bladder carcinoma, oncological treatment of malignant neoplasm, incidental diagnosis.

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Profesional paper

EVALUATION OF THE CLINICAL AND HISTOPATHOLOGICAL CHARACTERISTICS OF THE TUMOR AS FACTORS FOR THE OCCURRENCE OF METASTASES IN THE CERVICAL LYMPH NODES IN SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

Milosev Vladimir[1,2], Miloseva Dijana[1], Boskoska Blagica[2], Trokovski Nikola[3]

[1]Faculty of Medical Sciences, Goce Delcev University, Stip
[2]Department of Maxillofacial Surgery, Clinical Hospital, Stip
[3]Department of Plastic Surgery, Clinical Hospital, Stip

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ABSTRACT

Introduction: Squamous cell carcinomas in the maxillofacial region exhibit a significant predisposition for metastasizing to the cervical lymph nodes, which constitutes a negative prognostic factor. In clinical practice, the TNM classification is employed for treatment planning; however, it does not provide insights into the histological characteristics of the tumor, which offer predictive information for subsequent treatment and prognosis.

Patients and methods: This study was conducted on 74 patients who underwent surgery in the Department of Maxillofacial Surgery at the Clinical Hospital in Stip, during the period from February 2022 to March 2024. All patients underwent resection of the primary tumor and appropriate neck dissection. The clinical assessment included the location and size of the tumor, as well as nodal status. The histological evaluation encompassed depth of invasion, degree of differentiation, lymphovascular and perineural invasion, and the stage of the disease.

Objective: The aim of this study is to present an evaluation of the clinical and histopathological features of the tumor as factors influencing the occurrence of metastases in the cervical lymph nodes in cases of squamous cell carcinoma of the head and neck.

Results: We identified a correlation between the clinical nodal stage and the assessed histopathological characteristics of the tumor. Depth of invasion, poor pathological differentiation, and lymphovascular invasion were considered risk factors for the development of cervical lymph node metastases and an unfavorable prognosis.

Conclusion: The evaluation of the histopathological features of the tumor should be the initial step in investigating their role as significant predictors of the occurrence of neck metastases. The findings of this study may contribute to the establishment of criteria for assessing the risk of metastasis and the prognosis of patients with HNSCC.

Keywords: cervical lymph nodes, prognostic factors, elective neck dissection, HNSCC

INTRODUCTION

Squamous cell carcinoma of the head and neck represents the most prevalent and aggressive form of malignancy, characterized by a dismal prognosis and a significant propensity for metastasis (1). Its treatment encompasses radical surgical excision and elective neck dissection, succeeded by radiotherapy targeting the clinically positive neck (2). Patients diagnosed with squamous cell carcinoma at an early stage typically exhibit a favorable prognosis, whereas those presenting with evident cervical lymph node or distant metastases face a grim outlook. Cervical lymph node metastases diminish the

five-year survival rate to below 50%, thus rendering the management of cervical metastases a critical factor in enhancing survival rates for these patients (3). The most pivotal prognostic factor influencing the behavior and outcome of the tumor in SCC is the presence and extent of involvement of the cervical lymph nodes. Their diagnosis is established through radiological procedures (ultrasonography, CT, MRI) and fine needle aspiration biopsy (FNAB).

Squamous cell carcinoma primarily disseminates through the lymphatic vessels. The lack of fascial sheaths between the internal and external muscles facilitates the tumor's penetration into the muscles and surrounding structures. Numerous clinical and histopathological characteristics serve as predictors for the occurrence of neck metastases.

Tumor location - While the site of the tumor has been considered a determinant in several prior studies, there remains no definitive consensus regarding which localization poses a greater risk for metastasis. Typically, squamous cell carcinoma in the oral cavity exhibits a higher incidence of metastasis.

Tumor size - According to the TNM classification, tumor size is defined as the largest surface dimension, specifically the diameter of the tumor. Numerous studies have elucidated a correlation between tumor size and an elevated risk of neck metastases (4). T1 tumors have been documented to exhibit fewer metastases compared to advanced T3 and T4 tumors (5).

Depth of invasion - Depth of invasion is quantified by the vertical measurement from the skin surface (mucosa) to the maximum point of invasion (6). This factor is regarded as a more precise histological predictor of nodal metastases, local recurrence, and survival than tumor size. Bier-Laning et al. 2009, found that every 1 mm increase in depth of invasion elevates the probability of metastasis by approximately 5% (7).

Tumor differentiation–The histological grading of tumors according to Broder's classification–is divided into three categories: grade I (well differentiated), grade II (moderately differentiated), and grade III (poorly differentiated). The subjective assessment of the degree of keratinization, cellular and nuclear pleomorphism, and mitotic activity is taken into account (8). Nevertheless, an increasing number of authors highlight the poor correlation between histological grading and both prognosis and response to treatment. Nonetheless, the results of several prior studies suggest that histological grading serves as a significant and independent predictor of the occurrence of metastases in cervical lymph nodes in head and neck squamous cell carcinoma (9).

Lymphovascular invasion – Lymphovas-cular invasion, as part of the multifactorial grading system proposed by Jakobson, is classified according to the presence or absence of tumor cells located in the walls or lumens of blood and lymphatic vessels (10). Lymphovascular invasion has a significant relationship with the localization, size, and thickness of the tumor, histological grading, as well as metastasis in the cervical lymph nodes, local recurrence, and survival (11). Muscle infiltration is a factor that can be measured objectively. It delineates the presence of tumor cells in the immediate vicinity of the superficial or deep muscle tissue. It has been demonstrated to be a reliable and adequate predictive factor for metastasis to the lymph nodes (12). Byers et al. propose that the likelihood of occult metastases escalates if muscle invasion surpasses 4 mm (13).

The treatment of clinically negative cervical lymph nodes (N0) represents a significant challenge for maxillofacial surgeons, since there are no reliable parameters for predicting occult metastases. To assess their existence, some histopathological tumor characteristics, such as depth of invasion, degree of differentiation, lymphovascular and perineural invasion.

Recently, in its eighth edition, the American Joint Committee on Cancer/The Union for International Cancer Control (UICC) describes the depth of invasion (DOI) as a predictor of the occurrence of cervical lymph node metastases (14,15), and proposes the category T in the TNM classification for the depth of invasion (DOI) of the primary tumor. According to the pathohistological finding, the degree of tumor invasion is classified as thin T1 (<5 mm), intermediate T2 (5-10 mm) and thick T3, T4 (> 10 mm) (16).

In addition to the depth of invasion, predictive risk factors encompass tumor budding (TB), the pattern of invasion (POI), lymphovascular invasion (LVI), and perineural invasion (PNI), as well as the tumor-stromal ratio (TSR), which reflects the degree of differentiation (17, 18, 19). Depth of invasion (DOI) and tumor thickness–are these two distinct factors sufficient to provide prognostic information?

Although both factors signify invasion in depth, they are evaluated through different methodologies. Depth

of invasion (DOI) is determined by drawing a line from the basement membrane of the adjacent intact skin or mucosa to the deepest point of invasion (20), whereas tumor thickness is measured from the surface of the carcinoma to the deepest point of invasion. The average values for tumor thickness and depth of invasion reported in the literature vary, ranging from 1.5 to 10 mm (21).

Although the impact of Depth of Invasion (DOI) on the clinical staging of tumors, and consequently their prognosis, has demonstrated significant results, longer-term follow-up of prospective studies remains necessary to furnish sufficiently robust evidence regarding its role as a predictor of neck metastases and overall prognosis. In exophytic tumors, tumor thickness exceeds DOI, whereas in endophytic tumors, the converse is true; the thickness is less than DOI. Several studies indicate that depth of invasion (DOI) is a significant predictor of the occurrence of cervical lymph node metastases. Additionally, some studies identify DOI as an independent risk factor for recurrence and survival duration.

A limiting characteristic of the depth of invasion (DOI) is that it is determined through pathohistological evaluation conducted a few days after the surgical resection of the tumor. Unfortunately, there exists no reliable method for its assessment prior to or during surgery. It can only be evaluated from the material obtained through incisional biopsy; however, these results are often unreliable and may yield conflicting outcomes. Although the DOI cutoff values adopted by the American Joint Committee on Cancer (AJCC) are universal for all localizations within the maxillofacial region, various anatomical areas may possess distinct and specific cutoff values to enhance prognostic potential. In order to achieve a clear identification of high-risk predictive factors that contribute to the occurrence of neck metastases, the presence of metastasis is essential.

Five-year survival rates vary according to tumor size, with T1/T2 tumors classified as low-risk and T3/T4 tumors categorized as high-risk (22). The prognosis is also influenced by the location of the primary tumor, lymph node involvement, tumor thickness, and the status of surgical margins. Neck lymph node metastases are observed in approximately 40% of patients diagnosed with oral and maxillofacial squamous cell carcinoma. The detection of neck metastases at the time of initial diagnosis is critical for treatment planning, prognosis, and patient survival. This retrospective study aimed to investigate the role of different clinicopathologic features of the primary tumor as predictors of nodal neck metastases in patients with T1/T2/T3 head and neck squamous cell carcinoma.

METHODS AND MATERIAL

This study presents a prospective and retrospective analysis of 74 patients with histopathologically confirmed squamous cell carcinoma (SCC). Patients underwent surgical intervention at the Department of Maxillofacial Surgery, Clinical Hospital Stip, during the period from 2022 to 2024, with varying cancer localizations. Individuals with pathohistological findings indicative of cancer types other than squamous cell, those exhibiting distant metastases, and those receiving palliative radiotherapy were excluded from this analysis. Statistical analysis of descriptive parameters was conducted via SPSS 27.0. Fundamental information encompasses gender, age, tumor location, tumor size, histopathological characteristics of the tumor, and nodal status. The patho-histological diagnosis was rendered following the radical removal of the tumor by the pathologists of the Department of Pathology, Clinical Hospital Stip. Informed consent was obtained from all participants in this clinical study. These data are presented in tables, respectively.

RESULTS

Of the 74 patients included in this study, 49 (66.22%) were male and 25 (33.78 %) were female. Only one patient (1.35%) was under 50 years of age, 8 patients (10.81%) were 50-60 years of age, 34 patients (45.95 %) were 60-70 years of age, and 31 patients (41.89 %) were over 70 years of age. The distribution of patients by gender and age is presented in Table 1.

Table 1. Demographic data results

<table>
<tr><th></th><th colspan="2">Patient gender</th><th colspan="2">Age of patients by group</th></tr>
<tr><td></td><td>male</td><td>female</td><td>up to 50 years of age</td><td>1 (1.35%)</td></tr>
<tr><td rowspan="4"></td><td rowspan="4">49 (6.22 %)</td><td rowspan="4">25 (33.78 %)</td><td>50-60 age</td><td>8 (10.81 %)</td></tr>
<tr><td>60-70 age</td><td>34 (45.95 %)</td></tr>
<tr><td>over 70 years of age</td><td>31 (41.89 %)</td></tr>
<tr><td></td><td></td></tr>
<tr><td>Total number of patients</td><td colspan="4">74</td></tr>
</table>

In Table 2, we present the results of the evaluation of cancer localization by group. According to the localization in 17 patients (22.97%), the carcinoma is situated on the skin of the face; in 6 patients (8.11%), the localization is on the skin of the neck; in 6 patients (8.11%), the carcinoma is found on the nose; in 21 patients (28.37%), the localization is on the lower lip; in 3 patients (4.06%), it is located in the parotid gland; in 4 patients (5.41%), the carcinoma is found on the auricle; and in 17 patients (22.97%), it is localized in the oral cavity (buccal mucosa and tongue). Most of the tumors are localized on the lower lip and oral mucosa.

Table 2. Cancer localization by group

Cancer localization by group	facial skin cancer – 17 patients (22.97 %)
	lower lip cancer – 21 patients (28.37 %)
	parotid gland cancer – 3 patients (4.06 %)
	neck skin cancer – 6 patients (8.11 %)
	nose cancer – 6 patients (8.11 %)
	ear auricle cancer – 4 patients (5.41 %)
	oral cavity cancer – 17 patients (22.97 %)

In table 3, we present number of patients according to tumor size and clinical nodal status. According to tumor size, in 2 patients (2.70%), the diameter measures up to 1 cm; in 44 patients (59.46 %), it ranges from 1 to 3 cm; and in 28 patients (37.84%), the tumor exceeds 3 cm.

Table 3. Number of patients categorized by tumor size and clinical nodal status

Tumor size	Number of patients
to 1 cm	2 (2.70 %)
1-3 cm	44 (59.46 %)
up to 3 cm	28 (37.84%)
total patients	74
Clinical neck nodal status	Number of patients
N0	52 (70.2 %)
NI	16 (21.62 %)
NII	6 (8.11 %)
total patients	74

There are 52 (70.27 %) patients with N0 stage, 16 (21.62 %) patients with NI and 6 (8.11%)

patients with NII.

Table 4. Depth of invasion the tumor

Depth of cancer invasion	N-status (number of patients)
It reaches the lamina propria- 8 patients (10.81%) <2mm	N0
Dermal layer of skin- 16 patients (21.62 %) >3mm	N0
Subcutaneous fat – 11 patients (14.87 %) >4mm	NI(1)
Muscle layers – 32 patients (43.25 %) >5mm	NI (14) NII (4)
Surrounding glandular tissue – 3 patients (4.05%)	NI (1) NII (1)
Cartilage- 4 patients (5.40%)	NI (1)

The depth of tumor invasion and its relation with nodal status are depicted in Table 4.

In terms of the depth of invasion, 8 patients (10.81%) exhibited tumors that reached the lamina propria, 16 patients (21.62%) had tumors penetrating into the dermal layer of the skin, 11 patients (14.87%) showed penetration into the subcutaneous fat tissue, 32 patients (43.25%) demonstrated involvement of the muscle layers, 3 patients (4.05%) had involvement of the surrounding glandular tissue, and 4 patients (5.40%) exhibited tumors that penetrated into the cartilage. In eight patients in whom the tumor reached the lamina propria, no neck metastases were identified (N0). In 16 patients with tumor penetration into the dermal layer (>3mm), neck metastases were likewise not diagnosed. In 11 patients with penetration into subcutaneous fat tissue (>4mm), only one exhibited enlarged lymph nodes at the NI level. In 32 patients with infiltration of the muscle layers (>5mm), fourteen presented with NI level involvement, and four had neck metastases at the NII level. In 3 patients with malignant neoplasms of the parotid gland, one presented with involvement at the NI level, while another exhibited metastatic lymph nodes at the NII level. Ultimately, among 4 patients diagnosed with squamous cell carcinoma of the auricle, only one demonstrated metastases at the NI level. Radical excision of the lesion was conducted in all patients. In 22 patients with a radiographic diagnosis of node-positive neck, selective neck dissection was undertaken. Histopathological findings corroborated the

presence of metastatic changes in the lymph nodes.

Table 5. The degree of tumor differentiation and nodal status

Degree of differentiation – total number 74	Nodal status/ %
Well-differentiated carcinoma (G1)- 42 patients (56.76%)	N0
Moderately differentiated carcinoma (G2)- 27 patients (36.48%)	NI - 17 patients (22.97%)
Poorly differentiated carcinoma (G3)- 5 patients (6.76%)	NII- 5 patients (6.76%)

The evaluation of tumor differentiation and its relationship to neck metastases is presented in Table 5. According to the degree of tumor differentiation, 42 patients (56.76%) were diagnosed with well-differentiated carcinoma (G1), 27 patients (36.48%) with moderately differentiated carcinoma (G2), and 5 patients (6.76%) with poorly differentiated carcinoma (G3).

In a cohort of 42 patients with well-differentiated tumors, no instances of neck metastases were observed. Among 27 patients exhibiting moderate differentiation, 17 were diagnosed with Nodal Metastasis Level NI, while all 5 patients with poor differentiation presented with Nodal Metastasis Level NII.

Table 6. Tumor staging and Lymphovascular / Perineural invasion

Stage	Number of patients
Stage I	49 (66.22 %)
Stage II	19 (25.67 %)
Stage III	4 (5.41 %)
Stage IV	2 (2.70 %)
	total 74
Lymphovascular / Perineural invasion	Number of patients with Lymphovascular / Perineural invasion
Lymphovascular invasion	22 (29.73 %)
Perineural invasion	3 (4.05 %)
	total 25 of 74 (33.78 %)

The number of patients exhibiting lymphovascular and perineural invasion is detailed in Table 6. According to the histological stage of the disease, 49 patients (66.22%) are classified as stage I, 19 patients (25.67%) as stage II, 4 patients (5.41%) as stage III, and 2 patients (2.70%) as stage IV. Lymphovascular invasion was identified in 22 patients (29.73%), whereas perineural invasion was observed in 3 patients (4.05%). Among the total number of subjects, 43 exhibited an invasion depth exceeding 4mm, of which 22 demonstrated lymphovascular invasion histopathologically. An equivalent number presented with a positive neck nodal status. Perineural invasion was detected in only 3 subjects.

DISCUSSION

This study presents an evaluation of the clinical and histopathological features of the tumor as factors influencing the occurrence of metastases in the cervical lymph nodes in cases of squamous cell carcinoma of the head and neck. In the past, treatment planning and prognosis were based on TNM staging, excluding the biological characteristics of the tumor. Consequently, histopathological features of the tumor serve as a crucial factor for treatment planning, prognosis, and insights into the aggressiveness of the disease.

Previous studies on squamous cell carcinoma have shown that depth of invasion, tumor size, and stage of the disease are important parameters in predicting the occurrence of nodal metastases. Depth of invasion is considered an objective parameter and has been evaluated by several investigators for HNSCC (23).

In our study, among the 74 patients examined, only 5 exhibited poorly differentiated squamous cell carcinoma, while 27 presented with moderately differentiated squamous cell carcinoma and 42 patients were diagnosed with well-differentiated carcinoma. It is noteworthy that only 22 patients were found to have metastases in the cervical lymph nodes, and none of these patients belonged to the group with well-differentiated carcinoma.

Among our patients with a depth of invasion of up to 4 mm (totaling 24), no metastases were detected in the cervical lymph nodes; however, in those with a depth of tumor invasion exceeding 5 mm (totaling 43), cervical nodal metastases were identified in 15 patients at the NI level and in 4 at the NII level.

In patients with malignant neoplasms of the parotid salivary gland, out of a total of three, two exhibited neck metastases, one at the NI level and the other at the NII level. Among four patients diagnosed with squamous cell carcinoma of the auricle featuring cartilage invasion,

only one presented with neck metastases at the NI level.

In order to compare our results with similar findings, we conducted a thorough review of the literature and discovered a retrospective study by Rikardsen et al., which examined 133 patients with squamous cell carcinoma (SCC); of these, 42% were classified as well-differentiated, while 8% were deemed poorly differentiated (24).

In a study by Akhter et al., (25) of 50 patients with oral squamous cell carcinoma, 18% of well-differentiated patients had nodal metastases, 26% of moderately differentiated patients, and all poorly differentiated patients had cervical lymph node metastases.

In a study by Kurokawa et al.,(26) of 50 patients with SCC, 3.1% of well-differentiated patients had nodal metastases, and 33.3% of moderately differentiated patients had cervical metastases.

Some studies have compared tumor thickness and DOI (27, 28, 29). In the study by Dirven et al. (27), it was found that only 5.7% of patients had a different T stage when thickness was used instead of depth. However, the overall survival outcome was quite similar when thickness or depth were used as prognostic factors. Liu et al. (28) in their study found that both factors have a significant correlation in the occurrence of metastases in the cervical lymph nodes, and the boundary dimensions for the occurrence of cervical metastases were taken as 4.5 mm for depth and 8 mm for tumor thickness.

According to the results of the International Consortium for Outcome Research, a multi-institutional study conducted on 3149 patients showed that each increase in DOI by 5 mm also increases the T category (T1 <5mm, T2 5-10mm, T3/T4 >10mm) (29).

CONCLUSION

The histopathological characteristics of the tumor serve as a robust predictor of disease progression and metastasis. In instances where the depth of invasion (DOI) exceeds 5mm, elective neck dissection (levels I-III) is mandated. Conversely, in cases where the DOI is less than 5mm, stringent patient monitoring and regular evaluations are essential. Our study concludes that there is a heightened incidence of metastases in the cervical lymph nodes associated with moderately and poorly differentiated squamous cell carcinoma (SCC), as well as in tumors exhibiting a depth of invasion greater than 4mm. Lymphovascular invasion demonstrates a significant correlation with the occurrence of metastases in the cervical lymph nodes. Therefore, we are able to assess the aggressiveness of the tumor, predict the prognosis, and devise appropriate treatment strategies for the neck. The evaluation of the histopathological features of the tumor should be the initial step in investigating their role as significant predictors of the occurrence of neck metastases. The findings of this study may contribute to the establishment of criteria for assessing the risk of metastasis and the prognosis of patients with HNSCC .

Conflict of Interest: None declared

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Profesional paper

PILOT EVALUATION OF THE PEDIATRIC SLEEP QUESTIONNAIRE (PSQ) IN NORTH MACEDONIA: A SCREENING TOOL FOR DETECTING OBSTRUCTIVE SLEEP APNEA IN CHILDREN

Adrijana Ugrinoska Pandeva[1*], Tatjana Jakovska[1,2], Katerina Boshkovska[1,2] Vesna Dzambazovska[1]

[1]Public Health Institution University Clinic for Respiratory Diseases in Children Kozle, Skopje, Republic of North Macedonia

[2] Medical Faculty, Ss. Cyril and Methodius University Skopje, Republic of North Macedonia

*Corresponding author:
Ugrinoska Pandeva Adrijana, MD
University Clinic for Respiratory Diseases in Children "Kozle"
Kozle str, 1000 Skopje, Republic of North Macedonia
Tel: +389 77 813 573
Email: adrijanapandeva@gmail.com

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA) in children is a common but underdiagnosed condition characterized by recurrent episodes of upper airway obstruction during sleep. Timely recognition is crucial for preventing cognitive, behavioral, and cardiovascular complications. The Pediatric Sleep Questionnaire (PSQ) is one of the most widely used screening tools. Polysomnography (PSG) is the gold standard for the diagnosis of sleep-disordered breathing, but the test is expensive and not available in every hospital.

Objective: To conduct a pilot evaluation of the Macedonian-adapted Pediatric Sleep Questionnaire (PSQ) and to assess its feasibility and preliminary screening performance for detecting OSA symptoms among children in a tertiary pediatric center.

Material and methods: A cross-sectional pilot study was performed among 80 children (aged 2–16 years) attending the University Clinic for Respiratory Diseases in Children – Kozle, Skopje, North Macedonia, during two months period. Parents completed a translated and linguistically adapted Macedonian version of the PSQ, which evaluates snoring, apnea, sleepiness, and behavioral symptoms. Descriptive analyses were used to determine symptom frequencies and domain scores; PSQ scores ≥ 0.33 indicated a positive screen for OSA.

Results: The mean age of the participants was 7.0 ± 3.3 years (range 2–15); 52.5% were male. The mean PSQ score was 0.16, and 11.2 % (9/80) of children screened positive (PSQ ≥ 0.33). The most frequent symptoms were mouth breathing during sleep (39%), teeth grinding (34%), and habitual snoring (27%). Allergic rhinitis, asthma and recurrent upper respiratory infections were the most common comorbidities. No significant association was found between PSQ positivity and sex or any specific comorbidity ($p > 0.05$).

Conclusion: This pilot study demonstrates the feasibility of applying the Pediatric Sleep Questionnaire in the Macedonian pediatric population. The adapted PSQ showed good parental acceptability and identified children with typical OSA symptoms. These results provide a foundation for future large-scale validation and reliability testing of the Macedonian PSQ.

Keywords: Pediatric Sleep Questionnaire; pilot validation; obstructive sleep apnea; children; screening; North Macedonia.

INTRODUCTION

Obstructive sleep apnea (OSA) in children is characterized by recurrent episodes of upper airway obstruction during sleep, leading to disrupted sleep architecture and decreased oxygen saturation. Common symptoms include loud snoring, gasping during sleep, and daytime behavioral problems such as inattention and hyperactivity. While the prevalence of pediatric OSA ranges between 1% and 5%, it is believed to be underdiagnosed, especially in primary care settings. Left untreated, OSA may contribute to poor school performance, behavioral issues, growth retardation, and cardiovascular complications (1-3).

The Pediatric Sleep Questionnaire (PSQ), developed by Chervin et al. (2000), is one of the most widely used parent-reported screening tools for pediatric sleep-disordered breathing. It includes domains assessing snoring and breathing problems, daytime sleepiness, and behavioral symptoms associated with sleep fragmentation. The PSQ has demonstrated good reliability and sensitivity (≈0.80) in identifying children at risk of OSA when compared with polysomnography (PSG), the diagnostic gold standard (4, 5).

Because the Pediatric Sleep Questionnaire has not yet been validated in Macedonian, this study aimed to conduct a pilot evaluation of its feasibility and screening performance in children attending a tertiary pediatric center, in line with recommendations for pilot research (6,7).

Although polysomnography remains the diagnostic gold standard, its limited availability underscores the importance of validated questionnaires such as the PSQ for early screening.

OBJECTIVE

To conduct a pilot evaluation of the Macedonian-adapted Pediatric Sleep Questionnaire (PSQ) and to assess its feasibility and preliminary screening performance for detecting OSA symptoms among children in a tertiary pediatric center.

MATERIALS AND METHODS

This pilot validation study was conducted to evaluate the feasibility and preliminary performance of a Macedonian-adapted version of the Pediatric Sleep Questionnaire (PSQ) for identifying symptoms of obstructive sleep apnea in children. The study took place at the University Clinic for Respiratory Diseases in Children – Kozle, Skopje, North Macedonia, during two months period. Children aged 2–16 years who attended the clinic for respiratory complaints, sleep disturbances, or routine evaluations were consecutively invited to participate.

Questionnaire Adaptation and Data Collection

The original English version of the Pediatric Sleep Questionnaire (PSQ) developed by Chervin et al. (4) was translated into Macedonian by two bilingual pediatricians and reviewed by an expert panel consisting of pediatric pulmonologists, and a linguist to ensure cultural and conceptual equivalence. Minor wording adjustments were made to improve clarity and parental comprehension. Although the questionnaire has not been formally validated in Macedonian, this study represents its first pilot application.

The electronic version of the questionnaire was created and distributed using Google Forms to facilitate easy access for parents. Participation was voluntary and anonymous. Parents completed the survey either at the clinic or at home, with guidance from clinic staff if clarification was needed. The form included demographic data (child's age and sex), PSQ items grouped into domains—snoring and breathing, apnea symptoms, daytime sleepiness, and behavior—and additional questions regarding comorbidities such as asthma, allergic rhinitis, and obesity.

Each PSQ item was coded as Yes = 1, No = 0, or left blank (Don't know). The PSQ total score was calculated as the mean of positive responses across answered items; a score ≥ 0.33 indicated a positive screen for risk of OSA. Domain-specific averages were also computed to describe the distribution of symptoms.

Inclusion criteria were parents of children aged 2–16 years who were evaluated at the clinic during the study period. Exclusion criteria were incomplete questionnaire data and children with known neurological disorders or craniofacial abnormalities that could independently affect breathing during sleep.

Statistical Analysis

Data were exported from Google Forms to Microsoft Excel and analyzed using descriptive statistics. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Differences in PSQ positivity by sex and comorbidities were examined using the chi-square or

Fisher's exact test, as appropriate. A p-value < 0.05 was considered statistically significant.

For this pilot validation stage, internal consistency was assessed descriptively by evaluating the coherence of domain averages (snoring, apnea, sleepiness, and behavior). These data provide preliminary evidence of the questionnaire's feasibility and acceptability, serving as a foundation for future psychometric validation.

RESULTS

A total of 80 children participated in this pilot validation study, and all questionnaires were successfully completed, confirming good parental comprehension and feasibility of the adapted PSQ.

Participant Characteristics: A total of 80 children were included, Male 42 (52.5%), Female 38 (47.5%). The mean age was 7.04 years (SD 3.27) (median 7.0, range 2–16).

The mean PSQ score was 0.158 (median 0.12). Nine children (11.2%) screened positive using the PSQ (score ≥ 0.33). No significant difference in PSQ positivity was observed between males and females (p = 0.41). Key findings (Table 1)

Table 1. Demographic and clinical characteristics

Characteristic	Value
Number of participants (N)	80
Age, mean (SD)	7.04 (3.27)
Age, median (IQR)	7.0 (4.0-9.0)
Sex, Male n (%)	42 (52.5%)
Sex, Female n (%)	38 (47.5 %)
Mean PSQ score (overall)	0.158
PSQ positive (>=0.33), n (%)	9 (11.2%)

Out of 80 completed questionnaires, a substantial percentage of children were reported to experience symptoms commonly associated with OSA. Key findings (Table 2)

The most frequently reported symptoms were mouth breathing during sleep (38.8%), teeth grinding (35.0%), habitual snoring (26.9%), and night sweating (35.0%). Daytime sleepiness occurred in 15% and inattention or hyperactivity in 21%.

Table 2. Frequency of PSQ symptoms

Question	n Yes	% Yes
Does your child breathe through the mouth during sleep?	31	38.8
Does your child grind teeth during sleep?	28	35.0
Does your child snore often?	21	26.9
Does snoring occur most nights?	21	26.9
Does your child wake up frequently at night?	17	21.2
Is your child hyperactive?	16	20.8
Does your child have attention problems?	16	20.8
Does your child snore loudly?	15	19.2
Does your child have difficulty waking in the morning?	13	16.2
Does your child have restless sleep?	12	15.6
Does your child fall asleep while watching TV or sitting?	12	15.0
Does your child wake up gasping?	8	13.8
Does your child have problems organizing tasks or activities?	8	13.8
Does your child look sleepy during the day?	10	12.8
Does your child stop breathing during sleep?	9	11.7
Have you noticed pauses in your child's breathing?	9	11.7
Does your child have noisy breathing during sleep?	8	10.0
Does your child gasp or choke during sleep?	8	10.0
Does your child interrupt or bother others?	7	8.8
Does your child appear restless during the day?	6	7.5
Does your child wet the bed at night?	6	7.5
Does your child have nightmares frequently?	3	3.8
Does your child complain of morning headaches?	1	1.3
Does your child sleepwalk?	1	1.2
Sleepiness Avg	1	1.2

Comorbidities: Allergic rhinitis (60%) and recurrent upper-respiratory infections/otitis media (50%) were the most frequent comorbidities, followed by enlarged tonsils/adenoids (42.5%) asthma and overweight/obesity (21.2%). No significant associations were observed between PSQ positivity and comorbidities such as allergic rhinitis, asthma, recurrent upper-respiratory infections,

or obesity (all p > 0.05).

Key findings (Table 3 and Table 4)

Table 3. Prevalence of risk factors and comorbidities

Comorbidity	% Yes
Allergic rhinitis or seasonal allergies?	60.0
Smokers?	52.5
Frequent upper respiratory infections/otitis media?	50.0
Tonsills and adenoids?	42.5
Asthma?	21.2
Overweight or obesity?	21.2
Impaired/slow growth	~2.6

Table 4. Associations between comorbidities and PSQ positivity

Comorbidity	PSQ positive n (%)	PSQ negative n (%)	p-value
Tonsills and adenoids?	7	27	0.000
Allergic rhinitis or seasonal allergies?	7	41	0.005
Overweight or obesity?	4	13	0.015
Frequent upper respiratory infections/otitis media?	7	33	0.001
Asthma?	4	13	0.015
Smokers?	5	37	0.127

Domain analysis showed the highest average of positive responses in the snoring domain (0.22), followed by behavior (0.16), while sleepiness and apnea-related items were less frequent (0.11–0.15). This pattern indicates that snoring and behavioral symptoms are the most prominent features in the studied population. (Table 5)

Table 5: Mean domain scores (Snoring, Apnea, Sleepiness, Behavior)

Domain	Mean (0–1)	SD	Rank (Highest to lowest)
Snoring avg	0.220	± 0.07	1
Apnea avg	0.148	± 0.06	3
Sleepiness avg	0.113	± 0.05	5
Behavior avg	0.157	± 0.06	2
Other sleep avg	0.119	± 0.05	4

All items were answered by >90% of parents, and no difficulties were reported with the electronic completion process via Google Forms, supporting the feasibility and acceptability of the adapted PSQ.

DISCUSSION

This pilot study represents the first attempt to apply and preliminarily evaluate a Macedonian-adapted version of the Pediatric Sleep Questionnaire (PSQ) for screening symptoms of obstructive sleep apnea (OSA) in children. The results indicate that the questionnaire is feasible, well understood by parents, and capable of identifying children exhibiting typical sleep-disordered breathing symptoms such as snoring, mouth breathing, and restless sleep.

The overall prevalence of PSQ positivity in this cohort (11.2%) aligns closely with global estimates of pediatric OSA prevalence ranging from 6% to 12% (1–3). Comparable rates have been reported in similar hospital-based and community studies using the PSQ in various languages (4,5). The mean PSQ score in our sample (0.16) also mirrors that reported in other pediatric populations without confirmed OSA, suggesting that our cohort likely represents a typical clinical cross-section of children referred for respiratory or sleep-related concerns.

Symptom pattern and domain analysis

Domain analysis demonstrated the highest mean score for snoring-related items (0.22), followed by behavior (0.16), while apnea and sleepiness domains yielded lower averages (0.11–0.15). This distribution mirrors previously published findings where snoring and mouth breathing are consistently the most prominent symptoms detected by the PSQ (4, 5, 8, 9). These findings reinforce the central role of upper-airway obstruction and habitual snoring as clinical indicators of pediatric OSA. The lower frequencies of reported apnea and daytime sleepiness may reflect parents' limited ability to observe nocturnal breathing pauses or subtle daytime manifestations in younger children—a limitation also noted in prior validation research.

Behavioral disturbances such as hyperactivity and inattention were present in approximately one-fifth of participants, supporting existing evidence that sleep fragmentation in OSA contributes to neurobehavioral changes often mistaken for attention-deficit/hyperactivity disorder (ADHD)-like symptoms (9). This underscores the clinical relevance of including behavioral items within the PSQ domains.

Comorbidities and clinical associations

Allergic rhinitis, asthma, and recurrent upper-respiratory infections were common comorbidities in this study. However, no statistically significant association was found between these conditions and PSQ positivity. Similar observations have been reported in previous research, indicating that while allergic and inflammatory airway diseases can contribute to upper-airway obstruction, they do not independently predict OSA severity (10). These findings suggest that the PSQ identifies symptomatic risk independent of underlying respiratory comorbidities, which supports its clinical usefulness as a first-line screening tool in general pediatric practice.

Feasibility and practical implications

A key outcome of this pilot study was the demonstration of feasibility and acceptability of the PSQ in the Macedonian clinical context. All parents successfully completed the questionnaire electronically using Google Forms, and over 90% of items were answered, indicating strong comprehension and engagement. Digital administration proved convenient for both parents and clinicians and may represent an efficient model for broader community-based screening.

Given that polysomnography (PSG) remains limited to specialized centers in North Macedonia, the integration of a simple, validated tool such as the PSQ into primary care settings could substantially improve the early recognition of children at risk for OSA. The use of structured screening questionnaires has been shown to enhance diagnostic pathways and reduce the number of undetected cases, especially where resources are constrained.

Comparison with international evidence

A meta-analysis by Parenti et al. (5) reported pooled sensitivity and specificity values of 0.85 and 0.60 for the PSQ in detecting pediatric OSA when compared with PSG, confirming its robust diagnostic performance. The consistency of symptom patterns in our study with those in international cohorts supports the cross-cultural applicability of the PSQ and justifies progressing toward formal psychometric validation in Macedonian.

Limitations and future directions

This pilot study has several limitations. First, the adapted PSQ has not been formally validated in Macedonian, and psychometric properties such as internal consistency (Cronbach's α), test–retest reliability, and construct validity were not assessed. Second, the relatively small sample size limits generalizability. Third, the absence of polysomnographic confirmation precluded evaluation of diagnostic accuracy. Nevertheless, these limitations are inherent to pilot studies and provide the basis for a more comprehensive validation project.

Future research should focus on (a) formal linguistic validation of the Macedonian PSQ following international translation guidelines, (b) assessment of internal consistency and reliability using larger samples, and (c) comparison with PSG results to establish sensitivity, specificity, and predictive values.

Summary of clinical relevance

Despite these limitations, this pilot evaluation demonstrates that the PSQ can be successfully applied in Macedonian-speaking populations and effectively identifies children with symptomatic features of OSA. Its simplicity, low cost, and ease of administration make it particularly suitable for primary care physicians and school health programs as a first-line screening tool to prioritize referrals for specialized evaluation.

CONCLUSION

This pilot study demonstrates that the Macedonian-adapted Pediatric Sleep Questionnaire (PSQ) is a feasible and parent-friendly instrument for screening obstructive sleep apnea (OSA) symptoms in children. The PSQ was easily administered electronically, well understood by parents, and effectively identified key features such as snoring, mouth breathing, and behavioral disturbances. Although formal psychometric validation and comparison with polysomnography are still required, these findings provide foundational evidence supporting the PSQ's integration into primary and secondary pediatric care in North Macedonia. Broader application of this tool could enhance early recognition and timely referral of children at risk for OSA, contributing to improved respiratory and developmental outcomes.

Conflict of Interest: None declared

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Profesional paper

PSIKOZA POSTPARTUM DHE INTERPRETIMI I SAJ LIGJOR

Almira Xhaferi*[1], Kanita Xhaferi[2], Rihan Saiti[1], Rina Zejneli[2]

[1]Faculty of Medical Sciences, University of Tetova, Tetovo
[2]Faculty of Law, South East European University, Skopje

*Corresponding author: E-mail: xhaferialmira6@gmail.com

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ABSTRAKT

Hyrj: Psikoza postpartum është një çrregullim psikiatrik i rrallë, por i rëndë, që shfaqet pas lindjes dhe shpesh çon në humbje të aftësisë për të vlerësuar realitetin dhe sjellje të rrezikshme ndaj foshnjës. Nëse mbetet e patrajtuar, mund të rezultojë në pasoja serioze, përfshirë rrezik për nënën ose fëmijën. Njohja dhe ndërhyrja në kohë janë thelbësore, pasi kjo gjendje ndikon ndjeshëm në shëndetin mendor të nënës dhe bart implikime të rëndësishme ligjore në lidhje me përgjegjësinë penale. Ky studim synon të shqyrtojë statusin mjekësor dhe juridik të psikozës postpartum, duke vlerësuar njohjen e saj si një gjendje të veçantë psikiatrike dhe duke krahasuar qasjet klinike dhe juridike ndërkombëtare.

Materiale & Metoda: Ky studim paraqet një rishikim të literaturës mjekësore dhe juridike mbi psikozën postpartum, duke përfshirë udhëzime klinike, jurisprudencë ndërkombëtare dhe Kodin Penal të Maqedonisë së Veriut (Neni 127), me qëllim analizimin e praktikave të vlerësimit, strategjive të menaxhimit dhe implikimeve ligjore.

Përmbajtja Kryesore: Psikoza postpartum është një urgjencë psikiatrike që ndodh pak pas lindjes, e karakterizuar nga paqëndrueshmëria e humorit, simptoma psikotike dhe gjykim i dëmtuar. Etiologjia e saj është multifaktoriale, duke përfshirë predispozitën gjenetike, ndryshimet hormonale, mungesën e gjumit dhe faktorët e mundshëm imunitarë. Prevalenca globale varion nga 0.89 deri në 2.6 për 1,000 lindje, duke nënvizuar rëndësinë e identifikimit të hershëm. Vlerësimi klinik përfshin ekzaminim psikiatrik, mjete vlerësimi (p.sh., EPDS, MDQ), analiza laboratorike dhe neuroimazheri për të përjashtuar shkaqe organike. Menaxhimi kërkon ndërhyrje të menjëhershme, shpesh me hospitalizim, farmakoterapi (stabilizues të humorit, antipsikotikë, litium), psikoterapi dhe, në raste të rënda, terapi elektrokonvulsive. Në aspektin juridik, qasjet ndërkombëtare ndaj infanticidit maternal ndryshojnë ndjeshëm. Disa shtete, si Maqedonia e Veriut, Austria dhe Gjermania, e konsiderojnë gjendjen postpartum të nënës si rrethanë lehtësuese. Mbretëria e Bashkuar zbaton Infanticide Act 1938, ndërsa vende si Shtetet e Bashkuara, Franca dhe Italia zbatojnë përgjegjësi të zakonshme penale. Këto modele të ndryshme theksojnë ndërthurjen midis psikiatrisë dhe drejtësisë dhe nevojën për të balancuar mbrojtjen e foshnjës me njohjen e gjendjes së alteruar mendore të nënës.

Diskutim & Përfundime: Psikoza postpartum ndikon rëndë në gjykimin e nënës dhe kërkon ndërhyrje të menjëhershme dhe të strukturuar. Mangësitë aktuale në skrinimin klinik dhe kornizat ligjore në Maqedoninë e Veriut tregojnë nevojën për sisteme më të mira të identifikimit të hershëm dhe udhëzime të standardizuara ligjore. Forcimi i bashkëpunimit midis institucioneve psikiatrike dhe juridike është thelbësor për të vendosur procedura më të qarta dhe për të siguruar menaxhimin adekuat të rasteve të psikozës postpartum.

Fjalë kyçe: Psikoza postpartum, Çrregullimi bipolar, Infanticidi, Përgjegjësia penale.

HYRJA

Psikoza postpartum (pas lindjes) përbën një gjendje të rrallë, por shumë serioze psikiatrike, e cila mund të shkaktojë pasoja të rënda për nënën, fëmijën dhe familjen. Nëse nuk zbulohet dhe nuk trajtohet me kohë, gratë që vuajnë nga kjo gjendje rrezikojnë të kryejnë vetëvrasje ose vrasje të foshnjës. Zbulimi i hershëm dhe trajtimi adekuat janë vendimtarë për të ulur këto rreziqe dhe për të shmangur ndikimet e dëmshme tek nëna dhe fëmija. (1). Psikoza postpartum nuk është një diagnozë e veçantë në ICD-10, por ekziston si një përcaktues. (2). Ka mendime të ndryshme në literaturë nëse kjo gjendje duhet të konsiderohet si një çrregullim i veçantë apo një variant i skizofrenisë ose i çrregullimit bipolar. (2). Sipas Sit dhe Murray, psikoza postpartum përkufizohet si një episod i vetëm ose i përsëritur i simptomave të humorit dhe psikozës, i cili ndodh ekskluzivisht gjatë periudhës postpartum, nga lindja deri në një vit pas saj. (3).

Ndikimi në përgjegjësinë penale —Psikoza postpartum mund të shkaktojë sjellje ekstreme (p.sh. dëm ndaj vetes, vetëvrasje ose dëm ndaj foshnjës, infanticid). Studimi ligjor ndihmon të kuptohet nëse dëmi që ka shkaktuar një nënë me psikoz postpartum duhet të konsiderohet si rast penal, apo të trajtohet si rast i paaftësisë mendore në momentin e veprës, pra, të përcaktohet nëse gjendja mendore mund të shihet si rrethanë që justifikon ose lehtëson përgjegjësinë e nënës së diagnostikuar.

Mbrojtja e të drejtave të grave – Analiza ligjore shtron pyetjen nëse sistemi i drejtësisë është i ndjeshëm ndaj shëndetit mendor të nënave dhe nëse gratë marrin trajtimin e duhur apo vetëm ndëshkohen penalisht për veprën e kryer në momente të psikozës postpartum.

Parandalimi dhe politikat publike – Njohja ligjore e këtij fenomeni mund të çojë në hartimin e ligjeve dhe politikave që promovojnë ndërhyrje të hershme dhe masa parandaluese, duke mbrojtur nënat, fëmijët dhe familjet.

Balancimi i interesave – Ligji duhet të gjejë ekuilibrin midis mbrojtjes së viktimave (foshnjës, familjes) dhe mbrojtjes së grave që vuajnë nga një gjendje psikiatrike serioze.

Njohja ligjore dhe shëndetësore e psikozës postpartum është e rëndësishme për zhvillimin e politikave parandaluese dhe ndërhyrjeve të hershme. Kjo përfshin monitorimin e grave me histori të çrregullimeve afektive (si çrregullimi bipolar), të cilat kanë 30–40% rrezik për zhvillim të PPP pas lindjes. (4).

Neni 127 – Vrasja e fëmijës nga nënë gjatë lindjes

Vrasja e foshnjës gjatë lindjes paraqet një lloj të posaçëm të vrasjes së privilegjuar dhe dallohet nga veprat tjera për nga gjendja psikike e posaçme e kryerësit.

Veprën penale e kryen e ëma gjatë lindjes, ose menjëherë pas lindjes në një gjendje të shqetësuar, të shkaktuar gjatë lindjes. (61).

Bazuar në nenin e mësipërm nëna që e vret fëmijën e vet gjatë lindjes ose menjëherë pas lindjes, në gjendje të çrregullimit të shkaktuar nga lindja, do të dënohet me burg prej tre muaj deri tri vjet.

Veprimi i tentativës për këtë vepër është gjithashtu i dënueshëm. (5).

Lidhja me psikozën postpartum është:

Gjendja e nënës Psikoza postpartum është çrregullim i rëndë mendor pas lindjes, që shoqërohet me humbje kontakti me realitetin dhe sjellje të rrezikshme ndaj foshnjës.

Arsyetimi ligjor: Ligji e njeh këtë gjendje si faktor që ul përgjegjësinë penale, duke parashikuar dënim më të lehtë se vrasja e zakonshme.

Përputhja me realitetin klinik: Psikoza postpartum njihet si urgjencë psikiatrike që ndikon drejtpërdrejt në gjykimin e nënës, prandaj ligji e trajton ndryshe nga rastet e tjera të vrasjes.

Praktika gjyqësore: Gjykatat mbështeten në ekspertizën psikiatrike forensike; nëse konstatohet psikoza postpartum, zbatohet neni 127 me dënime më të buta dhe shpesh edhe trajtim psikiatrik.

QËLLIMI I HULUMTIMIT

Ky studim synon të vlerësojë statusin ligjor dhe mjekësor të psikozës postpartum. Konkretisht, hulumtimi ka për qëllim:

Të shqyrtojë nëse psikoza postpartum mund të konsiderohet si një "gjendje e veçantë psikike" sipas legjislacionit në fuqi.

Të shqyrtojë trajtimin e kësaj çështjeje në literaturën mjekësore dhe juridike, duke përfshirë analizën e studimeve klinike dhe të praktikës gjyqësore në vende të tjera.

Të krahasojë praktikat dhe qasjet e vendeve të tjera në lidhje me trajtimin ligjor dhe mjekësor të psikozës

postpartum, për të nxjerrë mësime dhe rekomandime për praktikën vendore.

Pyetjet Kërkimore

Hulumtimi synon të përgjigjet mbi aspektet mjekësore dhe ligjore të psikozës postpartum, duke u fokusuar në situatat e infanticidit dhe krahasimet ndërkombëtare. Pyetjet kryesore të studimit janë:

Cili është përkufizimi mjekësor, simptomatologjia dhe trajtimi.

Analiza e nenit 127 dhe masat e parashikuara për veprimet e mësipërme.

Vlerësimi i mundësisë që psikoza postpartum të konsiderohet "gjendje e veçantë psikike" për qëllime ligjore.

Krahasimi i praktikave ndërkombëtare ligjore dhe mjekësore në rastet e psikozës postpartum dhe infanticidit.

METODOLOGJIA

Hulumtimi është kryer si një literature review (shqyrtim i literaturës ekzistuese), duke përdorur burime të ndryshme për të mbuluar aspektet mjekësore dhe ligjore të psikozës postpartum. Shqyrtim sistematik i literaturës shkencore dhe burimeve juridike. Analizimi i literaturës mjekësore u bazua në literaturën mbi psikozën postpartum. Kërkimi u krye në PubMed dhe Google Scholar, duke përdorur terma si "Postpartum psychosis" dhe "Postpartum bipolar disorder", dhe u kufizua në artikuj të publikuar me rëndësi klinike për praktikuesit psikiatrikë.

Kodi Penal i Republikës së Maqedonisë së Veriut, sidomos neni 127. Literaturë krahasuese ndërkombëtare mbi trajtimin ligjor dhe mjekësor të rasteve të ngjashme.

Qasja metodologjike:

Analizimi i literaturës mjekësore për të identifikuar përkufizimin, vlerësimin klinik apo simptomatologjinë, etiologjinë, epidemiologjinë, vlerësimin si dhe trajtimin dhe menaxhimin e psikozës postpartum.

Analizimi i literaturës juridike dhe vendimeve gjyqësore për të shqyrtuar lidhjen me nenin 127 dhe praktikën ligjore.

Krahasimi i praktikave ndërkombëtare për të nxjerrë mësime dhe rekomandime për kontekstin lokal.

Kriteret e përfshirjes

Burime shkencore mjekësore që trajtojnë në mënyrë të drejtpërdrejtë psikozën postpartum, çrregullimin bipolar postpartum, ose çrregullimet psikiatrike pas lindjes me fokus në etiologji, epidemiologji, simptomatologji, diagnozë dhe trajtim (p.sh. Sit & Murray, 2023; Robertson et al., 2020; Bergink et al., 2016; Brockington, 2004).

Artikuj të publikuar në revista me peer review dhe libra akademikë të njohur ndërkombëtarisht në fushën e psikiatrisë klinike (p.sh. Kaplan & Sadock's Comprehensive Textbook of Psychiatry, 2019).

Studime sistematike dhe meta-analiza që ofrojnë evidencë për rrezikun e zhvillimit të psikozës postpartum te gratë me çrregullime afektive (p.sh. Wesseloo et al., 2016; Kępińska et al., 2024).

Burime që trajtojnë qasjen ligjore ndaj psikozës postpartum, përfshirë Kodi Penal i Republikës së Maqedonisë së Veriut (p.sh. Zejneli, 2007; Kodi Penal i RMV, neni 127), si dhe literaturë krahasuese ndërkombëtare mbi përgjegjësinë penale dhe interpretimin juridik të çrregullimeve mendore (p.sh. Ashworth, 2019; Dubber & Hörnle, 2014; Infanticide Act 1938; Strafgesetzbuch §216).

Burime forenzike dhe psikiatriko-juridike që analizojnë rolet e psikiatrit si ekspert ligjor dhe bashkëpunimin ndërmjet psikiatrisë dhe sistemit të drejtësisë (p.sh. Arboleda-Flórez, 2006; Sarkar, 2024; Parnas & Henriksen, 2018; Gjorgjevska & Naumovska, 2022).

Publikime në gjuhën angleze ose shqipe, të botuara në periudhën 2000–2025, për të reflektuar zhvillimet më të fundit në fushën klinike dhe ligjore.

PËRMBAJTJA KRYESORE

Simptomat

Në librin Kaplan & Sadock's Comprehensive Textbook of Psychiatry, simptomat e psikozës postpartum përshkruhen si një emergjencë psikiatrike që shpesh shfaqet brenda dy javëve pas lindjes. Kjo gjendje karakterizohet nga një kombinim i simptomave manike, depresive dhe psikotike. Disa nga simptomat kryesore përfshijnë: Deluzione dhe halucinacione: Mendime të pasakta dhe perceptime që nuk përputhen me realitetin. Labilitet i humorit: Ndryshime të shpejta dhe ekstreme të humorit. Mania: Një gjendje e ngritur e humorit, shpesh e shoqëruar me energji të shtuar dhe aktivitete impulsive. Depresioni: Një ndjenjë e thellë trishtimi dhe humbje e interesit për aktivitetet e përditshme. Sjellje e çrregullt: Veprime dhe reagime që janë të papritura dhe

të papërshtatshme. Dëmtim i perceptimit të realitetit: Vështirësi në dallimin e asaj që është real dhe çfarë nuk është. (6).

Etiologjia e Psikozës Postpartum

Gjetjet e literaturës tregojnë se etiologjia e psikozës postpartum (PPP) është multifaktoriale dhe rezulton nga ndërveprimi i faktorëve biologjikë, gjenetikë, hormonalë dhe mjedisorë. Disa studime kanë identifikuar predispozitën gjenetike dhe historinë personale ose familjare të çrregullimeve bipolare si faktorë kryesorë rreziku për zhvillimin e PPP. Pas lindjes, rënia e menjëhershme e hormoneve steroide – veçanërisht estrogjenit dhe progesteronit – shkakton ndryshime neuroendokrine që mund të ndikojnë në ekuilibrin e neurotransmetuesve të përfshirë në rregullimin e humorit dhe të perceptimit. Këto ndryshime, në prani të predispozitës gjenetike, mund të nxisin shpërthimin e simptomave psikotike.

Një tjetër faktor i rëndësishëm patogjenetik i evidentuar në literaturë është privimi nga gjumi dhe prishja e ritmeve cirkadiane në periudhën e menjëhershme pas lindjes, të cilat mund të veprojnë si nxitës të episodeve maniakale ose psikotike. Përveç kësaj, disa studime të fundit kanë sugjeruar përfshirjen e proceseve inflamatore dhe të ndryshimeve në sistemin imunitar, që ndodhin natyrshëm gjatë periudhës perinatale, si pjesë e mekanizmave të mundshëm biologjikë. Megjithëse janë shqyrtuar edhe faktorë psikosocialë, si stresi ose trauma e përjetuar, provat për rolin e tyre të drejtpërdrejtë në zhvillimin e PPP mbeten të paqëndrueshme.

Në përmbledhje, etiologjia e psikozës postpartum shihet si rezultat i një ndërveprimi kompleks midis predispozitës gjenetike dhe ndryshimeve hormonale pas lindjes, të përforcuara nga faktorë si privimi nga gjumi dhe rregullimet e mundshme imune. Ky kuadër patofiziologjik mbështet konceptin se PPP përfaqëson një çrregullim neuropsikiatrik me origjinë të shumëfishtë, ku komponentët biologjikë luajnë rolin dominues në shpërthimin e simptomave klinike. (7-11).

Epidemiologjia

Psikoza postpartum (PPP) është një çrregullim psikiatrik i rrallë, por klinikisht shumë i rëndësishëm, që ndodh zakonisht brenda javëve të para pas lindjes. Sipas të dhënave të rishikuara në mënyrë sistematike, prevalenca globale e PPP varion nga 0.89 deri në 2.6 raste për 1.000 lindje, duke e klasifikuar atë si një sëmundje me incidencë të ulët, por me pasoja potencialisht të rënda për shëndetin mendor të nënës dhe sigurinë e foshnjës. Një studim kohortë kombëtar në Suedi, që përfshiu më shumë se 1.6 milion gra, raportoi se 0.15% e tyre zhvilluan psikoze postpartum brenda tre muajve të parë pas lindjes, duke theksuar se megjithëse është e rrallë, PPP mbetet një emergjencë psikiatrike për shkak të shfaqjes së menjëhershme dhe rrezikut për vetëdëmtim apo dëmtim të foshnjës. Po ashtu, rishikime të tjera ndërkombëtare konfirmojnë se PPP shfaqet në 1–2 raste për çdo 1.000 lindje, me incidencë të ngjashme në vendet me të ardhura të larta dhe të ulëta, por me mundësi më të ulëta për diagnozë të hershme në vendet me mungesë të burimeve mjekësore. Këto gjetje nënvizojnë rëndësinë e monitorimit të grave në periudhën e hershme pas lindjes dhe identifikimit të hershëm të simptomave për parandalimin e komplikimeve serioze. (12-14).

Vlerësimi i psikozës postpartum (PPP)

Psikoza postpartum shpesh mbetet nën-diagnostikuar dhe nën-raportuar, për shkak se nuk ekzistojnë procedura standarde të shqyrtimit gjatë periudhave para dhe pas lindjes. Ndërsa fokusi kryesor zakonisht vendoset tek shëndeti fizik i nënës dhe foshnjës, ofruesit e kujdesit parësor duhet të përdorin pyetësorë të specifikuar për të vlerësuar gjendjen emocionale dhe mirëqenien e pacientes gjatë shtatzënisë dhe periudhës postpartum. Instrumente të shpejta dhe efektive, si EPDS (Edinburgh Postnatal Depression Scale) dhe MDQ (Mood Disorder Questionnaire), ndihmojnë në identifikimin e shenjave të depresionit dhe manisë tek gratë me rrezik. Ky vlerësim është i rëndësishëm për parashikimin e rrezikut për sëmundje psikiatrike gjatë periudhës kritike puerperale. Pas një historiku të plotë dhe ekzaminimi fizik, analizat laboratorike fillestare që përfshijnë CBC, elektrolitet, BUN, glukozën, kreatininën, vitaminën B12, folatin, tiaminën, kalciumin, testet e funksionit të tiroides dhe të mëlçisë, urinalizën, testin e drogës, kulturat e urinës dhe gjakut, si dhe imazherinë e trurit (CT/MRI), ndihmojnë në përjashtimin e shkaqeve organike që mund të paraqiten me simptoma psikozash. Këto përfshijnë çrregullime elektrolitike, hipoglicemi ose hiperglicemi, anomali të funksionit të mëlçisë, çrregullime të tiroides, uremi, abuzim me substanca, hiperkalçemi, infeksione dhe insulte të mundshme, veçanërisht tek gratë me histori të hipertensionit të lidhur me shtatzëninë, preeklampsisë ose eklampsisë. (15-18).

Trajtimi dhe Menaxhimi i Psikozës Postpartum

Identifikimi në kohë i psikozës postpartum është

jashtëzakonisht i rëndësishëm, pasi është një emergjencë psikiatrike me shfaqje të papritur, por zakonisht të shkurtër dhe me përgjigje të shpejtë ndaj trajtimit. Gratë në rrezik për dëmtim të vetes ose të foshnjës kërkojnë hospitalizim të menjëhershëm. Pasi të jenë përjashtuar shkaqet organike, trajtimi farmakologjik mund të përfshijë stabilizues të humorit, antipsikotikë atipikë dhe medikamente antiepileptike, si litium, valproat natriumi, lamotriginë, karbamazepinë, benzodiazepina, quetiapin dhe olanzapin. Përdorimi i litiumit profilaktik është i rekomanduar tek gratë me histori të çrregullimit bipolar ose psikozës postpartum, me rifillim menjëherë pas lindjes për të parandaluar rikthimin. Nivelet e litiumit në gjak duhet të monitorohen dy herë në javë gjatë dy javëve të para postpartum, dhe ushqyerja me gji duhet të shmanget gjatë marrjes së lithiumit për shkak të rrezikut për foshnjen. Barnat si SSRI, karbamazepina, valproati dhe benzodiazepinat me veprim të shkurtër konsiderohen relativisht të sigurta gjatë ushqyerjes me gji. Përveç trajtimit farmakologjik, psikoterapia është një adjuvant i dobishëm, ndërsa ECT është një ndërhyrje e sigurt dhe efektive për episodet akute, veçanërisht kur simptomat nuk kontrollohen me barnat psikiatrike. Vendimet për trajtimin medikamentoz gjatë shtatzënisë duhet të merren pas një diskutimi të kujdesshëm mbi përfitimet dhe rreziqet, pasi disa barna bartin rrezik për keqformime kongjenitale, sidomos gjatë tremujorit të parë të shtatzënisë. (19-30).

Kodi Penal i RMV (neni 127, par.1): përshkrimi dhe kuptimi i "gjendjes së veçantë psikike". (5):

Vrasja e fëmijës nga nënë gjatë lindjes

(1) Nënë që e vret fëmijën e vet gjatë lindjes ose menjëherë pas lindjes, në gjendje të çrregullimit të shkaktuar nga lindja, do të dënohet me burg prej tre muaj deri tri vjet.

(2) Veprimi i tentativës për këtë vepër është gjithashtu i dënueshëm. (5).

Gjatë lindjes

Në terminologjinë juridike të avancuar, kjo nënkupton:

Periudhën e procesit të lindjes kur gruaja është fizikisht duke sjellë fëmijën në jetë.

Nuk ka dallim në mënyrën e lindjes (natyrale, cezariane, e parakohshme, etj.) – e rëndësishme është që veprimet të ndodhin ndërkohë që gruaja është në procesin e lindjes.

Fokusimi i ligjit është tek gjendja psikike dhe fizike e menjëhershme e nënës, pra periudha kur trupi dhe mendja janë nën ndikimin e dhimbjes, stresit dhe tensionit të lindjes.

Në praktikë gjyqësore, kjo periudhë përfshin kohën nga fillimi i kontraksioneve aktive deri në daljen e foshnjës dhe veçanërisht momentet kur nëna nuk ka mundësi të gjykojë veprimet e saj në mënyrë të qartë.

Menjëherë pas lindjes

Periudha e zbatueshme zakonisht konsiderohet ditët e para pas lindjes, shpesh deri në 2–3 javë, varësisht nga ndikimi i lindjes në gjendjen emocionale dhe mendore të nënës.

Kriteri kryesor nuk është dita e saktë, por fakti se ndryshimet hormonale, lodhja ekstreme, stresi dhe çrregullimet psikike të lindjes janë ende të pranishme dhe ndikojnë në gjykimin dhe vetëkontrollin e saj.

Në rast gjyqësor, kjo periudhë përcaktohet nga ekspertiza psikiatrike, që vlerëson gjendjen shpirtërore të nënës në momentin e ngjarjes. (5).

Qëllimi juridik: të dallojë veprën penale të kryer në kushte të jashtëzakonshme psikike nga një vrasje e zakonshme, ku përgjegjësia penale është më e madhe.

Çrregullim të shkaktuar nga lindja

Gjendje e përkohshme: Nuk është një çrregullim kronik ose i përhershëm, por shfaqet si pasojë direkte e lindjes.

Ndikim në përgjegjësinë penale: Kjo gjendje mund të bëjë që veprimet e nënës të jenë të pamatura, të nxituara, ose të ndikohen nga emocionet ekstreme dhe dhimbja fizike.

Përjashtim nga vrasja e zakonshme: Ligji e sheh këtë gjendje si një rrethanë lehtësuese që zvogëlon përgjegjësinë penale në krahasim me një vrasje me dashje të ftohtë.

Gjendje të njohura në praktikë juridike dhe mjekësore

Shok pas lindjes (postpartum shock).

Depresioni postnatal i rëndë.

Çrregullime të përkohshme të gjykimit, ankth ekstrem ose agresivitet i nxitur nga dhimbja dhe lodhja.

Si vërtetohet

Ekspertizë psikiatrike/psikologjike/mjeko-ligjore.

Historia e lindjes (paplanifikuar, me komplikime, ose në kushte të rënda).

Dëshmitarë dhe raportime mjekësore.

Dënimi: 3 muaj deri në 3 vjet burgim.

Minimumi 3 muaj: për rastet kur veprimet tregojnë çrregullim më të theksuar shpirtëror ose planifikim të pjesshëm.

Maksimumi 3 vjet: për rastet kur vrasja kryhet në kushtet e një çrregullimi të lehtë ose të moderuar shpirtëror, i shkaktuar nga lindja.

Parësitë për vlerësim

Gjykata zakonisht merr parasysh:

Intensitetin e çrregullimit shpirtëror.

Natyrën e lindjes dhe kushtet fizike.

Nëse veprimi ishte i nxitur nga emocionet dhe dhimbja momentale.

Rrethanat e jashtëzakonshme (mosplanifikim, mungesë përvoje, mbështetje e pakët sociale).

Paragrafi i dytë i Nenit 127: Tentativa është e dënueshme

Tentativa është përpjekja për të kryer një vepër penale që nuk përfundon me sukses.

Në këtë rast, edhe nëse nëna nuk arrin të vrasë fëmijën, por ka ndërmarrë veprime të drejtpërdrejta dhe të qarta, ajo mund të ndiqet penalisht.

Analizë krahasuese juridike mbi vrasjen e foshnjes nga nëna menjëherë pas lindjes (infanticidi)

Në jurisprudencën penale bashkëkohore, koncepti i vrasjes së privilegjuar për rastet kur nëna privon nga jeta foshnjën e vet gjatë ose menjëherë pas lindjes përfaqëson një pikë takimi midis së drejtës penale dhe shkencave psiko-mjekësore. Ky fenomen kërkon ekuilibër midis nevojës për të mbrojtur jetën dhe detyrimit për të njohur gjendjen e veçantë psiko-fiziologjike të nënës në periudhën perinatale. (31-32).

Modelet normative ndërkombëtare

Në komparativë, dallohen tre qasje kryesore:

Modeli privilegjuar, ku ligji njeh gjendjen e nënës pas lindjes si rrethanë lehtësuese (p.sh. Maqedonia, Kroacia, Austria, Gjermania, Zvicra). (33).

Modeli special, ku ekziston një dispozitë e veçantë që e diferencion veprën, por e lidh me kategori si manslaughter (Mbretëria e Bashkuar). (34).

Modeli i përgjithshëm, ku nuk ekziston dispozitë e tillë dhe vepra trajtohet si vrasje e zakonshme (SHBA, Franca, Italia, Spanja, Polonia). (35).

Në sistemin e së drejtës penale maqedonase, neni 127 i Kodit Penal përcakton se nëna që, gjatë ose menjëherë pas lindjes, nën ndikimin e çrregullimeve të shkaktuara nga lindja, e privon nga jeta fëmijën e vet, dënohet me burgim prej tre muajsh deri në tre vjet. (36). Kjo dispozitë ilustron një ndër qasjet më të buta në rajon, duke njohur rrethanën e veçantë emocionale dhe fiziologjike të momentit të lindjes.

Në të kundërt, sistemet që nuk e njohin infanticidin si vepër të privilegjuar, si ai amerikan, francez, apo italian, e trajtojnë ngjarjen si murder ose omicidio volontario, me dënime identike me çdo vrasje tjetër – shpesh mbi 20 vjet burgim ose burgim të përjetshëm. (37). Këto sisteme juridike mbështeten mbi parimin e përgjegjësisë së plotë penale dhe nuk parashikojnë ulje dënimi për shkak të çrregullimeve emocionale që pasojnë lindjen, përveç rasteve të provuara psikiatrikisht si paaftësi mendore e plotë ose e pjesshme. (38).

Sistemi britanik si model i veçantë

Infanticide Act 1938 i Mbretërisë së Bashkuar përbën një model të ndërmjetëm, ku veprimi i nënës nuk trajtohet si vrasje, por si infanticide – pra një variant i manslaughter. (39). Dispozita parashikon se nëse mendja e nënës "është shqetësuar nga pasojat e lindjes apo të laktacionit", përgjegjësia penale reduktohet në mënyrë të ndjeshme. Ky sistem përpiqet të integrojë konceptet e psikiatrisë moderne me përgjegjësinë penale, duke vendosur një ekuilibër midis ndëshkimit dhe rehabilitimit. (40).

Rastet ilustrative në praktikën gjermane

Në Gjermani, ku ekziston dispozita për Kindestötung në Kodin Penal (StGB §216 e vijues), vrasja e foshnjës nga nëna gjatë lindjes ose menjëherë pas saj mund të dënohet me jo më pak se tre vjet burg, nëse vërtetohet se vepra është kryer nën ndikimin e procesit të lindjes. (41). Megjithatë, praktika gjyqësore tregon se dënimet shpesh janë të rënda, sidomos kur ekzistojnë elemente të qëllimit apo fshehjes. (42).

Një rast emblemë është ai i Wenden-Möllmicke (2008), ku u zbuluan trupat e tre foshnjave të ngrira në një frigorifer në shtëpinë e familjes Hilschenz. Hetimet provuan se foshnjat kishin lindur të gjalla dhe ishin vrarë menjëherë pas lindjes. (43). Ndonëse ligji gjerman njeh Kindestötung si dispozitë privilegjuese, prokuroria kërkoi dënime për Totschlag (vrasje me dashje), pasi veprimet pasuese – fshehja dhe ruajtja e trupave – tregonin qëllim dhe vetëdije të plotë për pasojat. Gruaja u dënua me 15 vjet burgim, çka dëshmon se zbatimi i normës privilegjuese

nuk është automatik, por varet nga provat për gjendjen mendore dhe mënyrën e veprimit. (44).

Një rast tjetër më i fundit, në Freital (Dresden, 2025), përfshinte një grua 24-vjeçare që lindte në fshehtësi dhe më pas asfiksoi foshnjën e saj, duke e fshehur trupin në mbeturina organike. Ekspertiza psikiatrike nuk konstatoi çrregullim të rëndë mendor, ndaj prokuroria kërkoi 7 vjet burg për vrasje, pa aplikim të dispozitës për Kindestötung. (45). Ky rast e përforcon parimin se, në mungesë të provave për çrregullim pas lindjes, sistemi gjerman nuk e trajton veprën si të privilegjuar. (46).

Reflektim teorik dhe politikë penale

Në analizë teorike, rregullimi i tillë përfaqëson përpjekjen për të ndërtuar një "etikë të butësisë" në të drejtën penale, ku ligjvënësi pranon se lindja e fëmijës mund të gjenerojë gjendje të jashtëzakonshme psiko-fiziologjike. (47). Megjithatë, në sistemet ku nuk ka dispozitë privilegjuese, logjika penale mbetet strikte: vepra konsiderohet shkelje e drejtpërdrejtë e së drejtës për jetën, dhe rrethanat personale të nënës i lihen diskrecionit të gjykatës si faktor lehtësues individual. (48).

Nga ana e politikës penale, ky kontrast reflekton dilemat midis humanizmit penal dhe rigorizmit juridik: a duhet ligji të njohë efektet e lindjes si shkak që ndikon në përgjegjësinë penale, apo duhet të ruajë barazinë absolute të subjekteve para ligjit? Përgjigjet ndryshojnë sipas traditës juridike, kulturës penale dhe politikave shoqërore të shtetit për mbrojtjen e nënës dhe fëmijës. (49).

Tabela krahasuese ndërmjet sistemeve ligjore

Shteti / Juridiksioni	Dispozita e veçantë për vrasjen e foshnjes nga nëna	Kriteret e aplikimit	Dënimi i parashikuar / praktik
Maqedonia e Veriut	Po – neni 127 i Kodit Penal ("vrasja e fëmijës gjatë lindjes")	Nën ndikimin e çrregullimeve të shkaktuara nga lindja	3 muaj – 3 vjet burg
Kroacia	Po – dispozitë për "uboj djeteta za vrijeme poroda"	Veprim gjatë lindjes / menjëherë pas saj, nën stres të rëndë	6 muaj – 5 vjet burg
Austria	Po – Kindestötung (§79 StGB)	Ndikim i procesit të lindjes / pas lindjes	6 muaj – 5 vjet burg
Gjermania	Po – §216 StGB, por praktikisht aplikohet rrallë	Vetëm nëse provohet çrregullim i lidhur me lindjen	3 vjet minimal; raste të rënda deri në 15 vjet (rasti Hilschenz)
Mbretëria e Bashkuar	Po – Infanticide Act 1938	Disturbim i mendjes nga lindja ose laktacioni	Trajtohet si manslaughter; dënim shpesh jo-burgimor
SHBA	Jo – nuk ekziston dispozitë federale për infanticid	Nuk ka parakusht biologjik; trajtohet si murder	Dënime shumë të rënda, deri në burgim të përjetshëm
Franca	Jo – trajtohet si meurtre/assassinat	Gjendja mendore vlerësohet vetëm si rrethanë lehtësuese	20 vjet – burgim i përjetshëm
Italia	Jo – trajtohet si omicidio volontario	Pa dispozitë speciale	21 vjet – burgim i përjetshëm
Spanja	Jo – homicidio/asesinato	Nuk njeh "infanticide"	10 – 25 vjet burg
Zvicra	Po – neni 116 CP ("infanticide")	Nëna vepron gjatë ose menjëherë pas lindjes, në çrregullim të lindjes	Deri 3 vjet burg

DISKUTIMI DHE PËRFUNDIMI

Raporti ndërmjet mjekësisë dhe drejtësisë është thelbësore për administrimin e drejtësisë, veçanërisht në rastet që përfshijnë çështje të shëndetit mendor. Ekspertët psikiatrikë luajnë një rol kyç si dëshmitarë të pavarur, duke ofruar vlerësime objektive mbi aftësinë mendore të individëve për të qëndruar në gjyq, për të kuptuar natyrën e veprës së kryer ose për të përcaktuar përgjegjësinë penale në raste të mbrojtjes për shkak të çrregullimeve mendore. Përmes intervistave klinike, analizës së dokumenteve dhe testeve psikologjike, ata formulojnë opinione që ndihmojnë gjykatën të kuptojë ndikimin e shëndetit mendor në sjelljen e të akuzuarve ose dëshmitarëve. Ky proces kërkon një kuptim të thellë të ligjit dhe etikës profesionale, pasi çdo raport psikiatrik mund të ketë ndikim të drejtpërdrejtë në vendimet gjyqësore dhe në fatin e individëve të përfshirë. (50-54).

Rezultatet e këtij shqyrtimi të literaturës tregojnë se psikoza postpartum (PPP) është një çrregullim i rrallë, por jashtëzakonisht i rëndë mendor, i cili ndikon ndjeshëm në perceptimin dhe aftësinë e gruas për të kuptuar dhe kontrolluar veprimet e saj. Në literaturën ndërkombëtare,

PPP njihet si emergjencë psikiatrike që kërkon trajtim të menjëhershëm dhe monitorim të kujdesshëm, veçanërisht tek gratë me histori të çrregullimeve afektive, si çrregullimi bipolar, që paraqesin një rrezik 30–40% për zhvillimin e këtij çrregullimi pas lindjes. (4).

Megjithëse në Maqedoninë e Veriut ekziston kuadri ligjor që rregullon vlerësimin e përgjegjësisë penale në rastet me çrregullime mendore, mungojnë mekanizmat praktikë të parandalimit dhe monitorimit. Aktualisht, nuk zbatohet asnjë formë e screening-ut psikiatrik apo hormonalo-psikologjik për gratë shtatzëna me çrregullime afektive, çka lë një boshllëk të madh në kujdesin perinatal dhe në parandalimin e PPP-së.

Kufizimet e studimit

Ky studim është i bazuar në literature review dhe analizë krahasuese, prandaj mungesa e të dhënave statistikore vendore dhe e rasteve gjyqësore të dokumentuara kufizon thellësinë empirike të analizës. Megjithatë, krahasimi me praktikat ndërkombëtare ka ofruar një bazë të vlefshme për të identifikuar boshllëqet në sistemin vendas.

Implikimet për praktikën dhe politikat publike

Rezultatet e këtij studimi sugjerojnë se nevojitet zhvillimi i protokolleve për identifikimin e hershëm të grave me rrezik për PPP, si dhe përditësimi i kuadrit ligjor për të reflektuar realitetin klinik të këtij çrregullimi. Krijimi i një mekanizmi të integruar monitorimi dhe trajtimi do të mund të parandalonte pasojat fatale si infanticidi apo vetëvrasja.

Psikoza postpartum (PPP) përbën një gjendje klinike të rrallë, por jashtëzakonisht të rëndë, e cila ndikon thellësisht në perceptimin, gjykimin dhe realitetin e nënës, duke ndikuar drejtpërdrejt edhe në përgjegjësinë e saj penale në raste si infanticidi. Ndërlidhja ndërmjet psikiatrisë dhe juridikut bëhet thelbësore në këto situata, pasi sistemi gjyqësor duhet të gjejë ekuilibrin midis kuptimit mjekësor dhe drejtësisë ligjore. Në Republikën e Maqedonisë së Veriut, neni 127 i Kodit Penal siguron bazë ligjore për ta trajtuar çrregullimin mendor pas lindjes si rrethanë të veçantë që ndikon në përgjegjësinë penale. Megjithatë, legjislacioni aktual ende mungon në udhëzime të qarta procedurale dhe forenzike për vlerësimin e rasteve të psikozës postpartum në praktikën gjyqësore. Për këtë arsye, është e domosdoshme forcimi i bashkëpunimit ndërdisiplinar dhe zhvillimi i literaturës që lidh psikiatrinë me juridikun, në mënyrë që të sigurohet një qasje më humane dhe e bazuar në prova në trajtimin e rasteve që përfshijnë çrregullime mendore pas lindjes. (55-60).

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Profesional paper

PIODERMITË TEK TE PORSALINDURIT

Visar Muça, Qëndresa Kadriu Muça, Gojart Sulejmani, Ferit Muça

Spitali i Përgjithshëm"Dr.Ferid Murad",Reparti i Pediatrisë me Neonatologji-Gostivar,Republika e Maqedonisë së Veriut

Email: dr.visar@yahoo.com

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ABSTRAKT

Hyrje: Infeksionet e lekurës tek të porsalindurit përfaqësojnë shkaqet më të shpeshta të morbiditetit dhe mortalitetit të femijëve të porsalindur.Shkaktohen nga bakteriet e sidomos nga Staphylokoket. Nëse nuk shërohen në kohë mund të shkaktojnë pneumoni, pleurit, endokardit, osteomielit, sepsë.

Qëllimi i punimit; ishte identifilimi i shkaktarëve më të shpeshtë të Piodermisë dhe percaktimi i ndieshmërisë sipas antibiogramit.

Materiali dhe metoda: janë analizuar 80 fëmijë të porsalindur të mjekuar në repartin e Pediatrisë tek të cilët janë izoluar bakterie patologjike gjatë dy viteve 2022-2023 në spitalin "Dr.Ferid Murad"në Gostivar. Prej tyre 36 fëmijë të porsalindur kanë qenë me piodermi.

Rezultatet: Sipas të dhënave tona konkludojmë se më prezente kanë qenë infeksionet e lekurës dhe atë me 45%, shkaktari më i shpeshtë ka qenë Staphylokoku Aerius me 61%. Sipas antibiogramit bakteria Staphylokokus Aerius ndieshmëri më të lartë tregoi ndaj Vankomicinës 94%,mandej ndaj Makrolidëve 72% dhe Cefalosporinës me 70%.

Diskutimi dhe përfundimi: Rezultatet tona treguan se infeksionet e lëkurës janë të shpeshta te të porsalindurit. Shkaktari më i shpeshtë ka qenë bakteria Staphylococcus Aerius. Mjekimi ka qenë me antibiotik sipas antibiogramit. Shumë me rëndësi është parandalimi i këtyre infeksioneve dhe atë me respektimin e rregullave të pergjithshme higjieno sanitare. Repartet Pediatrike dhe ato të Neonatologjisë duhet të konsiderohen si salla operacioni. Personeli duhet të ketë nivel të lartë të higjienës.

Fjale kyçe;fëmijët e porsalindur,infeksionet e lekurës

HYRJE

Piodermitë janë sëmundje ngjitëse të lëkures që shfaqet te foshnja e porsalindur,shpeshherë në formë epidemie, rreth ditës së 4-7- të. Shkaktohen nga bakteriet e sidomos nga staphylokoket dhe më rallë nga E.Coli, Proteus Mirabillis, Pseudomonas Aeruginosa.

Infeksionet e lekurës janë më të shpeshta tek të porsalindurit me reth 50% nga morbiditeti i përgjithshëm. Paraqiten në forma klinike të ndryshme,nga më e lehta Impetigo neonatorum (forma vesikulare), pastaj forma bulose ose Pemfigus neonatorum deri te forma më e rëndë Nekroliza Epidermale toxike. Mund edhe të komplikohen si Pneumoni, Septikemi, Osteomielit

dhe Enterit. Vesikulat apo bulat shfaqen kudo në trup, por më tepër në regjionet ingvinale, rreth kërthizes, në pjesën ekstensore të kofsheve, në sqetullat dhe në qafë. Sëmundjen mund ta përhapin mamitë, shërbyeset e reparteve të fëmijëve, nënat që vuajnë nga piodermitë dhe që janë në kontakt me foshnjat në mënyrë direkte ose indirekte me anën e teshave. Si burim infeksioni shërben edhe personeli mjekësor, i cili shpeshherë në mukozën e hundës strehon piokokë virulente. Prognoza mvaret nga faktori konstitucional si dhe nga gjendja nutritive dhe e përgjithshme e të porsalindurit.

QELLIMI I PUNIMIT

Eshte që ti paraqesim shkaqet më të shpeshta të infeksioneve të lekurës tek të porsalindurit,incidenca,si dhe ndieshmëria e tyre ndaj antibiotikëve.

MATERIALI DHE METODA E PUNES

Të ekzaminuarit janë fëmijë të porsalindur(mosha prej lindjes deri ne 28 dite) të mjekuar në repartin e Pediatrisë gjatë dy viteve 2022-2023 në spitalin "Dr.Ferid Murad" në Gostivar.Studimi është retrospektiv. Janë analizuar 80 fëmijë të porsalindur tek të cilët janë izoluar bakterie patologjike dhe njëkohësishtë është realize antibiogrami. Prej tyre 36 fëmijë të porsalindur kanë qenë me piodermi.

REZULTATET

Gjatë periudhes dy vjeçare në repartin e Pediatrisë në Gostivar janë mjekuar 98 fëmijë të porsalindur. Te 80 fëmijë janë izoluar bakterie patogjene.

Tab.1 Paraqesim infeksionet më të shpeshta në periudhen neonatale.

Lloji i infeksioneve	Të porsalindur me infeksione	%
Piodermi	36	45 %
Infeksione respiratore	32	40 %
Enterocolite	6	7,5 %
Sepsis neonatorum	6	7,5 %
Gjithsejt	80 të porsalindur me infeksione	100 %

Infeksionet më të shpeshta në këtë periudhë kanë qenë infeksionet e lekurës me 45%,mandej infeksionet respiratore me 40%

Tab.2 Tregon llojet e bakterieve tek infeksionet e lekurës.

Lloji i bakterieve	Të porsalindur me Piodermi	%
Staphyloc.Aureus	22	61 %
Staphyloc. Epidermidis	4	11
Escherichia Coli	6	17
Proteus mirabilis	2	5,5
Pseudomonas Aeruginosa	2	5.5
Gjithsejt	36	100%

Në ekzaminimin bakteriologjik më së shpeshti është izoluar stapylococcus aerius me 61%,mandej e.Coli me 17%,dhe më ralle Proteus Mirabilis dhe Pseudomonas Aeruginosa me nga 5,5%

Tab.3 Paraqesim ndieshmërin e bakteries Staphylococcus aureus ndaj antibiotikëve (antibiogrami)

Lloji i antibiotikëve	Te porsalindur me Piodermi	%
Cefalosporinët	25	70%
Makrolidet	26	72
Gentamicina	20	56
Vankomicini	34	94
Penicillini	1	2,8
Ampicilina	1	2,8
Orbenini	12	33%

Sipas antibiogramit bakteria Staphylococcus aerius ndieshmëri më të madhe tregoi ndaj Vankomicinës 94%,mandej ndaj Makrolideve 72% dhe Cefalosporinës me 70%.Ndjeshmëri më të vogël (rezistencë) tregoi ndaj Penicilinit dhe Ampicilinit.

DISKUTIMI

Sipas të dhënave tona konkludojmë se tek të porsalindurit më prezente kanë qenë infeksionet e lëkures me 45%,dhe se më së shpeshti është izolu bakteria Staphylococcus Aerius me 61% të rasteve.Mjekimi ka qenë me antibiotikë sipas antibiogramit dhe tretmanit lokal me eosin. Vesikulat dhe bulat hapen dhe lyhen me tretje aseptike. Mjekimi ka zgjate 7-10 ditë.

PERFUNDIMI

Rezultatet tona treguan se infeksionet e lëkurës tek të porsalindurit janë të shpeshta dhe atë me 45% krahasuar me numrin e përgjithshëm të morbiditetit neonatal.Rastet tona treguan se piodermitë mund të jenë edhe shumë serioze,por me tretman në kohë dhe

adekvat mund të sanohen dhe shërohen.Infeksionet janë zakonisht nozokomiale, brenda spitalore ,që meren me kontakt të drejtëpërdrejtë me material të ndryshëm që përdoren te fëmijët,pastaj nga higjiena jo e mirë e duarve të personelit,nëna etj.U vertetu se shkaktari më i shpeshtë qe Staphylococcus Aerius,prandaj është shumë me rëndësi parandalimi i këtyre infeksioneve dhe ate me respektimin e rregullave të përgjithshme higjieno sanitare.Repartet Pediatrike dhe ato të Neonatologjisë duhet të konsiderohen si salla operacioni.Çdo gjë që ka kontakt me të porsalindurin të jetë sterile.Mamia duhet të ketë nivel të lartë të higjienes.Personeli të mos vuan nga sëmundje qelbëzuese të lëkurës dhe izolimi i të porsalindurve që janë të dyshimtë se kane piodermi.

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Profesional paper

FORMAT MORFOLOGJIKE TË KOLELITIAZËS DHE NDIKIMI I TYRE NË ZHVILLIMIN E KOLECISTITIT

Agron Zuferi[1], Bekim Ismaili[2]

[1]Shërbimi Kirurgjikal, Spitali i Përgjithshëm Gostivar Maqedonia e Veriut
[2]Universiteti i Tetovës

Email: azuferi@yahoo.com

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ABSTRAKT

Qëllimi i këtij studimi është të analizojë format morfologjike të kolelitiazës dhe ndikimin e tyre në zhvillimin e kolecistitit akut dhe kronik. Studimi është realizuar në shërbimin kirurgjikal të Spitalit të Përgjithshëm Gostivar. Janë përfshirë 120 pacientë të diagnostikuar me kolelitiazë gjatë periudhës 2022–2024. U analizuan përbërja kimike dhe morfologjia e gurëve, si dhe lidhja e tyre me llojin e kolecistitit. Rezultatet treguan se gurët pigmentorë dhe me sipërfaqe të ashpër lidhen më shpesh me kolecistit akut, ndërsa gurët kolesterolikë të lëmuar me forma kronike. Studimi nënvizon rëndësinë e analizës morfologjike të gurëve në parashikimin e komplikimeve biliare dhe në planifikimin e trajtimit kirurgjikal.

Fjalë kyçe: kolelitiazë, kolecistit, gurë biliare, morfologji, inflamacion.

HYRJE

Kolelitiaza përbën një ndër sëmundjet më të zakonshme të traktit biliar, me prevalencë të lartë në popullatën adulte. Ajo rezulton nga çrregullime në përbërjen e bilës, stazë biliare ose infeksione të traktit biliar. Ndër faktorët kryesorë etiologjikë përfshihen: mbingopja me kolesterol, prania e bilirubinatit të kalciumit dhe ndryshimet në funksionin e fshikëzës biliare. Kolecistiti, si pasojë inflamatore e obstruksionit të duktusit cistik nga gurët, përfaqëson komplikacionin më të shpeshtë të kolelitiazës.

MATERIAL DHE METODA

Studimi është realizuar gjatë periudhës 2022–2024 në Shërbimin Kirurgjikal të Spitalit të Përgjithshëm Gostivar dhe janë përfshirë 120 pacientë të diagnostikuar me kolelitiazë dhe kolecistit, të cilët janë trajtuar kirurgjikisht. Analiza u krye mbi karakteristikat morfologjike dhe përbërjen kimike të gurëve biliare. Parametrat kryesorë të studiuar ishin: forma, ngjyra, struktura e sipërfaqes dhe lidhja e tyre me llojin e kolecistitit. Të dhënat u përpunuan në mënyrë analitike

përmes vlerësimit përqindor dhe korrelacionit klinik.

REZULTATE

Lloji i gurit	Përqindja (%)	Forma mbizotëruese	Lloji i kolecistitit
Kolesterolikë	58	Ovale / të lëmuara	Kolecistit kronik (60%)
Pigmentorë	25	Të parregullta	Kolecistit akut (72%)
Të përzier	17	Shtresuar	Kolecistit kronik (45%)

Rezultatet tregojnë se gurët me sipërfaqe të ashpër dhe pigmentorë kanë prirje më të madhe për të shkaktuar kolecistit akut, ndërsa gurët e lëmuar, kolesterolikë, lidhen me kolecistit kronik. Vërehet një korrelacion i dukshëm midis formës së gurëve dhe llojit të inflamacionit të murit të fshikëzës biliare.

DISKUTIM

Rezultatet e këtij studimi janë në përputhje me të dhënat ndërkombëtare që theksojnë rolin e morfologjisë së gurëve në patogjenezën e kolecistitit. Gurët pigmentorë, të cilët shpesh kanë përbërje të bilirubinatit të kalciumit dhe sipërfaqe të ashpër, shkaktojnë obstruksion të duktusit cistik dhe inflamacion akut. Në të kundërt, gurët kolesterolikë me strukturë të lëmuar dhe homogjene janë të lidhur me forma kronike të kolecistitit. Këto gjetje konfirmojnë nevojën për klasifikim morfologjik gjatë trajtimit kirurgjikal, pasi forma dhe përbërja e gurit mund të ndihmojnë në parashikimin e rrjedhës klinike.

PËRFUNDIME

Forma morfologjike e gurëve biliare ndikon drejtpërdrejt në zhvillimin e kolecistitit akut dhe kronik.

Gurët pigmentorë dhe me sipërfaqe të ashpër lidhen më shpesh me kolecistit akut.

Gurët kolesterolikë të lëmuar lidhen me kolecistit kronik.

Analiza morfologjike mund të ndihmojë në parashikimin e komplikimeve dhe në zgjedhjen e strategjisë kirurgjikale.

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Review

PËRDORIMI I PLAZMËS SË PASUR ME TROMBOCITE (PRP) NË LEZIONET MUSKULOSKELETALE

Albana Ahmeti

Corresponding Author: Albana Ahmeti, MD
E-mail: albana.ahmetti@gmail.com

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ABSTRAKTI

Lëndimet e sistemit muskuloskeletal janë një shqetësim i zakonshëm në sport, duke prekur atletët në të gjitha nivelet dhe duke rezultuar në përkeqësim të performancës dhe rehabilitim të zgjatur. Këto lëndime përfshijnë tendinat, ligamentet, muskujt, kërcin dhe inde të cilat kanë aftësi të kufizuara shëruese. Trajtimet tradicionale, duke përfshirë pushimin, terapinë fizike, medikamentet anti-inflamatore dhe kirurgjinë, nuk tregojnë gjithmonë rezultate optimale, veçanërisht për lëndimet me shërim të ngadaltë ose dhimbje të përsëritura.

Përparimet e fundit në mjekësinë rigjeneruese, veçanërisht injeksionet e plazmës së pasur me trombocite (PRP), janë shfaqur si një alternative premtuese për përmirësimin e riparimit dhe rigjenerimit të indeve.

Ky rishikim përmbledh përparimet në trajtimin me PRP për sëmundjet e lidhura me lëndimet sportive dhe çështjet përkatëse.

Fjalë kyçe; Plazma e pasur me trombocite (PRP), Sistemi muskuloskeletal, Mjekësia rigjeneruese, Mjekësia sportive, Qelizat staminale.

HYRJE

Sistemi muskuloskeletal (MSK) është një njësi dinamike dhe shumëfunksionale e trupit të njeriut që përbëhet nga eshtrat, ligamente, indi lidhës dhe tendinat, të cilat funksionojnë për të mbështetur trupin dhe për të ndihmuar në lëvizjen fizike. Si të tilla, dëmtimet në sistemin muskuloskeletal, duke përfshirë grisjet muskulare, fasciitin plantar, ndrydhjet e kyçit të këmbës, tendinopatinë e Akilit dhe dëmtimet e gjurit mund të shoqërohen me ndikime signifikante në aktivitetet e përditshme të një individi. Dëmtimet e muskujve janë të zakonshme në sporte dhe çojnë në paaftësi me kalimin e kohës.

Standardet aktuale të trajtimit për dëmtimet e sistemit muskuloskeletal përfshijnë përdorimin e agjentëve farmaceutikë, injeksioneve kortikosteroide, suplementet dhe kirurgji. Ndërsa këto qasje janë treguar të jenë efektive për disa pacientë si në afat të shkurtër ashtu edhe në atë afatgjatë, ato mund të shoqërohen me përmisim të limituar të simptomave, efekte negative dhe reduktim të aktiviteteve të jetës së përditshme. Disa ndërlikime të mundshme përfshijnë dëmtimin e organeve të shkaktuar nga barnat anti-inflamatore josteroide, përfitimet e kufizuara dhe përdorimet afatgjatë të injeksioneve kortikosteroide si dhe gjakderdhjen dhe ridëmtimin e shkaktuar nga operacionet kirurgjike. Qasjet më efektive si terapia fizike dhe trajtimet psikologjike janë provuar të jenë efektive në ofrimin e lehtësimit afatgjatë të dhimbjes dhe përmirësimeve në cilësinë e përgjithshme të jetës, por mund të kërkojnë angazhim më të gjatë kohor [1].

Injeksionet kortikosteroide aktualisht përdoren për të trajtuar lezione të shumta në sistemin muskuloskeletal. Bazuar në hulumtimet aktuale, injeksionet steroide

mbeten efikase vetëm për një mesatare prej tre muajsh dhe kanë efekte anësore të rëndësishme në organizëm [2].

Hulumtimet shkencore mbi agjentët farmaceutikë si aspirin, acetaminofen, oksikodon dhe substanca të tjera që modifikojnë dhimbjen kanë një rëndësi signifikante. Për shembull, barnat anti-inflamatore josteroide rrisin incidencën e toksicitetit renal dhe hepatik, gjakderdhjeve gastrointestinale dhe problemeve kardiovaskulare, ndërsa medikamentet opioide çojnë në rritjen e incidencës së konstipacionit, çrregullimeve të varësisë mendore, tolerancës, depresionit respirator dhe vdekjes [3, 4].

Këto efekte anësore kufizojnë përdorimin e këtyre barnave në praktikat klinike dhe kështu paraqesin një kufizim për popullatën e pacientëve që mund të trajtohen, duke hapur një mundësi për terapi alternative që modifikojnë dhimbjen.

Opsionet e trajtimit që po hulumtohen përfshijnë plazmën e pasur me trombocite (PRP). Surgjerohet që ky trajtim përmirëson cilësinë e jetesës së një individi, ruan efikasitetin afatgjatë dhe shoqërohet me më pak efekte anësore në krahasim me trajtimet standarde të kujdesit në lëndimet e shumta të sistemit muskuloskeletal si fasciiti plantar, tendinopatia e Akilit, dëmtimet akute të muskujve, lëndimet e gjurit dhe ligamenteve si dhe nekroza avaskulare e femurit [5].

Plazma e pasur me trombocite (PRP)

Plazma e pasur me trombocite (PRP) është një koncentrat trombocitesh, i nxjerrë nga gjaku i pacientit, i cili aktivizohet për të liruar faktorë rritjeje dhe citokina. Ky produkt ka treguar potencial për të reduktuar proceset inflamatore dhe për të përmirësuar sintezën e proteinave në indet e dëmtuara duke ndihmuar në rigjenerim. Efektiviteti i supozuar i PRP-së rrjedh nga faktorët e tij të rritjes, siç janë faktori i rritjes i derivuar nga trombocitet, faktori transformues beta, dhe faktorët e rritjes të ngjashëm me insulinën, si dhe aftësia për të rritur furnizimin me gjak në zonën e prekur [6]. PRP ofron një qasje minimale invasive për të rikthyer funksionin e kyçeve, lëvizshmërinë dhe për të rivendosur mekanizmat homeostatikë të trupit, duke stimuluar sintezën e kolagjenit tip II dhe vaskularizimin, duke restauruar acidin hialuronik dhe duke reduktuar inflamacionin. PRP gjithashtu ofron një mënyrë minimale invazive për trajtimin e dëmtimeve, duke zvogëluar efektet anësore të mundshme që trajtimet invazive aktuale mund të kenë për pacientët [7].

Ekziston nevoja në menaxhimin e dëmtimeve muskuloskeletale për të identifikuar opsione trajtimi që jo vetëm janë efektive, por gjithashtu lidhen me efekte anësore më të vogla dhe rikuperim më të shpejtë në aktivitetet e përditshme dhe rikthimin në aktivitet fizik. Aktualisht, terapitë farmakologjike të përdorura për trajtimin e dëmtimeve muskuloskeletale kanë disavantazhe dhe efekte anësore negative, duke përfshirë tolerancën, varësinë dhe toksicitetin [1]. Prandaj, është e domosdoshme një qasje alternative në trajtim. PRP ka treguar përfitime pa shkaktuar efektet anësore krahasuar me agjentët farmaceutikë aktualë dhe është lidhur me një rikuperim më të shpejtë në aktivitetet e përditshme dhe rikthimin në sport [8].

Komponentet e PRP

PRP përmban tre lloje kryesore të granuleve sekrecionuese: granule α, të cilat përmbajnë shumë faktorë rritjeje (GF) dhe citokina, granule të dendura α, të cilat lirojnë serotonin, polifosfate, kalcium, adenosine trifosfat (ATP) dhe adenosin difosfat (ADP) dhe lizosoma, të cilat përmbajnë enzima të ndryshme hidrolitike [9]. Si pjesë e procesit të shërimit të indeve, faktorët e rritjes (GFs) dhe citokinat luajnë role të rëndësishme si atraktantë për migrimin e qelizave, stimulues të proliferimit të qelizave dhe mitogjenë për të nxitur shërimin e indeve [10].

Aplikimi klinik i PRP-së në dëmtimet e ligamenteve, muskujve dhe tendinave

Tendinat janë një komponent kyç i sistemit motorik. Dëmtimet akute dhe kronike të tendinave trajtohen shpesh në mjekësinë sportive dhe praktikat ortopedike dhe zakonisht janë pasojë e ngarkesave të tepruara dhe të përsëritura. Për shkak të furnizimit të dobët me gjak dhe rigjenerimit të kufizuar, tendinat dhe ligamentet e dëmtuara shërohen ngadalë dhe jo plotësisht. Procedura e shërimit që përfshin proliferimin e qelizave dhe prodhimin e matriksit extracelular është e ngadalshme dhe çon në formimin e indit të pasur me kolagjen, i cili ka veti mekanike të papërshtatshme dhe e bën tendinën e shëruar të ndjeshme ndaj dëmtimeve të tjera [11,12]. Qelizat staminale të tendinave përgjigjen ndaj shumë stimuluesve biomekanikë dhe biokimikë dhe mund të diferencohen në tenocite dhe të proliferohen, duke lejuar që ato të luajnë një rol të rëndësishëm në rigjenerimin e tendinave. Studime të mëparshme kanë treguar se PRP i aktivizuar mund të stimulojë proliferimin e qelizave staminale, prodhimin e tenociteve dhe kolagjenit të mjaftueshëm [12].

Dëmtimet e muskujve janë të shpeshta, dhe rikuperimi i funksionit është jo i plotë për shkak të fibrozës. Studimet kanë treguar se faktori transformues beta brenda PRP-së jo vetëm që stimulon rigjenerimin e muskujve, por gjithashtu redukton ndjeshëm fibrozën [13].

Dëmtimet akute të muskujve dhe injektimi i plazmës të pasur me trombocite (PRP)

Hulumtuesit kanë treguar se PRP mund të ndikojë pozitivisht në një sërë dëmtimesh siç janë çarja e tendinave, dëmtimi i kërcit dhe tendosjet e ligamenteve. Ata synuan të studiojnë efektet e PRP-së në rikthimin në aktivitet pas një dëmtimi akut të muskujve nga sportet rekreative dhe konkurruese tek atletët dy vjet pas dëmtimit. Hulumtimi u përqendrua në tendosjet e muskujve të kofshës, gastroknemius dhe kuadriceps duke matur katër faktorë: (a) koha për t'u rikthyer në aktivitet nga data e dëmtimit deri në ditën kur arrihet gama e plotë e lëvizshmërisë (b) përmirësimi i forcës dhe aftësive funksionale pa dhimbje apo dhimbje të ngurtësuar (c) shkalla e përgjithshme e dhimbjes dhe (d) norma e rikthimit të dëmtimeve apo tendosjeve pas 12 dhe 24 muajsh. Hulumtuesit gjetën se PRP pati një ndikim signifikant në shkurtimin e kohës për të u rikthyer në sport [14].

Fasciiti plantar dhe injektimi i PRP

Fasciiti plantar është një problem shumë i zakonshëm tek vrapuesit dhe atletët e tjerë. Studimet sugjerojnë se PRP, në kombinim me ushtrimet e zgjatjes dhe forcës është më efektiv se injeksionet e kortikosteroideve për shkak të tendencës së qëndrueshme për lehtësim të dhimbjes, përmirësim të cilësisë së jetës dhe ulje të rreziqeve që lidhen me injeksionet më pak të përsëritura. Megjithatë, janë të nevojshme studime të ardhshme për të përcaktuar efektet afatgjata, efektet anësore të injeksionit PRP dhe krahasimin e përdorimit të PRP-së pa ushtrime të shoqëruara [15].

Lezionet e gjurit dhe injektimi i PRP

Lezionet kondrale kanë një shkallë të ulët të shërimit dhe rigjenerimit të kërcit fibroz krahasuar me kërcin hialin dhe për këtë arsye këto dëmtime janë të vështira për të u trajtuar, duke shkaktuar ulje të aktivitetit fizik dhe degjenerim të hershëm të kërcit. Trajtimi aktual për dëmtimet kondrale të gjurit është kirurgjia, e cila lë kërcin më të brishtë, më të dobët dhe nuk parandalon degjenerimin. Aktualisht, PRP po shqyrtohet si një mundësi alternative trajtimi. Atributet rigjeneruese të PRP-së, përfshirë rritjen e sintezës së kolagjenit tip II, rregullimin biologjik të homeostazës, restaurimin e acidit hialuronik, uljen e inflamacioneve dhe induktimin e kondo-gjenezës së qelizave staminale mezenkimale të cilat mund të nxisin procesin e shërimit të dëmtimeve kondrale dhe të zvogëlojnë dhimbjen nga dëmtimet si tendinopatia dhe osteoartriti. PRP ka potencialin të përmirësojë homeostazën e artikulacioneve, të zvogëlojë inflamacionin e indit sinovial dhe të rrisë cilësinë e lëngut sinovial krahasuar me kirurgjinë [16].

Dëmtimi akut i muskujve Hamstring dhe injektimi i PRP

Opsionet aktuale të trajtimit që përdoren më shpesh për dëmtimet akute të muskujve hamstring përfshijnë pushimin, akullin, kompresionin dhe ngritjen, medikamentet anti-inflamatore, programet e rehabilitimit dhe trajtimet elektoterapeutike. Hulumtuesit vlerësuan përdorimin e PRP për dëmtimet akute të muskujve hamstring. Konkretisht, hulumtuesit synuan të përcaktonin se si një injeksion i vetëm PRP, në kombinim me një program rehabilitimi, do të ndikonte në rikthimin në aktivitetin sportiv të atletëve pas dëmtimit të muskujve, krahasuar me programin e rehabilitimit pa përdorur PRP. Pacientët që morën një injeksion të vetëm PRP së bashku me një program rehabilitimi u rikuperuan më shpejt sesa pacientët që ndoqën vetëm programin e rehabilitimit pa përdorur PRP [17].

Lëndimi i ligamenit kolateral medial te gjurit (MCL) dhe injektimi i PRP

Një nga dëmtimet më të zakonshme të ligamenteve të gjurit, dëmtimi i ligamentit MCL, ka treguar përfitime nga terapia me PRP. Në një studim, pacientët morën tri injeksione të serisë me PRP, të pasuara nga ushtrime për rritjen e lëvizshmërisë dhe ushtrime progresive me ngarkesë rezistente. Rezultatet e këtij studimi sugjerojnë se përdorimi i PRP përmirësoi dhimbjen, ngurtësinë, ndjeshmërinë, stabilitetin e ecjes dhe ecjen me peshë pa dhimbje. Këto gjetje janë të rëndësishme sepse tregojnë se injeksioni intra-artikular i PRP për dhimbjet e pakontrollueshme pas një dëmtimi të ligamentit kolateral medial të gjurit mund të përmirësojë raportet subjektive të funksionit deri në gjashtë muaj pas trajtimit [18].

METODOLOGJIA

Artikulli përbën një rishikim të literaturës, i cili mbështetet në hulumtime dhe informacione shkencore nga burime të ndryshme, të cilat janë të gjitha të përmendura dhe të cituara në listën e referencave.

REZULTATET

Gjatë hulumtimeve të bëra është konstatuar se PRP ka një ndikim të rëndësishëm në zvogëlimin e kohës së pritjes për rikthim në aktivitetin fizik të pacientëve falë përbërësve si faktorët e rritjes dhe citokinat që luajne rol signifikant në procesin e shërimit të indeve. Në hulumtimet e mëtutjeshme është konstatuar gjithashtu se përdorimi i injeksioneve të PRP të kombinuara me programe rehabilitimi dhe ushtrime për rritjen e lëvizshmërise dhe forcës rezulton me efikasitet më të madh se sa përdorimi i programeve të rehabilimit dhe ushtrimeve fizike si opsion terapeutik i vetëm. Megjithëse rezultatet për përdorimin e injeksioneve të PRP duken premtuese, hulumtime shtesë janë të nevojshme në kuptimin e efekteve anësore të mundshme, protokolleve optimale të trajtimit dhe rreziqeve potenciale të terapisë me PRP.

DISKUTIMI DHE KONKULZIONI

Plazma e pasur me trombocite (PRP) është një opsion terapeutik revolucionar në mjekësinë rigjeneruese ku me ndihmën e faktorëve natyralë të rritjes që gjenden në gjakun e pacientit promovohet shërimi i indeve të dëmtuara. Një avantazh kyç i injeksioneve të PRP është reduktimi i nevojës për përdorimin e trajtimeve tradicionale si barnat anti-inflamatore, injeksionet kortikosteroide dhe operacionet kirurgjikale të cilat jo gjithmonë tregojnë rezultate optimale në lëndimet muskuloskeletale, madje rezultojnë ne një shkallë të lartë të efekteve anësore. Hulumtimet e shumta kanë konstatuar efikasitetin e aplikimit klinik të injeksioneve PRP në dëmtimet e ligamenteve, muskujve dhe tendinave duke pasur parasysh edhe koston e ulët dhe rreziqet minimale të këtij trajtimi.

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Review

THE USE OF ANTERIOR-SEGMENT OPTICAL-COHERENCE TOMOGRAPHY FOR THE ASSESSMENT OF THE IRIDOCORNEAL ANGLE AND ITS ALTERATIONS – LITERATURE REVIEW

Hristijan Duma[1,2]

[1]University clinic of eye diseases, Skopje, Rep. of North Macedonia
[2]University of Ss. Cyril and Methodius, Faculty of Medicine, Skopje

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ABSTRACT

The iridocorneal angle is a very important structure of the eye that has several important functions for the normal functioning of the eye. All the structures that form the iridocorneal angle are microstructures that require the use of different devices to visualize them.

Although gonioscopy remains the gold standard for visualizing and clinically evaluating the iridocorneal angle, anterior segment optical coherence tomography is increasingly playing an important role in the diagnosis and treatment of diseases that occur in the iridocorneal angle.

The advantages of this method are numerous, such as fast recording without contact with the patient's eye, the possibility of documenting and further processing the images. Also, the use of artificial intelligence through optical coherence tomography of the anterior segment provides the doctor with support for more accurate diagnosis and treatment of diseases.

The disadvantage of this method is that the doctor or technician who interprets this method must possess technological skills and good knowledge of this method, as well as the cost of the device itself, which not every health institution can afford.

Key words: Iridocorneal angle, Optical coherence tomography, Anterior segment.

INTRODUCTION

Although gonioscopy is currently the gold standard for clinical assessments and diagnoses of angle closure, being also characterized by the unique advantage of allowing a dynamic evaluation of the iridocorneal angle, it is an observer-dependent technique and, thus, is subject to intrinsic intra- and inter-individual variability. Furthermore, it may be challenging and uncomfortable for the patient, as it includes physical contact between the gonioscopic lens and the corneal surface. To overcome these limitations, anterior-segment optical-coherence tomography (AS-OCT) has recently emerged as an objective and noninvasive method to assess the anterior chamber and iridocorneal-angle anatomy. [1,2,3]

Anatomy of the iridocorneal angle

The iridocorneal angle is an anatomical space located between the peripheral part of the cornea and the anterior part of the iris. It forms the boundary between the anterior chamber of the eye and a structure known as the trabecular meshwork system, which is part of the drainage system for the aqueous humor. Major Anatomical Structures:

Trabecular meshwork: A network of lamellar trabeculae through which aqueous humor is filtered before entering the canal of Schlemm. It is responsible for most of the

drainage of intraocular fluid. Canal of Schlemm: A circular canal that receives fluid from the trabecular meshwork and carries it to the venous system of the eye. Obstruction in its function leads to increased intraocular pressure.

Scleral spur: A fibrous-bony structure that serves as an attachment point for the ciliary body and the trabecular meshwork. It plays an important role in maintaining the stability of the drainage apparatus.

Ciliary body: Structure responsible for the production of aqueous humor, but also for some parts of its drainage.

Schwalbe's line: Anatomical line that marks the end of Descemet's membrane and the beginning of the trabecular meshwork. It is an important landmark during gonioscopy.

Sampaolesi's Line: The Sampaolesi's line is a pigmented line and is most often found only in the lower part of the angle of the ventricle, in front of the Schwalbe ring in some eyes. [4,5,6]

MATERIAL AND METHODS

For material and methods, we used various sources to collect materials that we analyzed and processed. All of these sources are from evidence-based medicine.

Relevant AS-OCT Parameters

1. AS-OCT Parameters Concerning the Anterior Chamber in Its Entirety

The anterior chamber depth (ACD) is defined as the maximum distance from the corneal endothelium to the anterior surface of the lens, as shown in Figure 1A. In their study, Sng and colleagues reported that the two variables affecting ACD values the most were the lens vault (LV) and the posterior corneal arc length (PCAL) [7]. The LV is defined as the distance from the anterior pole of the lens to the horizontal line connecting the two scleral spurs (SSs), with the SS being defined as the point at which the curvature of the inner surface of the angle wall changes noticeably (often looking as an inward protrusion of the sclera), as shown in Figure 1B [8]. The PCAL is defined as the arc distance of the posterior corneal border between scleral spurs [8]. It has been previously shown that ACD is inversely correlated with age and hyperopic refractive errors [10,11,12], and that decreasing ACD is often associated with primary-angle closure (PAC) [12].

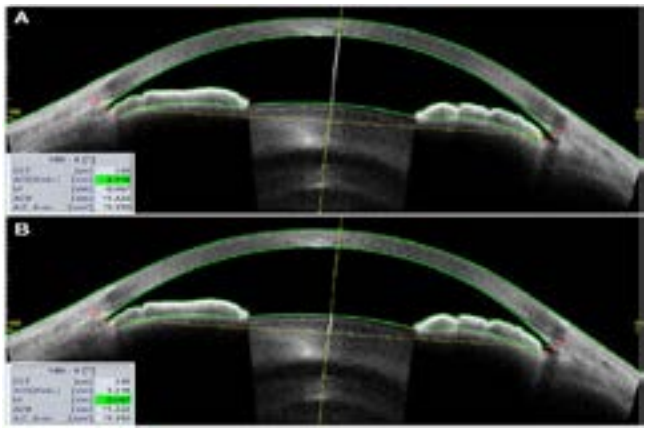

Figure 1. Tomey Casia 2 AS-OCT scan (Nagoya, Japan) of a patient with a narrow angle. (A) The white, bold vertical line from the corneal endothelium to the anterior surface of the lens corresponds to the anterior chamber depth (ACD), measuring 2.218 mm in the case reported, as shown in the bottom left table (green highlighted cell). (B) The white, bold vertical line from the anterior surface of the lens to the horizontal scleral-spur-to-scleral-spur line corresponds to the lens vault (LV), measuring 0.567 mm in the same patient.

Other AS-OCT parameters featuring the AC in its entirety are the anterior chamber width (ACW), area (ACA), and volume (ACV). ACW is defined as the horizontal line corresponding to the scleral-spur-to-scleral-spur distance, as shown in Figure 2A [11]. The ACA is defined as the area delimited by the corneal endothelium anteriorly, and the anterior iris/lens surface posteriorly (Figure 2B,C). The ACA shows inverse correlation to age, while it is directly correlated to the ACD and axial length [10,11,12]. It is unclear whether the ACA has any correlation with the central corneal thickness, as some studies reported inverse correlation between the two parameters [12], whereas others did not [15]. Automated algorithms incorporated into modern AS-OCT devices calculate the ACV based on the ACA acquired through multiple AS-OCT scans to give a three-dimensional measurement of the AC.

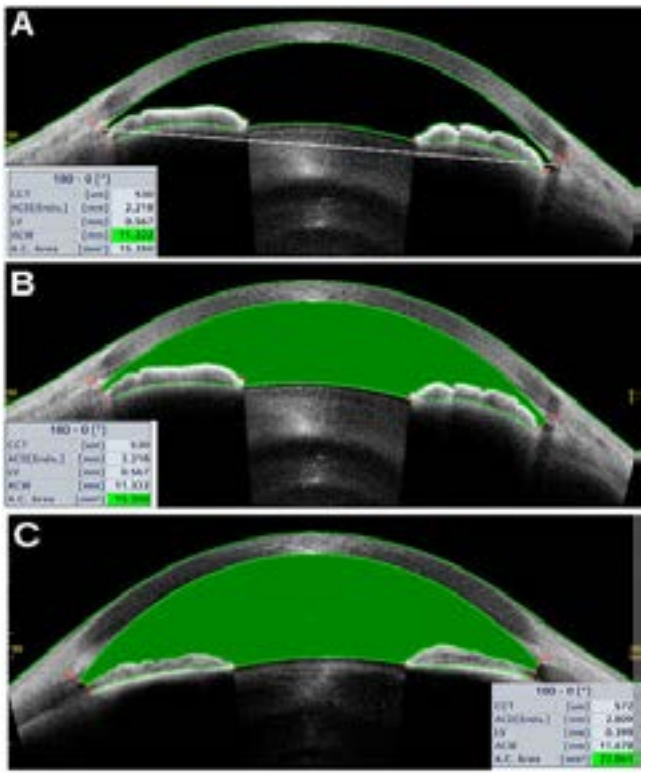

Figure 2. Tomey Casia 2 AS-OCT scans (Nagoya, Japan). (A) The white, bold horizontal line corresponding to the scleral-spur-to-scleral-spur line shows the anterior chamber width (ACW) and measures 11.322 mm in this patient with narrow angles. (B) The green area, delimited by the corneal endothelium anteriorly, and the anterior surface of the iris and lens posteriorly, corresponds to the anterior chamber area (ACA) and measures 15.35 mm2 in the same patient with narrow angles. (C) The ACA from a patient with open angles.

2. AS-OCT Parameters Focusing on Iridocorneal Angle Structures

Parameters of the Iridocorneal Angle

Angle Opening Distance (AOD) The distance between the corneal endothelium and the anterior iris surface, measured on a line perpendicular to the trabecular meshwork at a fixed distance (commonly 500 µm (AOD500) or 750 µm (AOD750)) from the scleral spur. Clinical Use: Quantifies how "open" the angle is.

Trabecular–Iris Space Area (TISA) The trapezoidal area bounded anteriorly by AOD500 or AOD750, posteriorly by a line from the scleral spur perpendicular to the inner scleral wall, superiorly by the inner corneoscleral wall, and inferiorly by the iris surface.

Angle Recess Area (ARA) Triangular area bordered by the angle recess, corneal endothelium, and anterior iris surface.

Trabecular–Iris Angle (TIA) The angular measurement formed at the iris recess between the inner corneoscleral wall and iris surface.

Scleral Spur Visibility Whether the scleral spur is seen (required as a landmark for most measurements). Grading: Fully visible, partially visible, or not visible.

Anterior Chamber Angle Width Some devices also measure this directly in degrees.

Comparison between AS-OCT and Gonioscopy

AS-OCT

A non-contact, high-resolution imaging technique using low-coherence interferometry to visualize cross-sectional anterior segment structures.

- Advantages: Non-contact – No need to touch the eye (better for infection control and patient comfort). Objective, reproducible images – Provides quantitative measurements of angle structures (e.g., angle opening distance, trabecular-iris space area). High-resolution detail of cornea, anterior chamber, iris, and angle. Documentation – Images can be archived and compared over time. Useful in opaque corneas (e.g., corneal edema), where gonioscopy visualization is limited.

-Limitations:

Cannot visualize pigmentation, fine structures like Schlemm's canal, or angle neovascularization. May underestimate angle width compared to gonioscopy. Cannot assess functional aspects like dynamic indentation. Expensive equipment.[17]

Gonioscopy

A contact clinical examination with a goniolens and slit lamp to inspect the angle.

-Advantages:

Direct visualization of anatomical landmarks (Schwalbe's line, trabecular meshwork, scleral spur, ciliary body band). Allows assessment of pigmentation, neovascularization, synechiae, angle recession, and other pathologies. Dynamic gonioscopy – Indentation to distinguish appositional vs. synechial closure. Inexpensive and accessible.

-Limitations:

Subjective and operator-dependent – Requires experience

and skill. Contact procedure – Discomfort and infection risk. No automatic documentation unless using a goniophotography attachment. [17,18,19]

Feature	AS-OCT	Gonioscopy
Contact / Non-contact	Non-contact	Contact
Visualization	Cross-sectional image, no pigmentation	Direct view of all angle structures
Quantification	Objective angle measurements	Subjective grading
Dynamic Assessment	Not possible	Possible (indentation gonioscopy)
Use in corneal opacity	Possible	Often limited
Skill Required	Less dependent on examiner	Highly examiner-dependent
Cost	High	Low

Gonioscopy remains the gold standard for qualitative assessment of the angle. AS-OCT is an excellent complementary tool, especially for: documenting angle anatomy quantitatively.

DISCUSSION AND CONCLUSION

Increasing evidence supports the use of AS-OCT to evaluate the anatomical details of the anterior chamber with a specific focus on the iridocorneal angle. This tool seems particularly helpful in the clinical assessment and follow-up of patients with angle closure and other angle anomalies.

On the one hand, AS-OCT makes it possible to acquire detailed images of the angle anatomy, which, with complimentary gonioscopic examination, may support clinicians in diagnosing iridocorneal-angle alterations and, therefore, eventually help them to determine whether any treatment is needed. On the other hand, AS-OCT scans may provide objective proof of the laser- or surgical-treatment outcomes, and may allow a more accurate follow-up with patients with angle abnormalities.

However, the above-mentioned AS-OCT advantages are counterbalanced by some limitations, which may explain why this technology is still considered a promising and helpful tool but not the gold standard.

First, AS-OCT only provides a static evaluation of the angle anatomy, whereas gonioscopy remains the only diagnostic procedure allowing its dynamic evaluation.

Second, technical limitations may affect, at least partially, the current clinical usefulness of AS-OCT. With the future advent of more sophisticated technology, the AS-OCT may provide more precise and detailed information about the anterior-segment anatomy, and this will hopefully improve the capacity of identifying iridocorneal-angle structures and detecting related anomalies.

Finally, although an increasing number of AS-OCT parameters may help us to better understand the anterior-chamber anatomy and its relationship to angle-closure disease, this may generate some confusion in evaluations of AS-OCT scans. Furthermore, it needs to be taken into account that at least some of the AS-OCT parameters may not show clinical significance and may go out of fashion in the coming years.

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Review

''КЛИНИЧКИ ГРЕШКИ ВО ДИЈАГНОСТИЦИРАЊЕТО НА РЕНАЛНА КОЛИКА И АКУТЕН АПЕНДИЦИТ –ПРЕГЛЕД НА ЛИТЕРАТУРА''

Валон Адеми[1], Иван Аргиров[1], Берат Далипи[1], Фати Ебиби[1], Радомир Гелевски[1]

[1]ЈЗУ Општа болница – Куманово

Email: valon_ademi@hotmail.com

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АБСТРАКТ

Вовед: Акутната болка во десната страна на абдомен претставува занчаен дијагностички предизвик за лекарите од ургентен центар, хирузите и уролозите. Реналната болка и акутниот апендицит често манифестираат слични клинички симптоми на болка, што резултира со терапевтско доцнење, непотребни радиодиганостички методи и во одредени случаи, непотребни хируршки интервенции.

Матријал и методи: Во нашата студија истражувавме литература објавени во период 2000-2024, поврзани со акутниот апендицит и реналната колика, спроведено фокусирање на неколку бази на податоци како што се Pub Med, Google Scholar, Medline, Scopus и PMC free article, кои содржат различни студии кои ги анализират најчестите клинички, лабораториски и радиолошки грешки и различни алгоритми и стратегии за дијагностицирање на ренална колика и акутен апендицит.

Дискусија: Истражувањата покажуваат дека делумната интерпретација на клиничките податоци значително придонесуваат кон дијагностички грешки помеѓу ренална колика и акутниот апендицит. Систематската проценка на симптомите, интеграцијата на лабораториските параметри и рационалната примена на радиолошките методи значително го намалуваат ризикот за погрешна дијагноза. Прекумерното фокусирање на локализацијата на болката или на уринарните симптоми (дисурија), која не е ексклузивна само за уретерални камења или леукоцитозата кои може да биде присутна кај двете патологији. Кај радиолошките грешки најчеста е фокусирање само во абдоминалната ултрасонографија која е со ограничена сензитивност кај обезните пациенти или кај оние со изразена интестинална гасна дистензија.

Заклучок: Акутната болка во десниот абдоминален регион бара структуриран и внимателен дијагностички пристап. Примена на алгоритмите „Clinical red flags“, „Stone score“ и Mantrels/Alvarado, како и раната мултидисциплинарна консултација, претставуваат најефективни стратегии за минимизирање на дијагностичките грешки.

Клучни зборови: Акутен апендицит, ренална колика, дијагностички грешки.

ВОВЕД

Акутната болка во десната страна на абдомен претставува занчаен дијагностички предизвик за лекарите од ургентен центар, хирузите и уролозите. Реналната болка и акутниот апендицит често манифестираат слични клинички симптоми на болка, што резултира со терапевтско доцнење, непотребни радиодиганостички методи и во одредени случаи, непотребни хируршки интервенции. Во овој труд ќе ги анализираат најчестите клинички, лабораториски и радиолошки грешки, како и стратегиите за подобрување на раната дијагноза. Иако патофизиологијата на двете состојби е различна, клиничката презентација често се преклопува, особено кај пациенти со атипични симптоми. Литературата известува дека до приближно

~10% од пациентите со почетна дијагноза ренална колика резултираат да имаат алтернативна етиологија (вклучувајќи апендицит).(1,2) Предоперативната дијагноза на акутен апендицит носи ризик од негативна апендектомија – во различни серии стапката на негативна апендектомија (negative appendectomy rate, NAR) варира и често се наоѓа во опсегот приближно 5–20%, при што кај жените и кај млади пациенти NAR обично е повисока отколку кај мажите.(3,4,5)

МАТРИЈАЛ И МЕТОДИ

Во нашата студија истражувавме литература објавени во период 2000-2024, поврзани со акутниот апендицит и реналната колика, спроведено фокусирање на неколку бази на податоци како што се Pub Med, Google Scholar, Medline, Scopus и PMC free article, кои содржат различни студии кои ги анализират најчестите клинички, лабораториски и радиолошки грешки и различни алгоритми и стратегии за дијагностицирање на ренална колика и акутен апендицит. Податоците се класифицирани во три типови дијагностички грешки: клинички, лабораториски и радиолошки грешки. Во клиничките грешки се опфатени локализацијата на болката, однесувањето на пациентот и придружните симптоми. Лабораториските грешки ги опфаќаат: хематурија, леукоцитоза и зголемен С-реактивен протеин (CRP). Радиолошките грешки се поврзани со ултрасонографијата, нативен ртг на уринарен тракт, компјутерската томографија (CT) без контраст и компјутерската томографија (CT) со контраст.

ДИСКУСИЈА

Истражувањата покажуваат дека делумната интерпретација на клиничките податоци значително придонесуваат кон дијагностички грешки помеѓу ренална колика и акутниот апендицит. Систематската проценка на симптомите, интеграцијата на лабораториските параметри и рационалната примена на радиолошките методи значително го намалуваат ризикот за погрешна дијагноза. Честа клиничка грешка е прекумерното фокусирање на локализацијата на болката, Имајќи предвид дека ретроцекалниот апендицит често предизвикува болка во лумбалната регија и десната страна на абдоменот, што се погрешно интерпретира како десна ренална колика. Исто така, камен на дисталниот дела на уретерот предизвикуваат болка во десната илијачна јама, што често погрешно дијагностицира како апендицит.(6,7) Кај клиничките грешки може да се спонме и однесувањето на пациентот кој исто е важен, параметар, пациентите со бубрежна колика се често се вознемирени, иритирани, ја менуваат телесната позиција и имаат тенденција активно да се движат во обид да ја намалат болката; напротив, пациентите со апендицит обично претпочитаат имобилност поради перитонизмот. Сепак, ова правило не е апсолутно – кај пациенти третирани со аналгетици, кај деца, кај постари лица или кај пациенти со пионефроза клиничката слика може да биде атипична. Кај клиничките грешки треба да се спомнат и уринарните симптоми или дисурија, која не е ексклузивна само за уретерални камења–пелвичниот апендицит може да го иритира дисталниот уретер и да предизвика дисурија.(8,9,10) Во лабораториските грешки значајна е погрешната интерпретација на хематуријата. Приближно 85% од пациентите со ренална колика имаат микроскопска хематурија, но во околу 15% од случаите со уролитијаза немат хематурија. Пелвичниот апендицит може да предизвика секундарна хематурија поради рефлексна иритација на уретерот. Многу мали камења може да не предизвикаат хематурија, што дополнително ја отежнува дијагностиката.(8,9,10) Леукоцитозата може да биде присутна кај двете патологији, но покачено CRP може да помогне во диференцијалната дијагноза; сепак, во раните стадиуми на апендицит, CRP може да биде во нормалени вредности.(11) Кај радиолошките грешки најчеста е фокусирање само во абдоминалната ултрасонографија. Ултразвукот е со ограничена сензитивност кај дебели пациенти или кај оние со изразена интестинална гасна дистензија. Стандардната нативен рентгенографија на уринарен тракт е корисна во проценката на уринарни камења, но уратните камења се радиотранспарентни и често не се видливи на обична рентгенографија. Флеболитите и апендиколитите може погрешно да се интерпретираат како уринарни конкременти. Компјутерската томографија без контраст претставува одличен метод за откривање камења, но е релативно неефикасна во раните воспалителни фази на апендицит. CT со контраст има супериорна дијагностичка вредност за апендицит, но камењата <3 mm често не се детектираат при нискодозни протоколи. CT со контраст останува „златен стандард“ за дијагноза на акутен апендицит.(12,13,14) Современата клиничка пракса промовира употреба на алгоритми за рано препознавање, како „clinical red flags“ за апендицит и „stone score“ за уролитијаза, како и употреба на клиничките скали Mantrels/Alvarado.

„Clinical red flags“ за акутен апендицит се: миграција на болката од периумбиликалниот регион кон десниот долен квадрант, позитивен McBurney's sign, болка што се зголемува при движење, кашлање или одење и изразена анорексија. Системските показатели вклучуваат: температура >38°C, леукоцитоза 10–12×10ϑ/L со неутрофилија и покачен CRP во зависност од фазата на воспаление. Сигнификантните физикални наоди вклучуваат позитивен rebound (Blumberg), мускулен дефанс, позитивен Psoas знак и тахикардија. Како втора стратегија може да се спомене клиничкиот алгоритам „stone score“ за уретерални камења: S–sex (мажи 2 поени, жени 0 поени), T–time (<6 часа 3 поени, 6–24 часа 1 поен, >24 часа 0 поени), O–origin (не-црна раса 3 поени, црна 0 поени), N–nausea (мучнина 1 поен, повраќање 2 поени), E–erythrocytes (>5 RBC/μL 3 поени, <5 RBC/μL 0 поени). Секој компонент носи поени и резултира со вкупен скор (0–13). Пациентите со 0–5 поени имаат низок ризик, 6–9 среден, а 10–13 висок. Пациентите со висок скор, во отсуство на „red flag“ критериуми, најчесто имаат уролитијаза. Клиничкиот алгоритам Mantrels (Alvarado) интегрира осум параметри—миграција, анорексија, гадење, болка во десниот долен квадрант, rebound, леукоцитоза, повишени WBC и неутрофилна „shift to left“. Пациентите со 0–4 поени имаат низок ризик и се следат; со 5–6 поени потребна е радиолошка проценка; со ≥7 поени потребна е итна хируршка консултација. (15,16,17,18,19)

ЗАКЛУЧОК

Акутната болка во десниот абдоминален регион бара структуриран и внимателен дијагностички пристап. Потпирањето исклучиво на локализација на болката, присуство на хематурија или ултрасонографија го зголемува ризикот од погрешна дијагноза. Прилагодувањето на радиолошките методи според клиничкото сомневање, контекстуалната анализа на лабораториските параметри, примена на алгоритмите „Clinical red flags“, „Stone score“ и Mantrels/Alvarado, како и раната мултидисциплинарна консултација, претставуваат најефективни стратегии за минимизирање на дијагностичките грешки.

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Review

THE HYPOTHESIS DEVELOPMENT IN SCIENTIFIC RESEARCH: THEORY, HISTORY, AND MODERN DEVELOPMENTS WITH EMPHASIS ON MEDICINE

Atilla Rexhepi, Levent Ismaili

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INTRODUCTION

The hypothesis is one of the most fundamental building blocks of scientific inquiry because it provides the intellectual, methodological, and analytical structure of the entire study [1]. In modern scientific methodology—particularly in medicine—research cannot advance without the formulation of clear, testable, and theoretically grounded hypotheses [1,2]. Hypotheses transform clinical questions into structured predictions, guide study design, direct data collection, and define the statistical tools required for analysis [3,4]. Although the concept of a scientific hypothesis appears simple, its philosophical, historical, and methodological evolution spans more than two millennia [5,6]. Understanding this evolution is essential for appreciating the central role hypotheses play in medical research today and for anticipating how hypothesis development will adapt in the era of big data and artificial intelligence [7,8].

History of Hypothesis Formulation in Scientific Studies

The concept of the hypothesis evolved from a philosophical to an empirical foundation. In classical philosophy, hypotheses were treated primarily as conceptual or explanatory constructs rather than empirically testable propositions [5]. The Renaissance marked a turning point, with the emergence of systematic observation and experimentation as foundations of scientific knowledge [6].

By the 17th and 18th centuries, hypotheses increasingly served as testable explanatory tools, supported by mathematical reasoning and experimental validation [3,5]. In the 19th century, Claude Bernard firmly established the hypothesis as the starting point of experimental medicine, emphasizing that scientific progress requires hypotheses to be verified or refuted through controlled experimentation [6].

During the 20th century, the formalization of statistical hypothesis testing transformed scientific research. Fisher introduced significance testing, while the Neyman–Pearson framework formalized decision rules for hypothesis testing [3,9]. Popper later proposed falsifiability as the defining criterion of scientific hypotheses, arguing that a hypothesis must be formulated in such a way that

it can be empirically refuted [5]. In modern evidence-based medicine, clearly defined and testable hypotheses remain fundamental to biomedical research design and interpretation [13, 14].

Definition of a Hypothesis in a Scientific Study

A hypothesis is generally defined as a testable statement that predicts a relationship between variables in a scientific study [1]. It articulates the expected association, effect, or mechanism that the research aims to investigate. Creswell defines a hypothesis as a "prediction about the expected relationship between variables derived from theoretical considerations" [1]. In quantitative research, which predominates in biomedical science, hypotheses are explicit statements that can be evaluated using empirical data and statistical inference [3, 4].

Modern scientific hypotheses possess several core characteristics. They must be testable using available methodological and analytical tools [3]. They must also be falsifiable; according to Popper, a scientific hypothesis must be formulated such that it can, in principle, be refuted by experience [5]. Hypotheses further require specificity, clearly defining the population, variables, and predicted relationship, and must be grounded in prior knowledge, deriving logically from existing theory, empirical evidence, or biological mechanisms [3,11,12].

In medical research, hypotheses are commonly expressed in pairs: the null hypothesis (H_0), which states that no effect or difference exists, and the alternative hypothesis (H_1), which represents the expected relationship or effect [3,4]. This dual structure enables formal statistical testing, inference, and quantification of uncertainty.

Value and Role of Hypothesis Formulation in Scientific Studies

Hypothesis formulation is fundamental to scientific research because it provides direction, focus, and methodological coherence [2]. In medical research, hypotheses translate clinical observations or gaps in knowledge into empirically testable predictions, ensuring that studies are systematic, efficient, and evidence-driven rather than purely descriptive [13, 2].

The formulation of a hypothesis shapes the entire research architecture. It determines the appropriate study design, population, sampling strategy, outcome measures, and statistical approach, thereby linking the research question to its methodological implementation [1,10]. Methodological literature emphasizes that the nature of the hypothesis dictates whether observational studies, randomized controlled trials, or mechanistic investigations are most appropriate [14,10].

Hypotheses also underpin statistical planning and analytic rigor. Pre-specified hypotheses guide sample size estimation, choice of statistical tests, and control of error, reducing the risk of bias and data-driven analyses [3,4]. Hypothesis-driven research enhances transparency, reproducibility, and scientific credibility—particularly in clinical trials and epidemiological studies [13,2]. Finally, hypotheses provide the framework for interpreting results, allowing findings to contribute meaningfully to cumulative knowledge, future research directions, and clinical translation [11,14].

Theoretical Foundations of Hypothesis Development in Medical Research

The formulation of a scientific hypothesis in medicine is not a purely intuitive act but is grounded in several well-established theoretical foundations.

1. The Scientific Method as the Foundational Framework

Hypothesis development is deeply rooted in the classical scientific method, which emphasizes systematic observation, careful problem definition, and formulation of testable predictions [5, 6]. The principle of falsifiability remains central to scientific inquiry [5]. In medical research, where variability and methodological complexity are substantial, adherence to the scientific method is essential for enhancing reproducibility and reducing bias [13].

2. Biological and Pathophysiological Plausibility

Medical hypotheses must align with established biological mechanisms. Grounding hypotheses in physiology, molecular biology, and pathology ensures that predictions are plausible and clinically meaningful [12]. Criteria for biological plausibility in epidemiology further support the formulation of coherent and mechanistically sound hypotheses 11,14].

3. Evidence-Based Medicine and Prior Empirical Knowledge

Evidence-based medicine integrates best available research evidence with clinical expertise and patient values [2]. Hypothesis development relies on critical appraisal of existing literature and identification of unresolved questions through systematic reviews and meta-analyses [14].

4. Epidemiologic and Causal Inference Theories

Epidemiologic theory provides essential conceptual foundations for hypothesis development in population-based research. Models of confounding, effect modification, and causal inference guide the formulation of hypotheses aimed at testing causal relationships. The Bradford Hill considerations remain influential, while modern counterfactual frameworks have refined causal reasoning in medical research [15].

5. Statistical Theory and Testability

Scientific hypotheses must be statistically testable. Core concepts such as null and alternative hypotheses, Type I and Type II errors, and statistical power derive from statistical inference theory [3, 4]. Proper statistical grounding ensures that hypotheses can be meaningfully evaluated.

6. Disease Model Frameworks

Medical research employs multiple disease models to shape hypothesis development, including the biomedical model, the biopsychosocial model, and epidemiologic frameworks such as the host–agent–environment model [14]. More recent systems biology and network medicine approaches address complex interactions across biological systems [16].

7. Ethical and Human-Subject Research Principles

Ethical theory is an indispensable pillar of hypothesis formulation in medicine. Principles such as beneficence, non-maleficence, respect for autonomy, and justice guide decisions regarding which hypotheses can be ethically tested in human subjects [18].

8. Contemporary Data Science and Precision Medicine Frameworks

Advances in genomics, machine learning, and biomedical informatics have expanded the theoretical foundations of hypothesis development. Precision medicine initiatives emphasize individual biological variability, while data-driven approaches enable discovery of novel patterns that may generate new hypotheses [7,8,17].

9. Distinct Types of Hypotheses in Medical Research

Medical research recognizes descriptive, associational, causal, and mechanistic hypotheses, each determining methodological and analytical strategies and reinforcing the hypothesis as the conceptual foundation of scientific inquiry [2,14]

Hypothesis Development in the Era of Artificial Intelligence

In the era of artificial intelligence, hypothesis development increasingly integrates traditional theory-driven reasoning with data-driven discovery. Machine learning algorithms can identify complex patterns in large datasets and generate candidate hypotheses beyond conventional approaches [8]. However, AI-generated hypotheses must be grounded in biological plausibility, causal reasoning, and ethical oversight before empirical testing [7,17].

Conclusion

The hypothesis remains the central organizing principle of scientific inquiry, particularly in medical research. Its evolution—from philosophical speculation to statistical and computational frameworks—reflects the maturation of science itself . Today, hypotheses underpin study design, statistical inference, and biomedical discovery. In the age of artificial intelligence, the hypothesis is evolving rather than disappearing; while AI accelerates hypothesis generation, rigorous, theory-driven hypothesis testing remains essential for producing reliable and clinically meaningful scientific knowledge.

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MOVING FORWARD BOUNDARIES OF MACULAR MEASUREMENTS IN GLAUCOMA - REVIEW ARTICLE

Dimovska Jordanova Vesna, Gineva Natasha, Osmani Ilir

Health Group "Promedika/Sistina Ophthalmology", Skopje, Republic of North Macedonia

Phone: +389 70 370 379
Email address: vesnajdimovska@gmail.com

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ABSTRACT

Epidemiological studies are presenting data that by 2040, 112 million people would be diagnosed with glaucoma. Up to 40% of patients are developing glaucomatous optic neuropathy without any evidence of increased intraocular pressure (IOP).

Apart from the IOP, as the only treatable risk factor, early recognition of the disease is crucial, enabling prompt and proper treatment. Over the years, study evidence confirmed close relationship, and even a correlation, between functional tests (perimetry) and newer imaging methods (Optical Coherence Tomography - OCT, Heidelberg Retinal Tomography - HRT, Scanning Laser Polarimetry - SLP). These methods are providing quantitative information confirming that structural damage in glaucoma most often precede functional changes, identified through the assessment of visual field.

The goal of the article is to present the most recent data and evidence that are emphasizing the significance of macular parameters, obtained by OCT, in early diagnosis of glaucoma.

At the introduction OCT-technology was available as time-domain (TD-OCT), that has shown certain limitations. Later on, with evolving of OCT-technology as spectral- domain (SD-OCT) and swept source OCT (SS-OCT), upgraded with segmentation algorithms, besides circumpapillary retinal nerve fiber layer (cpRNFL), the relevance of macular parameters was brought to light. This includes full macular thickness measurement (FMT), ganglion cell complex (GCC) and ganglion cell layer-inner plexiform layer measurement (GCL-IPL).

Conclusion: Glaucoma is still remaining not only a healthcare issue, but also a huge socio-economic burden with serious consequences. There is still a lack of "gold standard" for diagnosing glaucoma and assessing progression. Most recent guidelines are recommending combination of functional and imaging methods as standard diagnostic approach in patients with manifest glaucoma, as well as glaucoma suspects and pointing towards most promising measurements of macular parameters.

Key words: glaucoma, optical coherence tomography, macular measurements, progression

INTRODUCTION

"An optimal method for detecting glaucoma progression should not only give an indication whether or not the eye is changing over time, but also should estimate the rate of deterioration" (Medeiros, 2012)

The loss of retinal ganglion cells (RGCs) is early and crucial phenomenon in glaucoma. Retinal nerve fiber layer (RNFL) and retinal ganglion cells (RGCs) together comprise about 40% of the retinal thickness. Number of total RGCs varies in range of 0,7-1,5 million, with 50% localized within central 4-5 mm of the macular region and peak density of 15000 mm2. It makes only 7,3% of total retinal area, the part which could not be properly

assessed by visual field. [1]

According to different researchers, the first visual field damage occurs after RGCs are lost in range of 30-40% (Qigley et al 1998, Mackenzie et al.2017). Some evidence suggest this process could appear up to 5 years prior of detection of functional damage.[1] Therefore, making feasible early structural damage could represent key strategy for early glaucoma detection and prevention of significant vision loss.

Imaging diagnostic methods, such as optical coherence tomography as mostly used and considered a "gold standard" of imaging methods, provide quantitative information for assessment of structural parameters (ONH evaluation, retinal nerve fiber layer thickness, as well as different macular parameters).

Macular thickness and other macular measures are approved as a relevant parameters, due to the fact that macular thickness does not considerably change over time in healthy eyes. So, at the presence of reduced macular thickness, excluding pathology of macular diseases, it is most probably glaucoma. Also, evidence is stating that, the ganglion cell population in the macula, unlike the total number of the ganglion cells in the entire retina, is relatively stable among normal subjects. On the contrary, the optic nerve head varies individually in terms of size, shape, sloping, refraction, etc. [2],[3]

The new generations of OCT-technology, with upgraded segmentation algorithms, have further improved the precision and accuracy of the measurements, providing deeper insight and measurements of Ganglion Cell Complex (GCC), ganglion cell layer (GCL) and ganglion cell-inner plexiform layer (GCL-IPL). Now it becomes clear why the recent studies are more often focused on investigating the significance of macular parameters as biomarkers for early glaucoma detection and monitoring disease progression.

The relevance of Optical Coherence Tomography (OCT) in glaucoma

The diagnosis of glaucoma at early stages is a challenging task for the ophthalmologists.

The introduction of OCT, especially posterior segment OCT, has revolutionized the insight in number of macular diseases and glaucoma. Today it is leading and standard imaging method of choice for detection of structural changes in glaucoma. OCT is non-invasive, non-contact imaging technique that allows objective quantification in vivo at real time of key glaucomatous structural changes in the retina and optic nerve head (ONH). The obtained measurements are objective, with high sensitivity, specificity and reproducibility.

The earliest measurements of retinal thickness were performed with Retinal Thickness Analyzer (RTA) and presented by Zimmer and coworkers in 1998.[3]

The introduction of OCT technology was presented with time-domain (TD-OCT), which have shown lower diagnostic ability of macular measurements, compared to later more sophisticated technology of spectral domain OCT (SD-OC). The studies performed by TD-OCT have evaluated circumpapillary retinal nerve fiber layer (cpRNFL) as a structural parameter with higher diagnostic ability compared to macular measurements.

Advances in technology have enabled increasing of scanning speed, enhancing image quality and reducing scan artifacts. These improvements have lead to new generation OCT as spectral domain (SD-OCT), that has ability of:[4],[5],[6]

- enhanced acquisition speed, higher resolution and excellent reproducibility
- upgrade of segmentation algorithms
- assessment, identification and quantification of individual retinal layers
- detection and monitoring of glaucoma progression

SD-OCT has ability for assessment and interpretation of the following structural parameters:

• CpRNFL thickness - mostly used in glaucoma, with best diagnostic performance of global average cpRNFL and inferior sector average cpRNFL thickness

• Macular parameters

- Full macular thickness measurement (FMT) - distance from internal limiting membrane (ILM) to retinal pigment epithelium (RPE)
- Macular RNFL thickness (mRNFL)
- Ganglion cell layer (GCL)
- Ganglion cell-inner plexiform layer (GC-IPL)
- Ganglion Cell Complex (GCC)

Structural measurements obtained by SD-OCT in normal subjects could be related to misinterpretation due to:

√ Age - mean age related loss of entire retina is estimated at -0,24 µm/per year.

Histological studies have found reduction of RGCs count of 0,55-0,59%/per year, and reduction of RGCs density in central macula of 0,29%/per year

√ Gender - female gender was associated with thinner full retinal thickness

√ Axial length has inverse correlation with macular thickness

√ Ethnicity - study evidence reported African-American population with thinner macular thickness. [7]

OCT allows and provides large amount of in vivo information to be acquired without invasive intervention, effectively performing a "virtual biopsy" of the retina. In practice, clinicians and operators should stick to the rule for quantitatively and qualitatively reviewing scans before comparing them to the macula or RNFL normative databases. [3]

Structural/Macular parameters as biomarkers for glaucoma obtained by SD-OCT

The advent and improvement of OCT technology over the years has strengthened the relevance of structural parameters as indicators, or even predictors of early glaucoma. Maybe the most debatable issue between the glaucomatologists has become the identification (if possible at all), of individual structural parameter which would be considered as superior and outperforming the other OCT-measurements. Such consideration has not been recommended so far, mostly due to the lack of a "gold standard" for determination of the best parameter.

• Total macular thickness is a surrogate measure of tissue thickness loss due to glaucoma in the absence of other macular pathology.

Macular thickness in healthy eyes does not significantly change over time. In general, macular measurements have shown lower variability, high reproducibility and later reaching of measurements floor, compared to RNFL. Global (average), sectorial and local macular measurements have demonstrated high reproducibility. Therefore, those measurements could be able to detect change in later stages of the disease and provide monitoring of glaucoma progression. [8],[9]

However, disease surveillance in advanced glaucoma frequently relies on functional tests, due to the "floor effect" of structural tests and limited structure-function relationship.[9],[10]

• Most of the studies conducted with TD-OCT have found retinal nerve fiber layer (RNFL) to serve as proven and widely used parameter for evaluation of glaucoma in routine clinical practice. Circumpapillary RNFL thickness (cpRNFL) measured by SD-OCT have shown excellent short-term reproducibility, emphasizing average, superior and inferior thickness as most accurate parameters. [4], [6], [11], [12]

The role of macular RNFL (mRNFL) is poorly investigated as a separate parameter, due to insufficient data about characteristics, correlations and diagnostic possibilities of mRNFL.

Still, recent study evidence have shown that macular RNFL may provide more direct assessment of RGCs, compared with total (full) macular thickness measurement. Also, ganglion cell loss in glaucoma may lead to decrease in macular cellularity and macular thickness. Therefore, mRNFL is better surrogate marker for the glaucomatous damage in terms of a stronger correlation with visual function. [13] Some of the studies are reporting better diagnostic ability of macular parameters in eyes with larger optic disc [14]

• The macular ganglion cell complex thickness (mGCC) incorporates several layers, including ganglion cell layer (GCL), inner plexiform layer (IPL) and overlaying retinal nerve fiber layer (RNFL). Some of the studies elaborate possibility that precise segmentation of ganglion cell-containing retinal layers alone might facilitate better detection of glaucomatous damage, particularly as it is the loss of RGCs that is defining histological features of glaucoma. Hence, GCC is considered the earliest parameter undergoing changes in glaucoma and direct measure of the integrity of RGCs. Not less important, GCC may be the optimal outcome measure to be used for detection of glaucoma progression regardless of the disease severity [3], [9], [11], [12], [15]

Regarding GCC thickness values, studies report the range between 76,6-119,8 μm in normal eyes and 53,6-99,1 μm in perimetric glaucomatous eyes. [16]

Many studies have demonstrated the predictive value of GCC measurement in the diagnosis of glaucoma. Studies with SD-OCT have proven that GCC thickness measurements, including GCL, IPL and RNFL, was found to be as effective as cpRNFL and ONH evaluation in discriminating glaucomatous from healthy eyes. However, the GCC thickness is influenced by inter-individual variations in the human retina, as it contains

the macular RNFL. Therefore, measurements of the ganglion cell-inner plexiform layer thickness (GC-IPL) are thought to be less affected by inter-individual variation compared to RNFL thickness measurement. [17]

• The software of Ganglion Cell Analysis (GCA) provides measurement of GC-IPL. It represents confident measure due to lower thickness variability compared to RNFL, and thinning of this layer has shown good correlation with visual field damage. The minimum, infero-temporal and average GC-IPL thicknesses have shown highest diagnostic performance for early perimetric glaucoma, which is similar to that of the best RNFL and ONH parameters. According to these findings, macular GC-IPL thickness may be useful in advanced glaucoma when the ONH and RNFL parameters have reached the lowest value of measurements. [15], [17]

Main advantage of GC-IPL thickness as valuable and reliable parameter is the ability of discriminating glaucoma suspects and patients at different consecutive stages of glaucoma. Still, there is limited data in the literature regarding the extent of diagnostic ability and capacity of macular GC-IPL [4], [6], [15], [17]

RNFL damage most often occur either in superior or inferior sector (or both), in a focal or diffuse way. Correspondingly, superior and inferior GCC have more priority of glaucomatous damage in early glaucoma. Inferior thickness GCC is better predictor of early glaucoma, compared to superior and average GCC thickness. In general, GCC thickness has higher sensitivity and specificity for detection of early glaucoma, with significantly higher discriminating ability compared to full macular thickness. The role of GCC evaluation has special importance regarding identification of younger patients with pre-perimetric glaucoma and those with suspicious disc. [18]

Of course, ophthalmologists should interpret the results of macular measurements with caution, considering objective limitations of measurements, such as:

concurrent retinal disease (co-existing macular pathology)

poor image quality and low signal strength

measurements variability (although, macular measurements have low variability)

The other aspect of the measurements that could lead to misdiagnosing could be the presence of artifacts, mostly as a result of:

operator/machine errors

improper centration, segmentation errors

ONH anomalies and configuration (anatomical, refraction)

pathology as epi-retinal membrane (ERM) or vitreo-macular adherence

inflammatory diseases

Fig.1a, 1b, 1c

Novel metrics for assessment of structural damage in glaucoma

√ As no normative database is available yet for total macular thickness, using internal patient's controls to detect asymmetry is a powerful diagnostic tool. Examination of cup-to-disc asymmetry is a hallmark of glaucoma detection and it should be carefully evaluated. RNFL thinning asymmetry should be a sign of glaucoma, but significant symmetry of RNFL loss and macular thickness in both eyes, should suggest a diagnosis other than glaucoma. RNFL thinning is not always associated with glaucoma, and could be caused by other diseases. RNFL loss and progressive thinning of inner retinal layers could be associated with other systemic conditions, such as hypertension, diabetes or chronic kidney disease. [19]

Macular thickness maps are not new metrics, but should be evaluated and interpreted properly. [8]

Intra-eye asymmetry - between superior and inferior macula

Inter-eye asymmetry - between both eyes

√ New generations of OCT-devices have ability to obtain Bruch's Membrane Opening (BMO), taking BMO as an anatomical point of reference for measurement. It is defined as BMO - MRW (measuring the minimal distance from BMO to internal limiting membrane - ILM). It is proposed as a sensitive reproducible measurement of the ONH parameters (rim thickness and width, rim area, cup-to-disc ratio) that facilitates differentiation between glaucomatous and healthy eyes. It represents more logical reference measure for neuroretinal rim thickness evaluation [4], [6], [20]

√ Macular damage has been demonstrated to be more frequent in the inferior macula, in an area that projects to a localized region of the infero-temporal ONH. Some study evidence point towards this "macular zone of vulnerability" (MZV) as most likely the earliest sign of

glaucomatous damage. The area is commonly associated with the occurrence of disc hemorrhages, which are pathognomonic for normal tension glaucoma. [5], [7]

√ Newly developed macular topographic and volumetric measures {"macular shape measures") have shown ability of discriminating eyes with glaucoma from healthy eyes with clinically relevant accuracy. Those measures are capturing both topographical and volumetric features of the central perifoveal macular region. The shape biomarkers have advantage of not depending on segmentation of intraretinal layers and may prove to be helpful in patients were segmentation of macular layers is suboptimal. Perimacular retinal thickness may be a more accurate indicator than perimacular RNFL for the course and evolution of glaucomatous process in the early stages of glaucoma. Automated detection of eyes with a high risk of early glaucoma with high specificity could make glaucoma screening or risk stratification possible.[21]

√ One of the new measures that provoked a lot of controversies, with high expectations at the beginning and later failed clinical relevance is G/T- Ratio, defined as the ratio of mGCC to total retinal thickness. It was proposed by Kita and coworkers in 2013, but later studies by Hollo and coworkers in 2014 have reported contradictory results, finding G/T-ratio as parameter with lower diagnostic value compared to RNFL and macular measurements.[16])

√ One of the most debatable issues in glaucoma since the advent of OCT is the relationship between structural parameters (obtained by OCT) and functional tests (mostly with perimetry as a mainstay, and electrophysiological investigations).Most of the studies are referring inconsistent and limited relationship, although number of studies performed with SD-OCT are reporting good correlation between GCC thinning and visual field changes. Medeiros and coworkers in 2012 have proposed Combined Structure Function Index (CSFI) that improves detection, staging, prediction and assessment of glaucoma progression It represents estimated proportion of lost RGCs compared to the amount in age-matched healthy eyes.[22]

So far, there is no consensus yet for acceptance of a metric that would merge structural and functional findings and represent single value as numerical index of the relationship.[3], [22], [23]

Structural measurements as tools for detection and monitoring glaucoma progression

One of the most challenging issues in glaucoma, in terms of diagnostic accuracy and ability of imaging methods, is the capacity of structural measurements for early recognition and further monitoring of glaucoma progression.

Ideal parameter for progression assessment should be highly reproducible and useful during all stages of the disease. Detecting of glaucoma progression is difficult because of multiple factors that can affect its predictive accuracy, such as the variability of disease progression, glaucoma severity and age-related changes. Commonly, it takes over 5 years to occurring progression. In advanced glaucoma both functional and structural measures become less informative than during the early stages. Visual field remains the main method for detection of glaucoma progression, although in advanced glaucoma visual fields have reduced reproducibility with increased disease severity. Segmentation errors are more frequent with thinner RNFL, which may confound the identification of structural progression. Outer retinal layers are not affected in glaucoma. A cross-sectional study estimated that entire retina is thinning at a rate of -0,24μm per year. [5],[7],[9]

In general, global (average) cpRNFL thickness could be used in conjunction with global GC-IPL thickness in advanced glaucoma. But, many clinicians consider that once global cpRNFL thickness falls below 50μm due to the "floor effect", cpRNFL thickness is no longer useful and reliable biomarker of progression. Recent studies have debated that changes in mean global (average) GC-IPL thickness could represent more confident measure, as the GC-IPL may have more tissue remaining above its "floor level" at this point compared to cpRNFL.[6], [7[, [9] The "floor effect" represents the numerical value when the OCT-technology is not capable for further quantification of RNFL thickness. It is, so cold, the "tipping point", which is defined to be equal to 17% of RNFL thickness loss. It is the amount of structural loss needed when functional loss becomes detectable through visual field investigation (Wollstein and coworkers, 2015 - tipping point at 75,3μm) [24] When the RNFL thickness has reached floor effect, the tissue is so damaged that OCT can no longer detect structural changes, although perimetry still could register functional damage.[3],[20],[24]

Most of the researchers are advising performing OCT 2-3 times within the first year of diagnosing glaucoma, in order to determine the progression as early possible. [20]

Fig.2a and 2b

Randomized clinical trials and retrospective cohort studies have proposed number of risk factors that could serve as predictors of progression, such as: older age, thinner central corneal thickness (CCT), disc hemorrhages, larger α-zone of peripapillary atrophy, level of IOP (mean, peak, fluctuations), magnitude of fluctuations of ocular perfusion pressure and a diagnosis of pseudo- exfoliation glaucoma (PEXG)[5]

With improved image resolution and better segmentation algorithms, it has become achievable to measure the thickness of individual retinal layers, in addition to the full macular thickness or inner retinal layers. Based on available evidence, change in the average GC-IPL thickness of more than 2-4 μm could represent clinically significant glaucoma progression. Although the superiority of measuring individual layers, especially GCL deserves further investigation, the majority of studies investigating correlation between different structural measurements are reporting good inter-measurement agreement. Also, a strong correlation has been reported between the macular GC-IPL thickness and estimates of RGCs count.

Finally, regarding the role and relevance of macular SD-OCT imaging (and swept source -SS-OCT) in advanced glaucoma, there are confirmed advantages that should be considered by the clinicians.That include higher reproducibility, reaching measurements floor later than cpRNFL during the course of glaucoma, no significant increase in variability measurements with worsening of glaucoma until the end stage, and good correlation with visual field changes. [3],[5],[7],[13],[25]

OCT-Angiography (OCT-A)

Although OCT-Angiography (OCT-A) deserves our full attention as a "hot topic" due to the significance and usefulness in number of diseases with impaired blood vessels, here would be presented just a brief report on its significance in glaucoma. This fact is confirmed by the increasing performance and utilization of OCT-A in patients with glaucoma

The term Optical coherence tomography Angiography (OCT-A) comprises different OCT-based technologies which all allow non-invasive assessment of retinal perfusion, based on the movement of red blood cells. The main areas where OCT-A is currently used are investigation of perfusion and vascular structure of the macular retina, on one hand, and the disc and peripapillary retina on the other hand (glaucoma and other optic disc diseases) [26]

OCT-A is dye-free technique (which is advantage over Fundus Fluorescein Angiography -FFA), for non-invasive assessment of ocular microvasculature. It has provided evidence that retinal and choroidal vasculature impairment can occur during early stages of glaucoma. This suggests that OCT-A derived measurements could be used as biomarkers for enhancing detection and progression of glaucoma, as well opportunity to reveal novel insights regarding disease patophysiology. The detection of changes in early glaucoma could lead to paradigm shift in glaucoma monitoring. Together with OCT, it has become an essential tool not only in glaucoma detection and monitoring, but also in predicting progression and risk stratification. OCT-A has shown superficial vessel density to be reduced in glaucoma. OCT-A - derived vessel density parameters have lower measurement floor compared to conventional OCT-parameters, including GC-IPL. Therefore, macular vessel density parameters may have potential application in monitoring progression of severe cases of glaucoma, where patients have already reached the measurement floor with OCT parameters, such as cpRNFL and macular GC-IPL thickness. [6], [18]

Future expectations

Regarding the future improvement of OCT-technology, it is expected to facilitate early glaucoma diagnosing and enable the ophthalmologists and patients to benefit clinical management of glaucoma.

It is considered that using an artificial intelligence approach (AI) based on optic nerve head (ONH) morphological changes and visual field impairment patterns characteristic of glaucoma allows identification of primary open angle glaucoma (POAG) phenotypes. Such an objective AI-based approach will provide new insights into improvement of structure-function relationship and prediction of subsequent worsening of visual field in POAG-phenotypes.

Combination of Adaptive optics with OCT in AO-OCT has application to study glaucoma at cellular resolution scale in the living eye. Adaptive optics provides visualization of GCL, IPL, retinal pigment epithelium and choriocapillaris and could serve as surrogate biomarker for monitoring treatment efficacy through DARC technology (Detection of apoptosing retinal cells - Cordeiro, 2015). DARC is new technique that utilizes the unique optical properties of

the eye for direct visualization of retinal ganglion cell death. [6], [27]

The Visible- light OCT uses shorter (visible) wavelengths and also is expected to obtain additional information, such as stratification analysis of inner plexiform layer and oximetry of retinal vessels.[6]

Optical Coherence Tomography and Optical Coherence Tomography with Angiography have brought imaging methods to unexpectedly high diagnostic levels, so it is justified that ophthalmologists are eager to introduce new more sophisticated and improved generations that would facilitate early diagnosis, disease monitoring and proper management of glaucoma.

CONCLUSIONS

√ There is still missing a definition of diagnostic "gold standard" in glaucoma detection or assessment of glaucoma progression.

√ Imaging methods provide quantitative, standardized and objective information complementary to the qualitative and functional tests, considering them as unavoidable standard routine methods in clinical practice.

√ Imaging methods could not replace thorough clinical examination and should be interpreted individually and in relation to functional investigation data.

√ At present, macular thickness measurements have proven as excellent adjuvant modality in diagnosing glaucoma, comprehensively interpreted with measurement of RNFL, perimetry and ONH examination

√ There is inconclusive evidence (no consensus) of over performance of single structural parameter over the others.

√ Circumpapillary RNFL (cpRNFL) and recently ganglion cell iner plexiform layer (GC-IPL) have emerged with highest diagnostic ability in discriminating glaucoma from healthy eyes and in patients at different stages of glaucoma, as well as detecting progression.

√ Combination of multiple available structural and functional modalities, along with careful clinical examination and information, is the best approach to follow and predict glaucoma progression.

Conflict of interest statement. None declared

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Abreviations

IOP - intraocular pressure

RGCs - retinal ganglion cells

RNFL - retinal nerve fiber layer

OCT - optical coherence tomography

TD-OCT - time domain optical coherence tomography

SD-OCT - spectral domain optical coherence tomography

FMT - full macular thickness

GCL- ganglion cell layer

GC-IPL - ganglion cell-inner plexiform layer

GCC - ganglion cell complex

ONH- optic nerve head

BMO - Bruch's membrane opening

MZV - macular zone of vulnerability

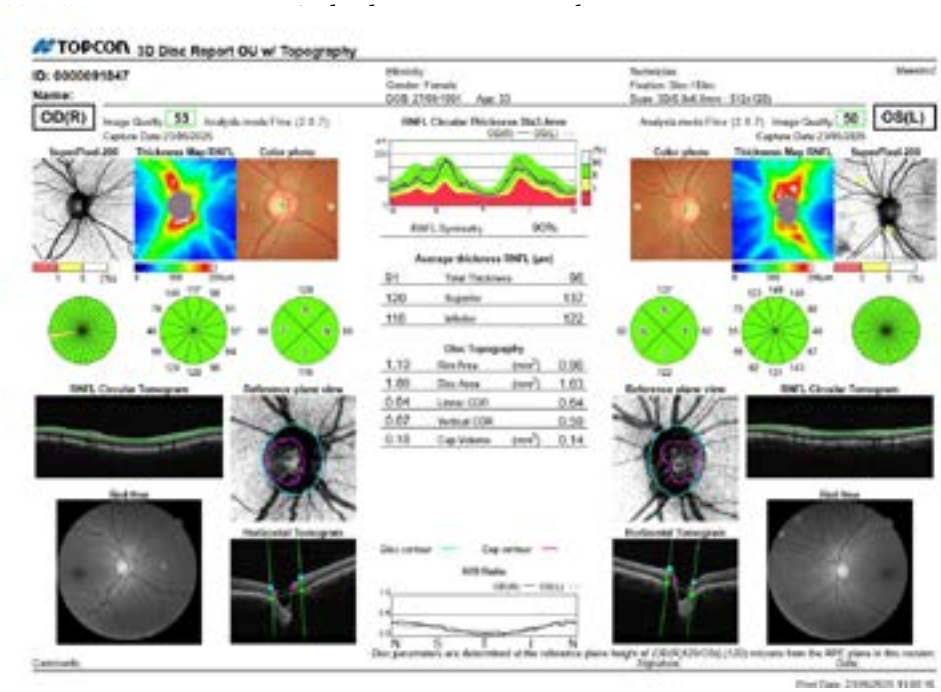

Fig.1a

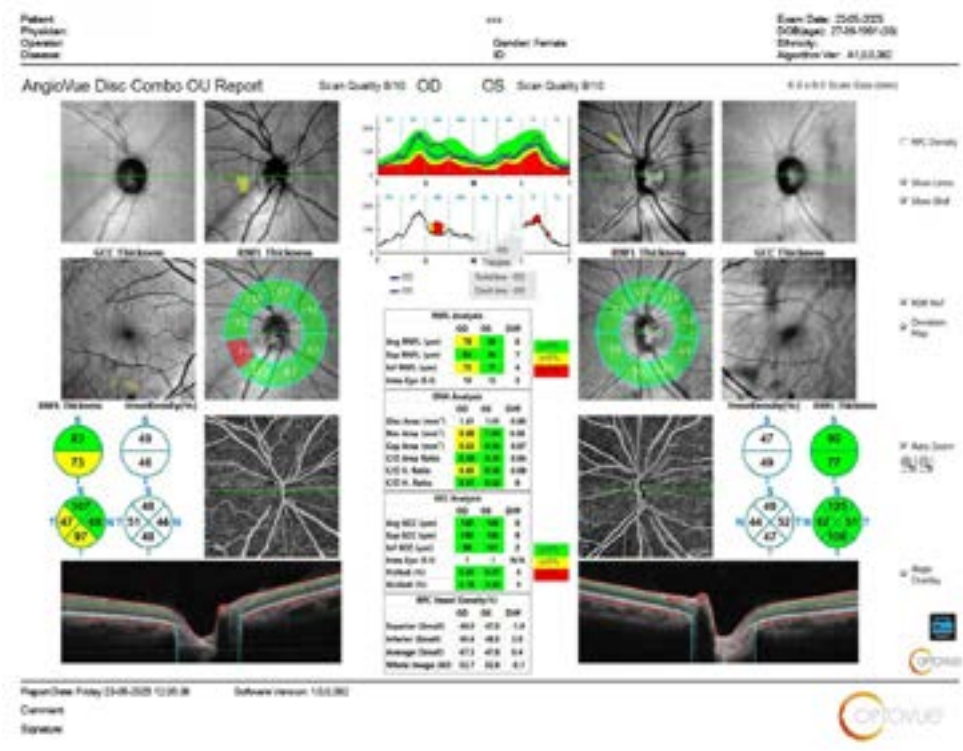

Fig.1b

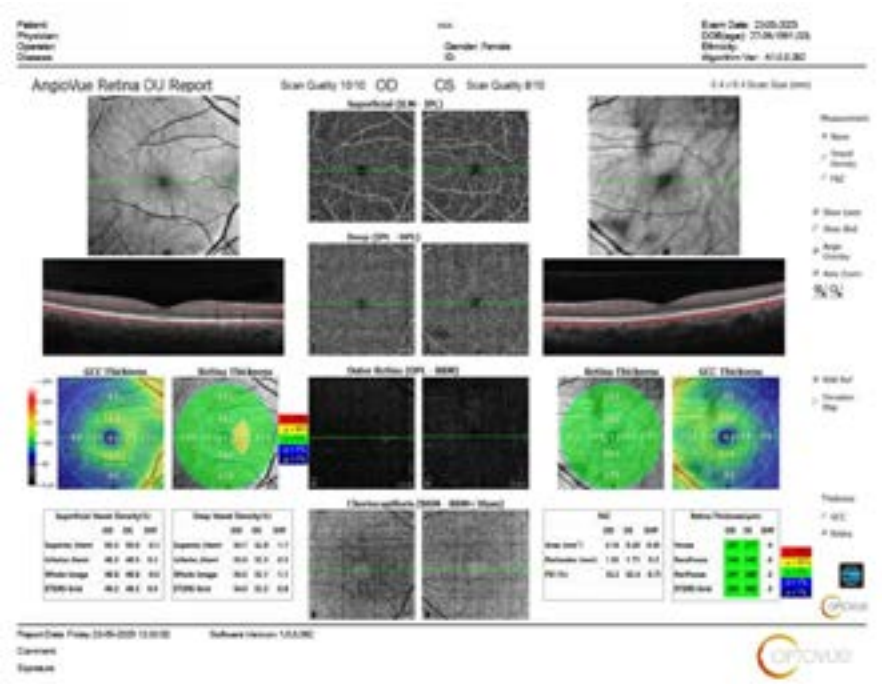
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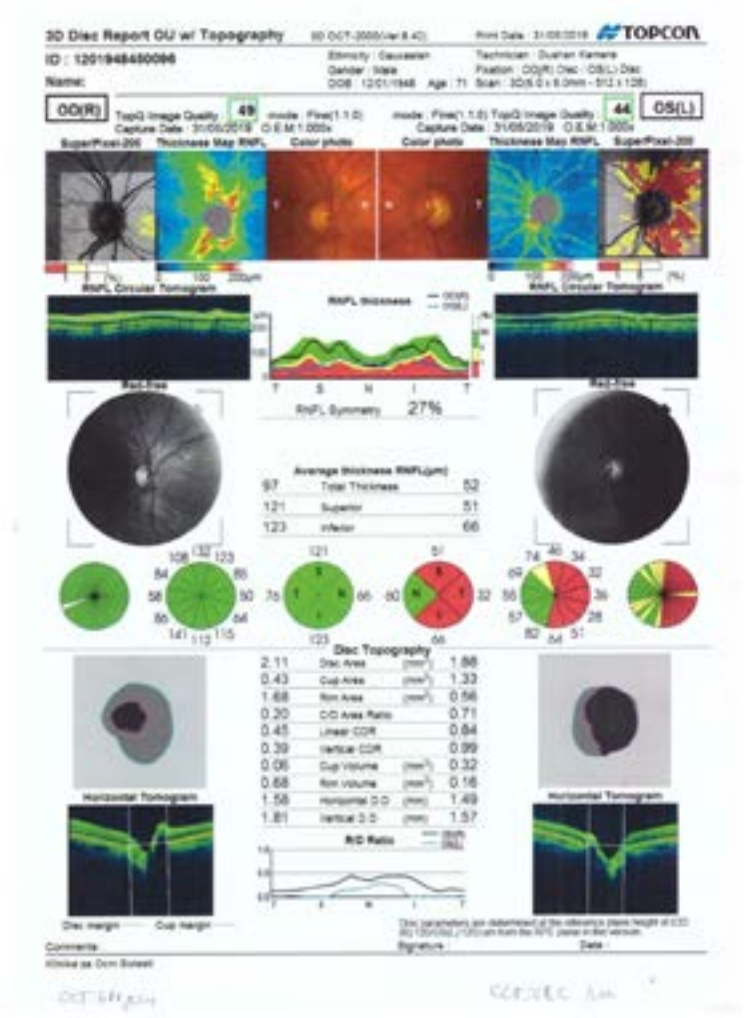
Fig.1c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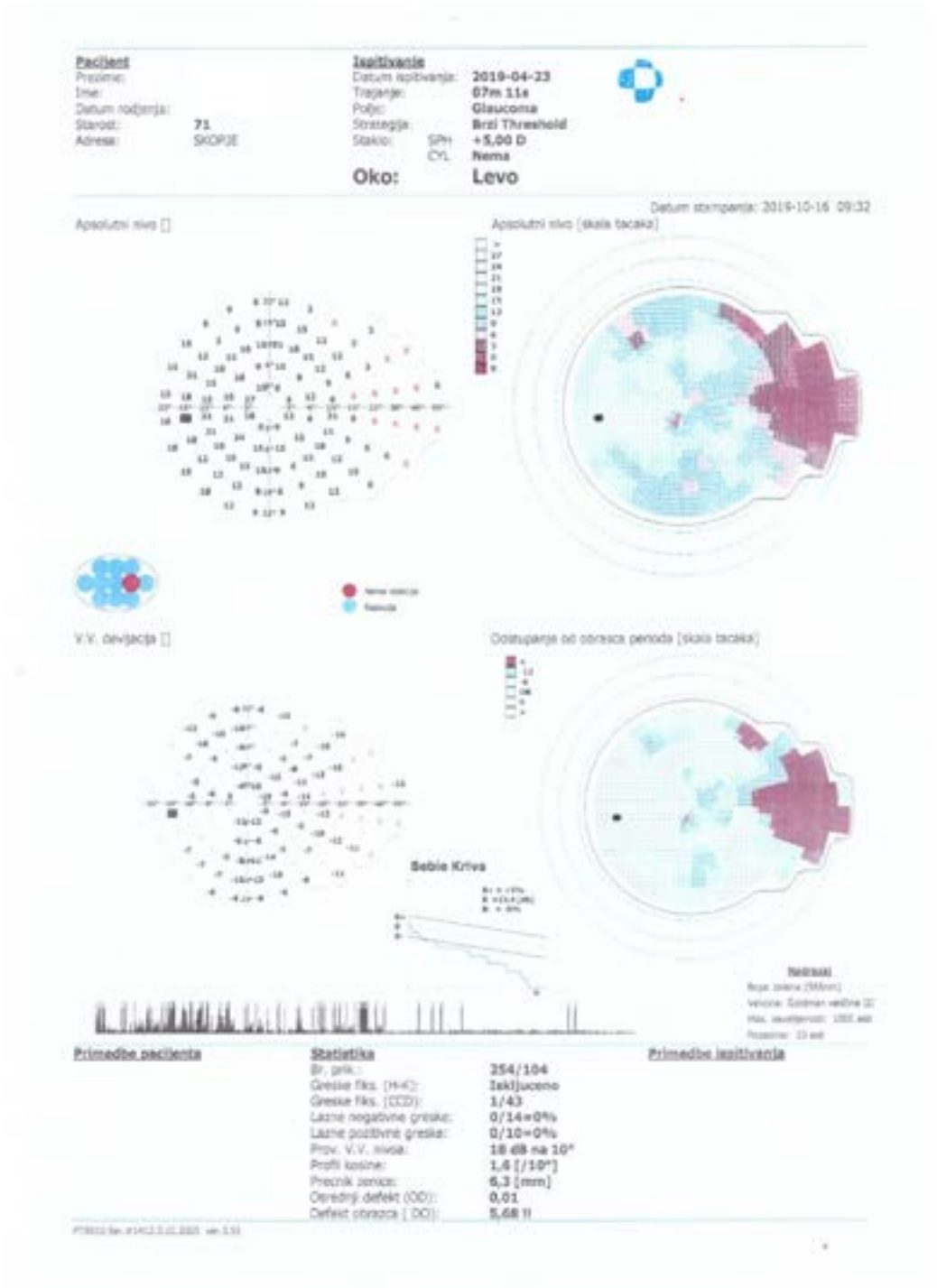
TOPCON
OD(R)
OS(L)
RNFL Symmetry 27%
Disc Topography

Fig.2a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Ime:
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Ispitivanje
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Trajanje: 07m 11s
Polje: Glaucoma
Strategija: Brzi Threshold
Staklo: SPH +5,00 D
CYL Nema
Oko: Levo
Datum stampanja: 2019-10-16 09:32
Apsolutni nivo []
Apsolutni nivo (skala tacaka)
V.V. devijacija []
Odstupanje od oblika perioda (skala tacaka)
Sebie Kriva
Primedbe pacijenta
Statistika
Primedbe ispitivanja
Br. grik.: 254/104
Greske fiks. (H-K): Iskljuceno
Greske fiks. (CCD): 1/43
Lazne negativne greske: 0/14=0%
Lazne pozitivne greske: 0/10=0%
Prov. V.V. nivoa: 18 dB na 10°
Profil kosine: 1,6 [/10°]
Precnik zenice: 6,3 [mm]
Opsednji defekt (OD): 0,01
Defekt obrasca (DD): 5,68 !!

Fig.2b

ОСВРТ КОН СТИГМАТА КАКО СОЦИЈАЛЕН ФЕНОМЕН ПРИ НАСЛЕДНАТА ТРАНСТИРЕТИНСКА АМИЛОИДОЗА

Ivan Barbov[1,2], Goce Kalcev[2]

[1]University Clinic for Neurology, Saints Cyril and Methodius University, Skopje, North Macedonia
[2]The National Alliance for the Neuromuscular diseases and Neuroscience GANGLION Skopje

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АПСТРАКТ

Авторите ценат дека овој ревијален труд (преглед на достапна стручна литература) е од есенцијално значење како за пациентите така и за медицинските лица бидејќи досега многу малку се пишувало и истражувало за стигмата како социјален феномен при наследната транстиретинска амилоидоза. Нашата визија е оваа творба да биде зачеток и поттик на многу интересни истражувања во блиска иднина, во корист на пациентите како и за надоградба на знаењата на медицинскиот персонал во однос на ова заболување.

Клучни зборови: стигма, пациенти, социјален феномен, наследна транстиретинска амилоидоза

Влијанието на Стигмата врз Пациентите и Нивните Семејства: Социјални и Психолошки Аспекти

Здравствената стигма се однесува на социјалната исклученост или маргинализација на поединци или групи кои се соочуваат со или се изложени на ризик од одредени здравствени состојби. Иако бројни истражувања се фокусираат на стигмата поврзана со здравствени проблеми и попреченост, како што се нарушувањата на менталното здравје, ХИВ, дебелината и семејствата на деца со попреченост, помалку внимание е посветено на стигмата која се јавува во контекст на наследните генетски нарушувања [1, 2]. Генетските болести често доведуваат до чувство на социјална девалвација и дискриминација, што делумно се објаснува со видливите физички симптоми кои ги предизвикуваат, а кои дополнително ја интензивираат стигмата [3]. Современото разбирање ја дефинира стигмата како релациски феномен поврзан со „девалвиран социјален идентитет“ на поединец или група. Овој концепт разликува два типа на стигма: онаа која се заснова на видливи карактеристики и онаа која се однесува на карактеристики што не се веднаш забележливи. Концептуалните анализи на стигмата ги истражуваат социјалните процеси што влијаат на поединците, кои во голема мера се манифестираат во нивните секојдневни искуства (3). Линк и Фелан (2001) ја дефинираат стигмата како комбинација од пет основни компоненти: етикетирање (кога разликите добиваат социјална значајност), стереотипизирање, разделување (кога етикетираните лица се сметаат за различни од останатите) и губење на статус и

дискриминација (кога учеството во заедницата е ограничено) (4). Овој процес на стигматизација создава перцепиран дисбаланс на моќ помеѓу оние што се стигматизирани и оние кои стигматизираат. Оваа дискриминаторна средина може да резултира со социјална исклученост како конечен исход од процесот на стигматизација.

Начините на наследување на генетските болести можат да влијаат на создавањето на потенцијалната стигма. Поврзаноста помеѓу генетската причина и стигмата е сложена, бидејќи иако стигмата што се јавува со наследните болести не секогаш е директно поврзана со нивната генетска основа; истражувањата покажуваат дека жените носители на болести кои се поврзани со Х-хромозомот често чувствуваат поголема вина и социјален притисок (5). Кога постои ограниченост во медицинските информации, луѓето често се потпираат на митови и погрешни претпоставки, што дополнително ја засилува стигмата поврзана со одредени состојби. Ова ја нагласува важноста на социјалната конструкција во обликувањето на искуството со болеста, особено во однос на тоа како се разбираат причините за болеста и како се објаснуваат од медицинската заедница и пошироката јавност. На пример, ако не се сфати целосно патогенезата на одредена генетска болест, луѓето често се потпираат на стереотипи и стари верувања, што го зголемува социјалниот стрес. Дополнително, стигмата честопати се засилува преку секојдневни социјални практики и односи, како што се непромислени коментари, дискриминација или изолација во социјалните мрежи. Овие практики создаваат континуиран циклус на маргинализација кој ја прави тешка за промена, бидејќи тие се вкоренети во нормите на секојдневниот живот и можат да останат невидливи или занемарени од пошироката јавност (6). Во овој контекст, клучна е улогата на едукацијата, подигнувањето на свеста и пристапот до точни медицински информации како алатки за намалување на стигмата и подобрување на поддршката за луѓето кои се соочуваат со генетски болести.

Семејствата кои ја чуваат болеста во тајност за да избегнат социјална стигма исто така покажува како здравствената стигма може да влијае на семејните динамики и психолошкото здравје на членовите на семејството (4). Воздржаноста од зборување за болеста може да создаде дополнителен стрес, изолација и чувство на неразбирање, што на крајот може да го отежне процесот на справување со болеста. Овие примери покажуваат колку е важен контекстот на културната и социјалната средина при разгледувањето на проблемите со стигмата и здравствените предизвици, како и како локалните верувања и практики кои можат да ги обликуваат стратегиите за справување со болестите (7).

Процесот на стигматизација и нејзините ефекти можат значително да се разликуваат во зависност од моментот кога одредена состојба станува видлива за другите. На пример, ако некоја состојба се манифестира рано во детството, како што е случај со некои физички деформации, или ако се појави подоцна во животот, како што е случај со невролошките пореметувања, тоа ќе влијае на начините и интензитетот на стигматизацијата (8). Кога овие промени стануваат видливи за околината, тие создаваат различни патишта за социјално исклучување и дискриминација, што го обликува целокупното доживеано социјално искуство на поединецот (9). Со други зборови, времето на појавата на овие карактеристики, како и реакциите на опкружувањето, имаат клучна улога во тоа како се обликува доживувањето на стигмата и колку сериозно таа ќе влијае врз животот на поединецот (10).

Поим за наследна транстиретинска амилоидоза

Наследната транстиретинска амилоидоза претставува прогресивна болест со хетерогени клинички манифестации. Се карактеризира со бавно прогресивна периферна сензомоторна и/или автономна невропатија и мултисистемско екстрацелуларно таложење на амилоид, што доведува додисфункција на различни органи и ткива. Наследната транстиретинска амилоидоза е предизвикана од промени (мутации) во TTR генот. Истите ја менуваат ДНК секвенцата, правејќи ја поинаква од онаа кај повеќето луѓе. Секое дете наследува две копии од секој ген: една од мајката и една од таткото. TTRA се наследува на автозомно доминантен начин. Ова значи дека наследувањето на само една копија од мутираниот ген може да јапредизвика оваа состојба. Нова мутација (de novo) исто така може да се случи, но тоа е поретко [11]. Идентификувани се повеќе од 120 TTR мутации. V122I, T60A, и V30M се најчестите варијанти. Сите мутации ја менуваат структурата на транстиретинот, со што се оневозможува неговото правилно формирање и функционирање. Наследната транстиретинска амилоидоза е системска, прогресивна мултисистемска болест, па од таму истата може да предизвика различни

симптоми. Карактеристична појава е периферната невропатија, или оштетување на периферните нерви [11]. Амилоидните наслаги може да предизвикаат конгестивна срцева слабост, хипертрофична кардиомиопатија, аритмија или синкопа [11]. Амилоидните депозити во гастроинтестиналниот тракт може да предизвикаат гадење и повраќање, хронична дијареа, запек, чувство на заситување после внесување мали количини на храна (рана ситост) и епизоди на дијареа и опстипација [11].

Наследната транстиретинска амилоидоза и социјалната стигма: Извори, последици и промени во перцепцијата

Резултатите од едно истражување [12] откриваат присуство на стигматизација кај пациенти погодени од ова заболување кои живеат во одреден географски регион, сметан за веројатно место на потекло на најчестата основна мутација на оваа болест. Главните наоди од студијата се сумираат во следниве точки:

- Стигматизација во контекст на социјално деградирање;
- Мулти- и трансгенерациската природа на болеста;
- Различни степени на интернализација на стигмата (пациентите покажуваат различни реакции на стигмата, што води до воздржаност во говорење за болеста, особено надвор од семејството, отпорност и преемотивни реакции на потенцијални негативни ставови);
- Намалување на стигмата и подобрување на социјалната прифатеност: пациентите истакнуваат дека во последните неколку децении стигмата околу фамилијарната амилоидоза значително се намалила, а социјалната прифатеност се подобрила.

Генерално гледано, овие наоди ја нагласуваат важноста на социјалните и културните фактори во искуствата на пациентите, како и потребата од продолжување на напорите за намалување на стигматизацијата и поддршка на овие индивидуи во нивниот секојдневен живот. Повеќето учесници во истражувањето ги опишале своите искуства со стигматизација како исклучиво поврзани со настани од нивното детство и помладите години [12]. Истовремено, беше забележано дека во претходните децении постоела значително помала социјална свест за амилоидната полиневропатија, отколку што е случај денес. Во тој период, заедниците можеби стекнале практично искуство со состојбата, но не стекнале доволно објективни информации за самата болест, нејзините карактеристики и начините на пренос. Како дополнителен аспект на општото непознавање на состојбата, некои пациенти ја поврзале својата стигматизација со недостатокот на информација. Тие го перцепираат непознавањето на ова заболување како главен фактор кој ги доведува другите да ги восприемат членовите на семејствата погодени од болеста како лица што треба да се избегнуваат [12].

Искуствата на учесниците со стигматизација се јасно поврзани со динамиката меѓу поединецот, неговото/нејзиното семејство и заедницата, при што различни индивидуии ја дефинираат и доживуваат стигмата на различни начини. Одредени семејства погодени од фамилијарната амилоидна полиневропатија се ограничени да зборуваат за болеста само во рамките на својот круг, а некои индивиди решаваат да ги напуштат своите родни градови поради чувството на исклученост и изолација [13]. Овој феномен на изолација и избегнување е пример за тоа како стигмата може да создаде силни социјални бариери и да ја погоди психолошкота благосостојба на луѓето погодени од болеста, формирајќи длабоки трауми кои влијаат на нивната идентификација и социјално функционирање. Овие наоди ја нагласуваат важноста на намалување на стереотипите и зголемување на едукацијата за ова заболување, за да се спречи понатамошното нарушување на социјалната интеграција на погодените индивиди и нивните семејства [14]. Исто така резултати од ова истражување покажуваат дека обрасците на стигма во заедницата доживеале значителни промени во последните неколку децении. Некои учесници ги опишале своите искуства со стигматизација како нешто што се случувало претежно во минатото. Тие извештаи беа дополнети со напомени за значителното подобрување на социјалната прифатеност на погодените индивидуи и намалување на интензитетот на стигматизацијата која тие ја доживеале [15]. Ова подобрување, најверојатно, се должи на повеќе фактори, вклучително и порастот на достапноста на медицински третмани, како и тековните клинични испитувања кои продолжуваат да се развиваат. Исто така, значајна улога имаат примарните здравствени работници, кои во последните години играат сè поголема улога во регионот, со воспоставување добро организирани упатни процедури и соодветно клиничко управување со болеста. Тие, исто така, придонесуваат за промоција на здравственото образование, што

помага во зголемувањето на свеста и намалувањето на погрешните разбирања за болеста во заедницата. Овие промени значително го намалиле товарот на болеста врз пациентите и нивните семејства, што се одразува на подобрена психолошка и социјална благосостојба. Овој развој на настаните укажува на тоа дека продолжените напори за образованието, подобрување на здравствената нега и зголемена поддршка од страна на здравствените професионалци и организациите, можат да имаат долгорочен позитивен ефект на намалувањето на стигмата и на подобрување на животните услови на лицата погодени од наследна транстиретиска амилоидоза.

Заклучоци

Стигмата која се јавува во контекст на наследните болести несомнено произлегува од интеракцијата на специфичните карактеристики на болеста и нејзиниот начин на наследување. Социјалните истражувачи треба да го проучуваат ефектот на стигмата и начинот на кој индивидуите и семејства ја управуваат оваа информација. Во овој контекст, важно е да се разгледаат процесите преку кои тие ги објаснуваат своите одлуки и практики, како и како овие одлуки влијаат на нивната социјална интеграција и врз перцепцијата на сопствената идентитетска вредност. Со оглед на овие нови предизвици, потребно е дополнително истражување и развој на стратегии за минимизирање на стигматизацијата и подобрување на општественото разбирање за наследните болести.

Conflict of interest: Nonce declared.

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CONGENITAL GRANULAR CELL EPULIS (CGCE) IN A FEMALE NEWBORN – CASE REPORT

Snezana Palcevska Kocevska[1,2], Aneta Demerdzieva[1,2], Marija Dimitrovska-Ivanova[3,2], Jana Jovanovska[1], Martina Serafimova[3]

[1]Acibadem Sistina Hospital, Skopje, Republic of Macedonia
[2]Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia
[3]Clinical Hospital, Stip, North Macedonia

Corresponding Author Snezhana Palchevska Kocevska, Acibadem Sistina Hospital in Skopje, Faculty of Medical Sciences Goce Delcev University, Stip; snezana.palcevska@ugd.edu.mk , mob. ++39071240909

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ABSTRACT

Congenital granular cell epulis (CGCE) is an exceptionally rare benign soft tissue tumor of the neonatal oral cavity, that usually originates from the neonatal gingiva and can lead to difficulty in breathing and feeding upon birth. It has predominance for females with an 8:1 ratio in relation to males and is exclusively encountered in the oral cavity.

We present a case of a full-term female neonate, born after a regularly monitored, uncomplicated pregnancy, in whom multiple papillomatous growths were identified in the oral cavity within the first hours of life. A larger papillomatous lesion measuring 2 cm was noted on the tongue, accompanied by several smaller nodules measuring 0.4–0.6 cm nearby, as well as an additional lesion on the mandibular alveolar ridge. The neonate was under medical supervision and exhibited no significant respiratory or feeding difficulties.

Complete surgical excision was the treatment of choice and was performed under general anesthesia on the second day of life. The postoperative course was uneventful, with stable vital signs maintained throughout. Histopathological and immunohistochemical analyses confirmed the diagnosis of CGCE.

Postoperatively, the infant was regularly followed by the neonatologist, with no recurrence of the lesions observed, satisfactory healing, and normal growth and development.

This case highlights the unusual multifocal presentation of CGCE, including involvement of both the tongue and mandible, and emphasizes the importance of prompt recognition, surgical intervention, and histopathological confirmation to ensure optimal neonatal outcomes.

Keywords: Newborn, Multifocal oral mass, congenital granular cell epulis, multidisciplinary management.

INTRODUCTION

Congenital granular cell epulis is a unique and rare benign lesion that occurs in the alveolar ridge mucosa of the jaw of the newborn. An example of neonatal oral disease is the congenital granular cell lesion (CGCL), it is also known as congenital epulis. This is a gingival congenital benign rare tumor whose evolution ceases after birth (1). Therefore, it occurs exclusively in newborns babies (2). The etiopathogenesis of congenital epulis remains incompletely elucidated, although the condition demonstrates a marked predilection for female neonates, femele : male ratio is 8:1. The lesion exhibits considerable variability in size and may present as either a solitary or multiple nodular mass arising from the alveolar ridge. It

presents as a submucosal mass of varying size, usually single [3] but multiple cases have also been reported [4] .

In most cases, congenital epulis is asymptomatic and therefore may not be detected until birth. Prenatal diagnosis is uncommon and mostly confined to the third trimester. Multifocal lesions or occurrences in atypical intraoral locations–such as the tongue, as shown in our case , are exceedingly uncommon and contribute to the clinical diversity of this entity. Nevertheless, when the lesion attains substantial dimensions, it can contribute to clinically significant complications, including difficulties with feeding and, less commonly, respiratory compromise.

Given its rarity, distinctive clinical behavior, and the potential for diagnostic confusion with other neonatal oral masses, CGCE represents a condition of significant clinical interest. Early recognition and appropriate management are essential to prevent functional complications and to ensure optimal neonatal outcomes.

This report describes a rare case of multifocal CGCE affecting the tongue and lower jaw in a full-term female newborn. The unusual location and multiple lesions, along with a smooth recovery after surgery, underscore the importance of reporting such cases.

CASE PRESENTATION

The patient was a full-term female neonate, born after a regularly monitored pregnancy with no reported complications, infection screening swabs during pregnancy were negative. The perinatal and postnatal course was unremarkable. The infant had a birth weight of 3250 g and Apgar scores of 9/9/10 at 1α, 5α, 10, respectively.

Upon initial oral examination, papillomatous growths were identified on the tongue, comprising one larger lesion measuring 2 cm in diameter and several smaller nodules ranging from 0.4 to 0.6 cm surrounding it. In addition, a smaller lesion was noted on the mandibular alveolar ridge.

A cranial ultrasound (CNS echography) performed shortly after birth was within normal limits for age, and no other congenital anomalies were detected.

Given the potential for functional interference and the benign clinical appearance, complete surgical excision under general anesthesia was performed on the second day of life. The procedure was uneventful, and normal feeding was established immediately postoperatively.

Histopathological and immunohistochemical analyses of the excised lesions confirmed the diagnosis of congenital granular cell epulis (CGCE). Postoperative follow-up at 6 days and 6 months demonstrated complete healing without recurrence, and the neonate remained in excellent overall health.

DISCUSSION

Congenital granular cell epulis (CGCE) is a very rare benign tumor of the neonatal oral cavity, with fewer than 250 cases reported in the literature. The anxiety of the family because of the appearance of the lesion makes the physician who is responsible for the diagnosis and treatment of these disorders have a major role in the proper management of these cases .(5). It occurs almost exclusively in females and typically appears as a solitary lesion on the maxillary alveolar ridge.

The present case is unusual because of the multifocal presentation, with a large lesion on the tongue, smaller nodules around it, and an additional lesion on the mandible. Such atypical locations and multiple lesions are exceptionally rare. Interestingly, despite the size and number of lesions, the neonate had no feeding or breathing difficulties, which is not always the case in larger CGCE.

Most cases are diagnosed after birth, but a few reports have shown that CGCE can be detected prenatally by ultrasound or MRI, usually in the third trimester. Early detection could help plan delivery and prepare the neonatal care team, especially if lesions are large or could interfere with feeding or respiration. However, small lesions often remain undetected before birth.

Surgical excision is the treatment of choice and is usually curative, with recurrence being extremely rare. Histopathology and immunohistochemistry confirm the diagnosis and help differentiate CGCE from other oral masses. Histopathologically, CGCE is characterized by large polygonal granular cells with eosinophilic cytoplasm and small, uniform nuclei, typically negative for S-100 protein, distinguishing it from granular cell tumors seen in older children and adults. Immunohistochemical confirmation is essential in atypical or multifocal cases to establish the diagnosis and exclude other entities such as oral teratomas, neuroectodermal tumors, or hemangiomas.

This case highlights the importance of careful postnatal oral examination, awareness of rare multifocal presentations, and consideration of the potential for prenatal detection in selected cases.

CONLUSION

Congenital granular cell epulis (CGCE) is an uncommon tumor seen only in the newborn. (6) It usually tends to grow on anterior alveolar ridge of the newborns, more on the maxilla than on the mandible(7). This case demonstrates an unusual multifocal distribution, involving both the tongue and the mandible, highlighting the broad clinical variability of CGCE.

Early prenatal recognition of CGCE is of critical importance. Prenatal imaging using ultrasound or MRI can identify large or multifocal lesions, allowing for timely planning of delivery and preparation for potential airway management. Early detection also facilitates multidisciplinary coordination to ensure optimal neonatal care. The neonatal disease may be perceived before birth, on examination of prenatal care, such as ultrasound [8] .Although most cases are traditionally diagnosed postnatally, the integration of prenatal screening can significantly improve perinatal outcomes. Recognizing atypical or extensive oral lesions before birth enables clinicians to anticipate challenges, reduce complications, and provide targeted interventions immediately after delivery.

Early diagnosis and surgical treatment of CGCE are essential to avoid functional impairment. The prognosis is excellent following complete excision (9). For multiple CGCTs, simple surgery has been adopted (10). This report highlights the importance of being aware of atypical presentations of CGCE, conducting thorough oral examinations of newborns, and proactively using prenatal imaging in suspected cases.

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MULTIDISCIPLINARY MANAGEMENT OF AN PRETERM INFANT WITH CMV INFECTION: A CASE REPORT

Mevlane Islami Limani[1], Elizabeta Petkovska[1], Orhideja Stomnaroska[1], Sanja Ristovska[1], Afrodita Stomnaroska-Jovanovski[2]

[1]University Clinic of Gynecology and Obstetrics, Neonatal Intensive Care Unit, Skopje, North Macedonia
[2]Private General Hospital – ReMedika, Skopje, North Macedonia

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ABSTRACT

This case report presents the complex clinical course of a female preterm neonate born at 31+4 weeks of gestation, with low birth weight (970g) and reduced Apgar scores (6/5/5). The infant was hospitalized for 119 days in the neonatal intensive care unit (NICU), where she underwent extensive diagnostic evaluations and multidisciplinary treatment. Laboratory testing confirmed CMV DNA positivity in both blood and cerebrospinal fluid (CSF), indicating active congenital infection. Neuroimaging revealed periventricular leukomalacia (PVL) and hydrocephalus, which were managed through serial lumbar punctures and close neurological monitoring. Persistent thrombocytopenia prompted hematology consultation, while elevated direct bilirubin levels led to gastroenterology. Pediatric cardiology evaluation identified a left-to-right shunt at the foramen ovale and incomplete interventricular septal continuity. Ophthalmologic assessment revealed aggressive posterior retinopathy of prematurity (AP-ROP), treated with intravitreal anti-VEGF injection and followed closely due to post-injection hemorrhages. Additional investigations included TORCH screening, immunological testing, brain MRI, and auditory and visual assessments. The multidisciplinary team included neonatologists, neurosurgeons, hematologists, gastroenterologists, cardiologists, and ophthalmologists. Treatment involved antiviral and antibiotic regimens , supportive care, and structured follow-up for neurodevelopment, hearing, and vision. This case highlights the importance of early diagnosis and coordinated multidisciplinary management in congenital CMV infection, particularly in preterm infants with neurological, hematological, hepatobiliary, cardiac, and ophthalmologic complications. It underscores the value of integrated clinical protocols and long-term follow-up to improve prognosis and reduce morbidity in this vulnerable patient population.. It also highlights the need for heightened clinical vigilance and collaborative care to mitigate long-term morbidity and optimize neurodevelopmental outcomes.

Keywords : congenital cytomegalovirus; preterm neonate; periventricular leukomalacia; retinopathy of prematurity; multidisciplinary care

INTRODUCTION

Congenital cytomegalovirus (CMV) infection is the most common intrauterine infection worldwide, affecting approximately 0.5–2% of all live births. It is recognized as the leading non-genetic cause of sensorineural hearing loss and neurodevelopmental impairment in infants. In addition, congenital CMV is associated with visual disorders and long-term morbidityCDC+1.

While most term infants with congenital CMV remain asymptomatic at birth, preterm neonates, especially those with very low birth weight, are at significantly higher risk of severe, multi-system complications. The clinical presentation in preterm infants can include central nervous system involvement (e.g., periventricular leukomalacia, ventriculomegaly), hematologic abnormalities (e.g., thrombocytopenia), hepatobiliary dysfunction (e.g., cholestasis), ocular pathologies (e.g., retinopathy), and congenital heart anomalies.

Early diagnosis and timely initiation of antiviral therapy have been shown to improve long-term outcomes, particularly in symptomatic infants. However, management remains complex and requires a multidisciplinary approach involving neonatology, infectious disease specialists, neurology, ophthalmology, cardiology, hematology, and gastroenterology.

This case report aims to highlight the challenges and importance of early recognition and coordinated care in a very preterm neonate with symptomatic congenital CMV infection and multiple organ involvement. Through a detailed clinical course, we emphasize the role of integrated diagnostic strategies and long-term follow-up in improving prognosis in this vulnerable patient.

CASE PRESENTATION

A female preterm neonate was delivered at 31 weeks and 4 days of gestation via cesarean section due to fetal distress. The birth weight was 970 grams, classifying her as very low birth weight. Apgar scores were 6, 5, and 5 at 1, 5, and 10 minutes, respectively. Immediately after birth, due to signs of respiratory distress, the infant was intubated in the delivery room. Upon admission to the neonatal intensive care unit (NICU), conventional invasive mechanical ventilation was initiated using Synchronized Positive Pressure Ventilation with Volume Guarantee (SPPV+VG) mode. The first dose of exogenous surfactant was administered via endotracheal tube (ETT) for the treatment of respiratory distress syndrome (RDS). The infant remained on invasive mechanical ventilation for 23 days. Following extubation, she was placed on non-invasive respiratory support with CPAP-NIV for an additional 27 days. Oxygen therapy was then continued with high-flow nasal cannula (HFNC) for 29 days, followed by low-flow oxygen delivered via face mask until respiratory stability was achieved.

Laboratory Findings

Serial investigations revealed significant multisystem involvement:

Hematology:

Severe thrombocytopenia: platelet counts fluctuated between 80 → 31 → 55 → 19 → 31 → 41 → 33 → 28 → 39 ×10⁹/L

CRP: markedly elevated (11.1 → 86.6 mg/L), then decreased progressively (4.8 → 1.8 → 1.7 → 0.9 mg/L)

Leukocytes: 9.7 → 20.4 → 26.7 → 12.0 ×10⁹/L

Biochemistry:

Glucose: fluctuating values (2.8 → 3.7 → 1.0 → 4.2 → 3.8 mmol/L) with episodes of hypoglycemia

Total bilirubin: 113 → 250 → 148 → 78 μmol/L

Direct bilirubin: 38.8 → 132 → 95.4 μmol/L

AST: 95 → 337 → 178 U/L

ALT: 20 → 231 → 108 U/L

LDH: 2376 → 707 → 378 U/L

Alpha-1 antitrypsin: 1.497 g/L

Ceruloplasmin: 25.0 mg/dL

Hemostasis:

PT = 12.6 sec

APTT = 43.5 sec

TT = 28.1 sec

D-dimer: 2304 mg/mL (markedly elevated)

Infectious Disease Workup:

TORCH screening: CMV IgG = 118 (positive)

CMV IgM = 6.53 (positive)

PCR-CMV DNA: positive in blood and CSF

Neuroimaging (cranial ultrasound and brain MRI) revealed periventricular leukomalacia (PVL) and progressive ventriculomegaly. Hydrocephalus was managed conservatively through serial lumbar punctures and close neurological monitoring in collaboration with pediatric neurosurgery. Ophthalmologic examination showed aggressive posterior retinopathy of prematurity (AP-ROP), which was treated with intravitreal anti-VEGF injections. Post-treatment retinal hemorrhages were observed and closely followed.

Echocardiography identified a persistent left-to-right shunt via the foramen ovale and partial interventricular septal discontinuity. Hematology consultation was obtained for refractory thrombocytopenia, while gastroenterology was involved in managing prolonged cholestasis.

Further investigations included TORCH screening, immunologic testing, brain MRI, auditory brainstem response (ABR) testing, and visual assessments. Antiviral therapy with ganciclovir was initiated and continued

as per protocol. Antibiotic therapy and comprehensive supportive care were provided throughout the 119-day NICU stay.

The infant was discharged with a structured multidisciplinary follow-up plan, including neurology, audiology, ophthalmology, and developmental pediatrics.

Outcome

The infant remained hospitalized for 119 days in the NICU. At discharge, she was clinically stable in terms of respiratory function, feeding orally, and gaining weight adequately. Persistent ventriculomegaly required further monitoring.

She was transferred to the pediatric neurosurgery clinic for continued management of hydrocephalus and was discharged on oral acyclovir therapy (tablets) planned for 6 consecutive months as part of long-term antiviral treatment.

A structured multidisciplinary follow-up plan was established, including neurology, neurosurgery, audiology, ophthalmology, gastroenterology, hematology, and developmental

DISCUSSION

Congenital cytomegalovirus (CMV) infection is a significant public health concern and the most frequent congenital viral infection worldwide. While the majority of full-term infants with CMV are asymptomatic at birth, up to 10–15% may present with clinical signs, and the risk of severe manifestations is notably higher in preterm and very low birth weight neonates. The presented case illustrates the complex and multisystem involvement of congenital CMV infection in a preterm infant, underscoring the diagnostic and therapeutic challenges associated with such cases.

Neurological involvement, particularly periventricular leukomalacia (PVL) and hydrocephalus, is a well-documented consequence of intrauterine CMV infection. PVL is particularly concerning as it is a strong predictor of future neurodevelopmental delays, including cerebral palsy. In our case, early neuroimaging and serial monitoring allowed timely identification and management of hydrocephalus, avoiding the need for surgical intervention during the neonatal period.

Thrombocytopenia and cholestasis are frequently observed hematologic and hepatobiliary complications of congenital CMV. In this case, persistent thrombocytopenia prompted evaluation for alternative etiologies, although ultimately attributed to CMV-related bone marrow suppression. Similarly, cholestasis, along with elevated direct bilirubin and liver enzymes, necessitated ongoing gastroenterology input and supportive management.

The occurrence of aggressive posterior retinopathy of prematurity (AP-ROP) in this infant adds another layer of complexity. While ROP is primarily related to prematurity and oxygen exposure, CMV has been implicated in potentiating retinal damage through inflammatory and vascular mechanisms. The use of intravitreal anti-VEGF agents remains standard for AP-ROP, although the presence of post-treatment hemorrhages, as observed in this patient, raises the need for vigilant ophthalmologic follow-up.

Cardiac findings, including a left-to-right shunt and incomplete interventricular septal formation, although possibly incidental, may reflect developmental disturbances secondary to intrauterine infection and prematurity. Comprehensive cardiac assessment is essential to exclude hemodynamically significant anomalies in this context.

Early antiviral treatment with valganciclovir has been associated with improved auditory and neurodevelopmental outcomes in symptomatic infants. Although therapy carries potential side effects, such as neutropenia, its benefits in high-risk cases—like the one presented—outweigh the risks when closely monitored.

This case underscores the importance of a multidisciplinary approach to the management of congenital CMV in preterm neonates, involving neonatology, infectious disease specialists, neurology, ophthalmology, cardiology, hematology, and gastroenterology. Long-term follow-up is crucial to monitor developmental progress and intervene early in case of emerging deficits.

CONCLUSION

This case highlights the complex and multisystem manifestations of congenital CMV infection in a very preterm infant, illustrating the importance of early diagnosis, comprehensive evaluation, and coordinated multidisciplinary management. The involvement of the central nervous system, hematologic abnormalities, hepatobiliary dysfunction, ocular pathology, and cardiac anomalies demonstrates the wide-ranging impact of congenital CMV, particularly in the context of prematurity.

Timely initiation of antiviral therapy, close clinical monitoring, and structured follow-up are essential to mitigate long-term morbidity and optimize neurodevelopmental outcomes. This report emphasizes the need for heightened clinical vigilance and integrated care protocols in neonatal units, especially when caring for preterm infants with unexplained systemic signs. Continued research and awareness are needed to improve early detection strategies and refine management approaches for congenital CMV infection in high-risk populations.

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II. Faqja e dytë – abstrakti dhe fjalët kyqe: Abstrakti duhet të shkruhet me maksimum prej 150 fjalësh për abstraktet e pastrukturuara, dhe me 250 fjalë për abstraktet e strukturuara (pjesët përmbajtësore: objekti/ete studimit ose hulumtimit, procedurat bazë, siç është përzgjedhja e subjekteve apo kafshët laboratorike, metodat vrojtuese dhe analitike, pastaj, rezultatet/gjetjet përfundimtare (të dhënat dhe rëndësia e tyre statistikore, nëse është e mundur), dhe konkluzionet kryesore. Vini theksin mbi aspektet e reja dhe të rëndësishme të studimit apo vrojtimit. Nën abstraktin indentifikoni dhe shkruani fjalët kyqe: 3-5 fjalë apo fraza të shkurtëra që do të ndihmojnë në paisjen me tregues të punimit dhe publikimit të abstraktit. Përdorni terme nga lista e Index Medikus për Nëntituj Mjekësor (Medical Sub-Headings [MeSH]); nëse nuk ka term të përshtatshëm në MeSH për disa terme të reja, mund të përdorni termet e dhëna.

III. Faqja e tretë dhe të tjerat – teksti i plotë i artikullit: Teksti i plotë i artikujve hulumtues ose vrojtues normalisht, por jo domosdoshmërisht, duhet të jetë i ndarë në paragraf me këta nëntituj: hyrja, metodat dhe materialet, rezultatet dhe diskutimi.

1. Hyrja: Krijoni një kontekst apo prapavijë (trualli) të studimit (që në fakt është natyra e problemit dhe rëndësia e tij). Për të bërë këtë duhet të bëni një hulumtim të literaturës – duke kërkuar, gjetur dhe lexuar punimet përkatëse, që duhet të jenë si referencë në dorëshkrimin tuaj. Sqaroni hipotezat tuaja dhe planifikoni t'i testoni ato, si dhe përshkruani qëllimet tuaja. Kini qëndrim të qartë se çka prisni të gjeni dhe arsyet që ju udhëhoqën tek hipotezat që keni krijuar. Objekti i hulumtimit më së shpeshti fokusohet kur parashtrohet si pyetje. Mos përfshini të dhëna apo rezultate nga puna që do të raportohet.

2. Metodat & Materialet: Ky paragraf duhet të përfshijë atë informacion që ishte në dispozicion në kohën që plani apo protokoli i studimit po shkruhej. Të gjitha informacionet e marra gjatë studimit i takojnë paragrafit të Rezultateve.

Përshkruani përzgjedhjen tuaj të pjesëmarrësve së vrojtimit ose eksperimentit (pacientët ose kafshët laboratorike, përfshirë kontrollat) qartë, duke përfshirë kriteret e përshtatshme (inkluzive) dhe përjashtuese (ekskluzive).

Parimi udhëheqës duhet të jetë i qartë se si dhe pse studimi është bërë në një mënyrë të caktuar. Jepni detaje të mjaftueshme për metodat, mjetet dhe materialet (jepni emrin dhe adresën e prodhuesit në kllapa), dhe procedurat për të lejuar të tjerët të kuptojnë dhe riprodhojnë rezultatet tuaja.

Nëse një metodë e caktuar që është përdorur është e njohur, atëherë nuk është e nevojshme të jepet përshkrim komplet i saj. Mund t'i referoheni punimit në të cilin së pari herë është përshkruar dhe të

Additional Information for Authors

I. First page - front page: It should contain: (a) title of paper, a short, but informative; (b) the first name, initials of middle name and last name of each author; (c) the institution; (d) the name of the department that is attributable to the scientific work; (e) the name and address of the author with whom to correspond about the manuscript (f) source/support in the form of grants, equipment, drugs, or all.

II. Second page - abstract and keywords: The abstract should be written with a maximum of 150 words for unstructured abstracts and 250 words for structured abstracts (containing parts: objective(s) of study or research, basic procedures, such as selection of subjects or laboratory animals, observational and analytical methods, then, the main findings/results (data and their statistical significance, if possible), and the main conclusions. Emphasize the new and important aspects of the study or observation.

Below the abstract identify and write the keywords: 35 words or short phrases that will assist in indexing the paper and publication of the abstract.

Use terms from the list of Index Medicus for Medical Sub-Headings (MeSH); if there is no appropriate MeSH term for some newly introduced terms, we can use the given terms.

III. Third and further pages – full text of the article: The full text of research or observational articles should normally be, but not necessarily, divided into sections with the following headings: introduction, material and methods, results and discussion.

1. Introduction: Provide a context or background for the study (that is, the nature of the problem and its significance). To do this you must complete a literature review – searching for, finding and reading relevant papers, which must be referenced in your manuscript. Explain your hypotheses and the plan to test them, and describe your aims. Clearly state what you expect to find and the reasoning that led you to the hypotheses that you have made. The research objective is often more sharply focused when stated as a question. Do not include data or conclusions from the work being reported.

2. Methods & Material: This section should include only information that was available at the time the plan or protocol for the study was being written. All information obtained during the study belongs in the Results section.

Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria.The guiding principle should be clarity about how and why a study was done in a particular way.

Give sufficient details of the methods, apparatus and materials (give the manufacturer's name and address in parentheses), and procedures to allow others to understand and reproduce your results.

If a particular method used is well known then there is no need to give a complete description. You can reference the paper in

përmendni ndonjë modifikim/ndryshim që keni bërë. Jepni arsyet për përdorimin e tyre dhe vlerësoni kufizimet e tyre. Në fund, përshkruani se si i keni analizuar të dhënat tuaja, duke përfshirë metodat statistikore dhe pakon programore që keni përdorur.

Autorët e dorëshkrimeve të rishqyrtuara duhet të përfshijnë një paragraf që përshkruajnë metodat që kanë përdorur për lokalizimin, përzgjedhjen, ekstrahimin dhe sintetizimin e të dhënave. Përdorni formën joveprore të foljes, në vetën e tretë, kur dokumentoni metodat, gjë që do të fokusonte vëmendjen e lexuesit tek puna që është bërë e jo tek hulumtuesi (P.sh. Janë marrë, janë realizuar, janë prezantuar etj.)

2. a) Statistikat: Përshkruani metodat statistikore me detaje të mjaftueshme për t'ia mundësuar një lexuesi me njohje në atë fushë t'i qaset të dhënave origjinale për të verifikuar rezultatet e raportuara. Kur është e mundur, përcaktoni sasinë e zbulimeve dhe prezantoni ato me indikatorë përkatës të gabimeve në matje apo pasiguri (siç janë inter-valet e besueshmërisë). Evitoni mbështetjen vetëm në testet statistikore të hipotezave, siç janë vlerat p, që dështojnë të transmetojnë informacion të rëndësishëm mbi madhësinë e efektit. Jepni detaje rreth përzgjedhjes së rasteve (randomizimi) dhe përshkruani metodat dhe sukseset e vrojtimit gjatë realizimit të studimeve të verbuara. Definoni termet statistikore, shkurtesat dhe më së shumti simbolet. Specifikoni programin kompjuterik që është përdorur.

3. Rezultatet: Ky paragraf duhet t'i bëjë gjetjet tuaja të qarta. Prezantoni rezultatet tuaja në rend logjik në tekst, tabela dhe ilustrime, duke dhënë së pari rezultatet kryesore ose më të rëndësishme. Mos i përsërisni të gjitha të dhënat në tabela apo ilustrime, në tekst. Nënvizoni ose përmbledhni shkurtimisht vetëm vrojtimet më të rëndësishme.

Kur të dhënat përmblidhen në paragrafin e Rezultateve, jepni rezultate numerike jo vetëm si derivate (për shembull, përqindja) por gjithashtu si numra absolut nga të cilët derivatet janë llogaritur, dhe specifikoni metodat statistikore që janë përdorur për t'i analizuar ato.

Kufizoni tabelat dhe figurat në aq sa janë të nevojshme për të sqaruar argumentin e punimit dhe për të vlerësuar të dhënat ndihmëse. Duke përdorur grafikonet për të reprezentuar të dhënat tuaja si alternativë e tabelave, do të rrisë kuptueshmërinë e lexuesit. Mos i dyfishoni të dhënat në grafikone dhe tabela. Duhet të jeni të qartë se cili lloj i grafikoneve është i përshtatshëm për informacionet tuaja. Për shembull, për të reprezentuar korelimin mes dy ndryshoreve, preferohet grafiku vijëzor, krahasuar me grafikun rrethor apo në formë shtyllash.

Sa i përket të gjitha paragrafeve, qartësia dhe të qënit i thuktë është kyçe. Mos prezantoni të njëjtat të dhëna më shumë se një herë. Kufizojeni veten në të dhënat që ndihmojnë në adresimin e hipotezave tuaja. Kjo është e rëndësishme edhe nëse të dhënat i aprovojnë ose nuk i pranojnë ato. Nëse keni bërë analiza statistikore, duhet të jepni vlerën e probabilitetit (p) dhe të tregoni se është shprehës (sinjifikant në nivelin që ju po testoni. Varësisht nga analizat e përdorura, gjithashtu mund të jetë e rëndësishme të jepni intervalet e besueshmërisë së rezultateve (Confidence

which it was first described and mentioned any modifications you have made. Give the reasons for using them, and evaluate their limitations. Finally,, describe how you analysed your data, including the statistical methods and software package used.

Authors submitting review manuscripts should include a section describing the methods used for locating, selecting, extracting, and synthesizing data.

Use the third person passive voice when documenting methods which would focus the readers' attention on the work rather than the investigator.(e.g. Were taken, was performed, were presented itd.)

2. a) Statistics: Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as p values, which fail to convey important information about effect size. Give details about the randomization and describe the methods and success of observations while using blinded trials. Define statistical terms, abbreviations, and most symbols. Specify the computer software used.

3. Results: This section should make your findings clear. Present your results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all the data in the tables or illustrations in the text. Emphasize or summarize only the most important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.

Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Using graphs to represent your data as an alternative to tables will improve the reader's understanding. Do not duplicate data in graphs and tables. You need to be clear what type of graphs is suitable for your information. For example, to represent the correlation between two variables, a line graph is preferred to a pie chart or a bar chart.

As with all sections, clarity and conciseness is vital. Don't present the same data more than once. Restrict yourself to the data that helps to address your hypotheses. This is important whether the data supports or disproves them. If you have carried out a statistical analysis, you should give the probability (P) value and state it is significant at the level you are testing. Depending on the analysis used, it may also be important to give the confidence intervals of the results, or the statistical parameters such as the odds ratios. Provide a caption for each figure making the gen¬eral meaning clear without reference to the main text, but don't discuss the results. Let the readers decide for themselves what they think of the data. Your chance to say what you think comes next, in the discussion.

3. Tables: Each table should be inserted at the point of the text where they have to be placed logically, typed by the same rules

Interval – CI), ose parametrat statistikorë si proporcionet e rastit (odds ratio). Bëni përshkrimin tek secila figurë duke bërë të qartë domethënien e përgjithshme pa referencë në tekstin kryesorë, por mos diskutoni rezultatet në të. Lëreni lexuesin të vendosë vetë se çfarë mendon për të dhënat. Mundësia juaj për të thënë se çfarë mendoni, është në vazhdim, tek diskutimi.

3. Tabelat: Secila tabelë duhet të vendoset në vendin e tekstit ku duhet të vihet logjikisht, e plotësuar me të njëjtat rregulla sikur teksti i plotë. Mos i dërgoni tabelat si fotografi. Secila tabelë duhet të citohet në tekst. Tabelat duhet të jenë me numra ashtu që të jenë në koordinim me refer-encat e cituara në tekst. Shkruani një përshkrim të shkurtë të tabelës nën titullin. Çdo sqarim shtesë, legjendë ose sqarim i shkurtesave jostan¬darde, duhet të vendoset menjëherë poshtë tabelës.

4. Diskutimi: Ky paragraf është pjesa ku ju mund të interpretoni të dhë-nat tuaja dhe të diskutoni duke ballafaquar dhe krahasuar gjetjet tuaja me ato të hulumtuesve të mëparshëm. Rishikoni referencat e literaturës dhe shihni nëse mund të përfundoni se si të dhënat tuaja përkojnë me atë që keni gjetur.

Ju gjithashtu duhet të llogarisni rezultatet, duke u fokusuar në mekaniz¬mat në prapavij të vrojtimit. Diskutoni nëse rezultatet tuaja mbështesin hipotezat tuaja origjinale. Gjetjet negative janë aq të rëndësishme në zhvillimin e ideve të ardhshme sikur gjetjet pozitive.

E rëndësishme është se, nuk ka rezultate të këqija. Shkenca nuk të bëjë me të drejtën dhe të gabuarën, por merret me zgjerimin e njohjeve të reja.

Diskutoni si janë paraqitur gabimet në studimin tuaj dhe çfarë hapa keni ndërmarrë për të minimizuar ato, kështu duke treguar se ju çmoni ku¬fizimet e punës tuaj dhe fuqinë e përfundimeve tuaja. Duhet gjithashtu të merrni në konsideratë ndërlikimet e gjetjeve për hulumtimet në të ardhmen dhe për praktikën klinike. Lidhni përfundimet me qëllimet e studimit, por evitoni qëndrimet dhe përfundimet e pakualifikuara, që nuk mbështeten në mënyrë adekuate nga të dhënat. Shmangni prioritetet deklarative apo të aludoni në punën që nuk është krahasuar.

5. Referencimi: Referencat janë baza mbi të cilën është ndërtuar raporti juaj. Shqyrtimi i literaturës dhe leximi i referencave gjithmonë duhet të jetë pikë fillestare e projektit tuaj. Ky paragraf duhet të jetë i saktë dhe të përfshijë të gjitha burimet e informacionit që keni përdorur.

Në formatin "Vancouver", referencat numërohen një nga një, sikur që shfaqen në tekst dhe identifikohen me numra në bibliografi..

Një punim mund të ketë më së shumti një autor dhe 4 koautor. Koautori i fundit duhet të jetë mentori ose koautori më i afëërt me punimin. Pas emrave të autorëve shkruhet titulli i artikullit; emri i revistës i shkurtuar sipas mënyrës së Index Medicus; viti i botimit; numri i vëllimit; dhe numri i faqes së parë dhe të fundit.

Referencat e librave duhet të jepen sipas emrit të autorit, titulli i librit (mund të citohet edhe titulli i kapitullit para titullit), vendi i botimit, botuesi dhe viti.

as for the full text. Do not send tables as photographs. Each table should be cited in the text. Tables should be numbered so that they will be in sequence with references cited in the text. Provide a brief explanation of the table below the title. Any additional explanations, legends or explanations of non¬standard abbreviations, should be placed immediately below the table.

4. Discussion: This section is where you interpret your data and discuss how your findings compare with those of previous researchers. Go over the references of your literature review and see if you can determine how your data fits with what you have found.

You also need to account for the results, focusing on the mechanisms be¬hind the observation. Discuss whether or not your results support your original hypotheses. Negative findings are just as important to the de¬velopment of future ideas as the positive ones.

Importantly, there are not bad results. Science is not about right or wrong but about the continuing development of knowledge.

Discuss how errors may have been introduced into your study and what steps you took to minimise them, thus showing that you appreciate the limitations of your work and the strength of your conclusions. You should also consider the implications of the findings for future research and for clinical practice. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. Avoid claiming priority or alluding to work that has not been compared.

5. Referencing: The references are the foundation on which your report is built. Literature searches and reading of references should always be the starting point of your project. This section must be accurate and in¬clude all the sources of information you used.

In the Vancouver format, references are numbered consecutively as they appear in the text and are identified in the bibliography by numerals.

One article can have one author and 4 co-author. Last co-author is the mentor of the article or closest co-author of the paper." The authors' namer are fol-lowed by the title of the article; the title of the journal abbreviated ac-cording to the style of Index Medicus; the year of publication; the volume number; and the first and last page numbers.

References to books should give the names of any editors, place of publication, editor, and year.

In the text, reference numbers are given in superscript. Notice that issue number is omitted if there is continuous pagination through¬out a volume, there is space between volume number and page numbers, page numbers are in elided form (51-4 rather than 51-54) and the name of journal or book is in italics. The following is a sample reference:

Në tekst, numrat e referencave jepen me indeks të sipërm. Vëreni se çështja e numrave neglizhohet nëse ka numërtim të vazhdueshëm përg¬jatë gjithë vëllimit, ka hapësirë mes numrit të vëllimit dhe numrit të faqes, numrat e faqeve janë në këtë formë: 51-4 në vend të 51-54, dhe emri i revistës ose librit është në italic. Në vazhdim është një shembull i referencës:

Artikujt e revistave:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. N Engl J Med 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. BMJ 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997;349: 1498-504.

Librat dhe tekste tjera:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. National service framework for coronary heart disease. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Kamberi A, Kondili A, Goda A, dhe bp; Udhërrëfyes i shkurtër i ShoqatësShqiptaretëKardiologjisëpërparandalimineSëmundjes AterosklerotikeKardiovaskularenëpraktikënklinike,Tiranë,2006
7. Azemi M, Shala M, dhe bp. Pediatria sociale dhe mbrojtja shëndetësore e fëmijëve dhe nënave. Pediatria, Prishtinë 2010; 9-25

Shmangni përdorimin e abstrakteve si referenca; "të dhëna të papublikuara" dhe "komunikime personale". Referencat e pranueshme, por ende të papublikuara lejohet të merren, vetëm nëse shënoni se janë "në shtyp".

6. Mirënjohjet: Ju mund të keni dëshirë të falënderoni njerëzit që ju kanë ndihmuar. Këto mund të rangohen prej atyre që ju kanë përkrahur me teknika eksperimentale deri tek ata që ju kanë këshilluar deri në bërjen e dorëshkrimit final.

7. Formati i fajllit të të dhënave për ilustrimet (figurat): JPG

Nëse përdoren fotografitë e pacientëve, qoftë subjekti, qoftë fotografitë e tyre nuk duhet të jenë të identifikuara, ato duhet të shoqërohen me lejen e shkruar nga ta për përdorimin e figurës. Format e lejuara janë në dispozicion nga redaksia.

Nëse fajllet e të dhënave janë shumë të mëdha për t'u dërguar me e-mail, rekomandohet dërgimi me CD në adresën tonë.

8. Legjendat për Ilustrimet (Figurat)

Legjenda e tabelës duhet të vendoset mbi tabelë. Referenca e një tabeleje, e cila është marrë nga ndonjë publikim tjetër, duhet të vendoset poshtë tabelës. (Është përgjegjësi e autorit të sigurojë lejen e ribotimit nga botuesit e atij botimi) Legjenda e figurës duhet të vendoset në fund të faqes. Referenca e figurës e marrë nga ndonjë tjetër publikim vendoset në fund të legjendës. (Leja e ribotimit duhet të sigurohet nga botuesi i këtij botimi).

Journal articles:

1. Lahita R, Kluger J, Drayer DE, Koffler D, Reidenberg MM. Antibodies to nuclear antigens in patients treated with procainamide or acetylpro¬cainamide. N Engl J Med 1979;301:1382-5.
2. Nantulya V, Reich M. The neglected epidemic: road traffic injuries in developing countries. BMJ 2002;324: 1139.
3. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997;349: 1498-504.

Books and other monographs:

4. Colson JH, Tamour NJJ. Sports in juries and their treatment. 2nd ed. London: S. Paul, 2006.
5. Department of Health. National service framework for coronary heart disease. London: DoH, 2000.

   www.doh.gov.uk/nsf/coronary.htm (accessed 6 Jun 2003).
6. Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

Avoid using as references abstracts; "unpublished data" and "personal communications". References to accepted but yet unpublished articles are allowed to be made, only if you note "in press".

6. Acknowledgements: You may wish to acknowledge people who have helped you. These can range from those who supported you with exper¬imental techniques to those who read or offered advice on your final manuscript.

7. Data file format for illustrations (figures): JPG

If photographs of patients are used, either the subjects should not be identifiable or their pictures must be accompanied by written permis-sion to use the figure. Permission forms are available from the Editor.

If data files are too big for transmission as an Email attachment submis¬sion of a CD to our address is recommended.

8. Legends for Illustrations (Figures)

The legend of a table has to be placed above the table. The reference of a table, which has been taken from another publication, must be placed below the table. (It is the author's responsibility to obtain the permission of reproduction from the publishers of the publication.) Figure legends are to be placed at the end of the paper. The reference of a figure taken from another publication stands at the end of the legend. (Permission of reproduction must be obtained from the publishers of this publication).