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ММР

Original article

STIGMA AND ASSOCIATED QUALITY OF LIFE IN PATIENTS WITH SKIN DISEASE

СТИГМА И ВЛИЈАНИЕ ВРЗ КВАЛИТЕТ НА ЖИВОТ КАЈ ДЕРМАТОЛОШКИ ПАЦИЕНТИ

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Abstract

Introduction. Skin and skin problems lead to a specific set of psychological manifestations of shame, embarrassment, poor self-image and self-esteem for many. The perception of one's own attractiveness is determined by social experiences and existing cultural values. Most of us respond positively to those who are attractive and negatively to those who are unattractive. Therefore, patients with skin diseases have an increased risk of developing feelings of stigmatization and self-injurious ideas.

Attracting attention to others, skin changes lead to situations of avoidance, public ignoring, distancing and reactions of disgust. Ginsburg and Link[1] identify six (6) aspects associated with stigma-anticipation of rejection, feeling guilty, sensitivity to the "attributes" of others, guilt and shame, secrecy, absence of positive attitudes. The authors consider that a basic predictor of stigma is the feeling of rejection. Gupta *et al*. [2] in their research they confirm that 26% of patients with dermatological disease were publicly shunned. Sampogna *et al.* [3] talk about frequent or continuous humiliating experiences where shame is one of the leading emotions that follow the experienced unpleasant experiences. Ginsburg *et al*. [1] talk about how 99 out of 100 patients described real stigmatizing experiences related to their appearance. The feeling of shame and stigmatization leads to a disturbed quality of life and sexual life, as its important component.

Although completely and insufficiently, it has been investigated that individuals with skin disease can stigmatize themselves in conditions where they themselves do not accept their own appearance, assuming that others will react in the same or similar way.

Method. The research was conducted as a clinical, prospective study at the University Clinic of Dermatology. Seventy respondents participated in the research, who answered the questions questionnaires, after previously signed consent to participate.

Results. In our study, the way the patient subjectively experiences and copes with the disease or the perception of the disease as a problem that includes preoccupation with the disease, stigmatizing feelings and experiences related to it, reduced self-esteem was shown to have a greater impact on what concerns the feeling of well-being.

Conclusion. The overlapof the prevalence of experiencing stigmatization, reduced self-esteem among respondents with skin disease and their impact on quality of life may lead to various therapeutic possibilities that will result in reducing the consequences of it.

Keywords: skin disease, stigma, stress, quality of life

Абстракт.

Вовед. Кожата и кожните проблеми кај многумина доведуваат до специфичен сет на психолошки манифестации на срам, засраменост, сиромашна слика за себе и самопочит. Перцепцијата за сопствената привлечност е детерминирана од социјалните искуства и постоечките културолошки вредности. Повеќето од нас позитивно реагираат на оние кои се атрактивни и негативно кон оние кои се неатрактивни. Според тоа, пациентите со кожни болести имаат зголемен ризик за развој на чувства на стигматизираност но и самоповредувачки идеации.

Привлекувајќи го вниманието кај другите, кожните промени доведуваат до ситуации на избегнување, јавно игнорирање, дистанцирање и реакции на згроженост. Ginsburg и Link [1] идентификуваат шест (6) аспекти кои се асоцирани со стигмата-антиципација на отфрлање, чувство на грешност, сензитивност кон „атрибутите“ на другите, вина и срам, тајновитост, отсуство на позитивни ставови. Авторите сметаат дека основен предиктор на стигмата е чувството на отфрленост. Gupta *и сор*. [2] во своите истражувања потврдуваат дека 26 % од пациентите со дерматолошко заболување биле јавно избегнувани. Sampogna *и сор.* [3] зборуваат за чести или континуирани понижувачки искуства каде срамот е еден од водечките емоции кои се надоврзуваат на доживеаните непријатни искуства. Ginsburg *и сор.* [1] зборуваат за тоа дека 99 од 100

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пациенти опишале вистински стигматизирачки искуства врзани за нивната појава. Чувството на срам и стигматизираност доведуваат до нарушен квалитет на животот и на сексуалното живеење, како негова важна компонента.
Иако целосно и недоволно, испитано е дека индивидуите со кожна болест можат самите себеси да се стигматизираат во услови кога и тие самите не ја прифаќаат сопствената појава, претпоставувајќи дека и другите ќе реагираат на ист или сличен начин.
Методи. Во истражувањето кое беше дизајнирано како клиничка проспективна студија учествуваа седумдесет испитаници, кои одговорија на зададени прашалници, по предходно потпишана согласност за учество.
Резултати. Во нашето истражување се потврди дека начинот на кој пациентите ја перцепираат кожната болест и се справуваат со неа на начин кој подразбира преокупираност со болеста, чувство на стигматизираност и доживувања асоцирани со стигма влијае врз чувството на благосостојба кај пациентите.
Заклучок. Препознавањето на застапеноста на доживувањето на стигматизираност, намалена самодоверба кај испитаниците со кожна болест и нивното влијание врз квалитетот на живеење може да доведе до разни терапевтски можности кои ќе резултираат со редуцирање на последиците од истата.

Клучни зборови: кожна болест, стигма, стрес, квалитет на живот

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real stigmatizing experiences related to their appearance [1]. The feeling of shame and stigmatization lead to a disturbed quality of life and sexual life, as its important component. Stigma in an individual can appear in different ways and mainly conditioned by two types of negative experiences. In the first case, stigma refers to a direct negative experience when the individual is faced with direct rejection. In the second case, stigma occurs when a person witnesses someone else's experience linked to stigma. Bondura talks about how we humans gather more information about our environment by looking at the experiences of others. In doing so, we expect to be treated in a similar way to how others have been treated, depending on how similar we are to others or behave similarly [4]. Third, although not to that extent specific to stigma, is when the environment does not reject directly, but considers it acceptable to treat and treat people as curiosities because of their skin condition or illness.
Finally, although fully and insufficiently investigated, individuals with skin disease can stigmatize themselves in conditions where they themselves do not accept their appearance, assuming that others will react in the same or similar way.
It is surprising how little research has been done on the true nature of stigmatizing experiences. A better understanding of what stigma actually looks like, under what conditions it occurs, as well as knowledge of the characteristics of those who stigmatize is necessary. Experiences with stigmatization have a huge impact on the individual's well-being, his quality of life, and therefore deserve a deeper analysis.

Introduction

Skin and skin problems lead to a specific set of psychological manifestations of shame, embarrassment, poor self-image and self-esteem for many. The perception of one's own attractiveness is determined by social experiences and existing cultural values. Most of us respond positively to those who are attractive and negatively to those who are unattractive. Therefore, patients with skin diseases have an increased risk of developing feelings of stigmatization and self-injurious ideas. Attracting attention to others, skin changes lead to situations of avoidance, public ignoring, distancing and reactions of disgust. Ginsburg and Link[1] identify six (6) aspects associated with stigma-anticipation of rejection, feeling guilty, sensitivity to the "attributes" of others, guilt and shame, secrecy, absence of positive attitudes. The authors consider that a basic predictor of stigma is the feeling of rejection. Gupta *et al.* [2] in their research they confirm that 26% of patients with dermatological disease were publicly shunned. Sampogna *et al.* [3] talk about frequent or continuous humiliating experiences where shame is one of the leading emotions that follow the experienced unpleasant experiences. Ginsburg *et al*. alk about how 99 out of 100 patients described

Objectives of the research

Social stigmatization, physical limitations, employment problems and others psychosocial comorbidities and their impact on patients' quality of life with skin disease.

Material and methods

Study design

The research was conducted as a clinical, prospective study at the University Clinic of Dermatology. Respondents with a diagnosed skin disease according to the criteria of ICD 10 (International Classification of Diseases) were included in the research.

Sample

Subjects with the following diagnosed skin diseases were included in the research: Vitiligo, Urticaria, Dermatitis atopica, Alopecia areata.

Population

70 subjects with a diagnosed skin disease took part in

the research, and at the beginning of the research, aDLQI[1]-A scale for assessing the impact of dermatological disease on the psychosocial functioning and quality of life of the respondents.

Methodology

The examination was conducted using the following structured tests and procedures:
- A non-standardized questionnaire for demographic, socioeconomic data designed for research purposes and containing the following data:
a) general data: gender, age, education, employment, profession, ethnicity, marital status.
b) age when the disease was diagnosed, length of it, number of hospitalizations due to the disease, type of treatment and therapeutic response.

- DLQI[2]- A scale for assessing the impact of dermatological disease on the psychosocial functioning and quality of life of the respondents.

The scale was designed in 1994 and is the first dermatologically specific instrument for investigating the impact of skin disease on the respondent's daily physical, social and psychological life. Its value has been described in more than 1000 publications, including many multinational studies.
The instrument contains 10 questions that evaluate the impact of the dermatological problem on the respondent's life in a certain period of time. The minimum value obtained -0, indicates the absence of influence, and the maximum value -30, particularly large influence. The scale has a particularly important role in assessing the limitations that the skin disease causes in the patient's daily functioning.
The DLQI-questionnaire is a self-assessment instrument, it is simple to apply and without the need for detailed explanations. It usually takes two minutes to complete.

Results

At the beginning of this section, the data obtained by processing and analyzing 70 subjects, patients with a diagnosed dermatological disease, aged from 21 to 59 years, with an average age of 41.2±10.7 years, are presented. The gender structure of the respondents consisted of 31(44.29%) male patients and 39(55.71%) female patients (Table 1, Figure 1).

Table 1. Demographic characteristics of the respondents

Variable	n(%)
Sex	
Men	31(44.29)
Women	9(55.71)
Age	
N (70) mean ±SD (41.2±10.7) min - max (21-59)	
Education	
1	12(17.14)
2	36(51.43)
3	4(5.71)
4	18(25.71)

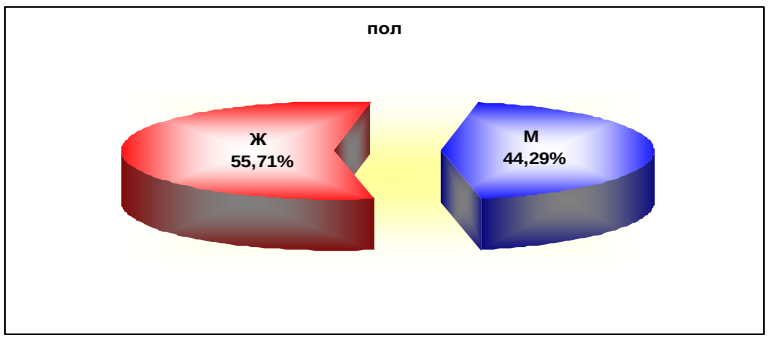

Fig. 1. Graphic representation of the gender distribution of respondents

The results of the questionnaire for assessing the degree of influence of the dermatological disease on the disruption of the quality of life among the respondents [1] showed that in the majority of patients the dermatological disease has a large and extremely large impact - 39 (55.71%). Dermatological disease has no impact on the quality of life only in 6 (8.57%) of the patients (Table 2, Figure 2).

Table 2. Distribution of Dermatology life quality index

DLQI	n (%)
Without effect	6(8.57)
Little effect	15(21.43)
Moderate	10(14.28)
Golem	29(41.43)
Extreme	10(14.28)

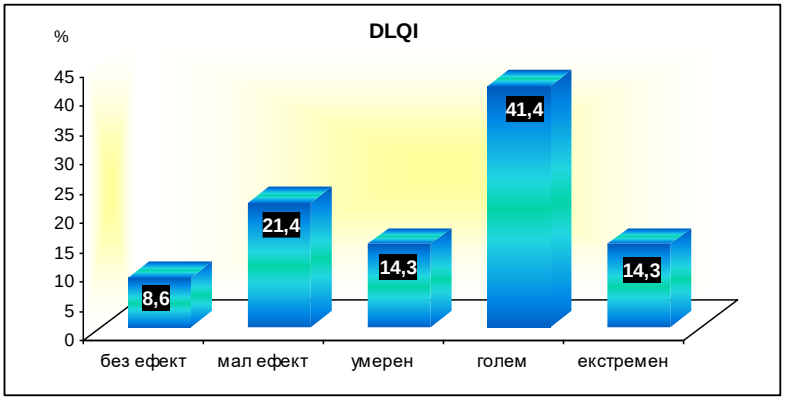

Fig. 2. Graphic display of Dermatology life quality index

Discussion

The purpose of the conducted research was to determine the existence of the complex relationship and the impact of the skin disease and the experience of it on the quality of life.

In our study, the way the patient subjectively experiences and copes with the disease or the perception of the disease as a problem that includes preoccupation with the disease, stigmatizing feelings and experiences related to it, reduced self-esteem was shown to have a greater impact on what concerns the feeling of well-being.

Early experiences and cultural stereotypes related to skin conditions are factors that greatly influence the way of dealing with the skin disease and thus directly the quality of life associated with the disease.

Unexpectedly, in the research we came across an interesting finding, which is little described in the literature and refers to the specificities related to the cultural ideal of how someone should look. What people fear the most is being judged, shunned, ridiculed because of their appearance and appearance. Anticipating negative criticism leads to low self-esteem and self-blame which, on the other hand, conditions a reduction of social capacities.

In the research carried out, the quality of life was affected in a large number of subjects with skin disease, which is in line with other studies that supported it.present the finding that the stress reaction in response to the disease affects the exacerbation of the skin condition, which in turn affects the quality of life.

The impact of the skin disease on the quality of life is conditioned by the disease itself, by stressful situational events (social stigmatization), anticipatory social stigma and changes in the previous life style.imposed by the disease itself. Psychosocial themes and manifestations are an integral part of skin disease and rightfully so-they attract attention in daily practice and also indicate the necessity of biopsyhosocial approach in patients with dermatological diseases.

Conclusion

The overlapof the prevalence of experiencing stigmatization, reduced self-esteem among respondents with skin disease and their impact on the quality of life and changes in the lifestyle imposed by the disease itself can lead to various therapeutic possibilities that will result in reducing the consequences of the disease.

Conflict of interest statement. None declared.

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Original article

RETROSPECTIVE ANALYSIS OF PREGNANCY TERMINATION DUE TO SEVERE CONGENITAL ANOMALIES

РЕТРОСПЕКТИВНА АНАЛИЗА НА ПРЕКИН НА БРЕМЕНОСТ ПОРАИ ТЕШКИ КОНГЕНИТАЛНИ АНОМАЛИИ

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Abstract

Introduction. The most common reasons for termination of pregnancy in the second trimester are foetus mortus, premature rupture of the membranes, congenital fetal malformations (FM), severe intrauterine retardation of the fetus, cervical insufficiency.
Aim. To analyze the incidence, distribution and characteristics of severe FM in termed pregnancies at the Clinic for Gynecology and Obstetrics in the "Remedika Hospital"- Skopje, North Macedonia and to better manage termination of pregnancy (TP) at our Clinic.
Methods. This was a retrospective cross-sectional study in which all data obtained about the mother, obstetric characteristics and indications were analyzed by using the electronic system (BIRPIS). In addition, all maternity records of patients in whom pregnancy was terminated in the second trimester due to severe congenital malformations at our hospital between January 2019 and December 2021 were analyzed. The detected anomalies were grouped as isolated structural, multiple congenital and chromosomal disorders. Congenital malformations were also divided into subgroups according to the main organ systems involved according to the EUROCAT classification. The groups were classified according to their character traits and compared with each other.
Results. In a period of three years (2019-2021), 27 terminations of pregnancy were registered, of which 40.8% in 2019, and in 2020 and 2021, 29.6% each. The average age of patients was 33.5±5.7 years; two of the patients smoke. A significantly high number of 17(63.0%) chromosomal anomalies were registered ($p<0.05$) (Difference test, p=.0024), followed by 22.2% isolated anomalies and 14.8% multiple anomalies. In 48.1% of cases male gender was determined and in 37.0% female; the percentage difference was not significant for $p>0.05$. The average gestational week was 16.7±3.4, ranging from 12 to 22 gestational weeks.
Conclusion. A significant part of TP between 12-22 g.w. with an average gestational week of 16.7±3.4 of the pregnancy for fetal anomalies were due to genetic-chromosomal diseases with the most frequent representation of Down syndrome in 33.3% of cases, followed by Edward syndrome in 11.1%. Of isolated and multiple malformations, the majority of anomalies were central nervous system defects, followed by abdominal wall defects and orofacial clefts. This pattern is consistent with previous studies.

Keywords: fetal malformations, congenital anomalies, termination of pregnancy

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Апстракт

Вовед. Најчести причини за прекин на бременост во втор триместар се Foetus mortus, предвремена руптура на мембраните, вродени фетални малформации (ФМ), тешка интраутерина ретардација на плодот, цервикална инсуфициенција.
Цел. Да се анализира инциденцата, дистрибуцијата и карактеристика на тешките ФМ кај терминираните бремености на Клиниката за гинекологија и акушерство во ПЗУ “Ремедика”-Скопје, и да го менаџираме прекинот на бременоста (ПБ) во нашата клиника подобро.
Методи. Преку ретроспективна пресечна студија беа анализирани сите колектирани база податоци од мајката, акушерските карактеристики и индикациите со помош на електронскиот систем (BIRPIS) и матичните родилни дневници на нашата болница помеѓу Јануари 2019г. и Декември 2021г. на пациентки кај кои е извршен прекин на бременост во втор триместар поради тешки конгенитални малформации. Откриените аномалии беа групирани како изолирани структурни, мултипни вродени и хромозомски нарушувања. Конгениталните малформации исто така беа поделени во подгрупи според инволвираните главни органски системи според EUROCAT класификацијата. Групите беа класифицирани според нивните карактерни карактеристики и беа споредувани една со друга.
Резултати. Во период од три години 2019-2021г. се регистрираат 27 прекини на бременост, од кои 40.8% во 2019г., и во 2020 и 2021г. по 29.6%

(Табела 1). Просечната возраст на пациентките е 33.5±5.7г., две од пациентките пушат.Се регистрираат сигнификантно најголем број 17(63.0%) за p<0.05 (Difference test, p=.0024) на хромозомски аномалии, 22.2% изолирани аномалии и 14.8% мултипни аномалии. Во 48.1% одреден е машки и кај 37.0% женски пол, процентуалната разлика е не сигнификантна за p>0.05. Просечната гестациска недела изнесува 16.7±3.4, во ранг од 12 до 22 гестациска недела.

Заклучок. Значителен дел од ПБ помѓу 12- 22 г.н. со просечна гестациска недела 16.7±3.4 од бременоста за фетална аномалија се должат на генетскохромозомални заболувања со најчеста застапеност на Down syndrome во 33.3%,последуван од Edward syndrom во 11.1%. Од изолирани и мултипни малформации,поголемиот дел од аномалиите во групата на изолирани малформации беа централни нервни системски дефекти, проследени од дефекти на абдоминалниот ѕид и оро-фацијални расцепи. Овој модел е во согласност со претходни студии.

Клучни зборови: фетални малформации, конгенитални аномалии, прекин на бременост

Introduction

Congenital abnormalities or congenital anomalies are defined as structural malformations detected prenatally, after abortion, at birth, or post-mortem [1]. Congenital malformations (CM) differ in terms of their effect on live births and are classified as major or minor congenital abnormalities. Major congenital malformations are defined as any birth defects associated with physical or cosmetic damage [1]. Major malformations are severe if the newborn cannot survive without medical or surgical intervention or results in the death of the newborn/stillbirth [14]. The incidence of congenital malformations varies by race, which may be explained by genetic/epigenetic variation and the effects of specific risk factors for certain races or populations [1]. Major CMs show considerable variation worldwide with prevalence ranging from <1% to 8%, and they cause 20% and 30% of perinatal deaths [14]. Today advances in ultrasonography and the genetic field are increasing rates of prenatal diagnosis of fetal malformations. Therefore, termination of pregnancy as an option is increasingly offered to patients. This approach may also introduce some medical, ethical, and legal issues [20]. When congenital malformations are associated with a poor prognosis, termination of pregnancy (TP) is an option for parents depending on many factors including laws, religious beliefs, the type and severity of CM, economic considerations, and education, among others. TB is a controversial topic in many countries with legal provisions, as well as the legal gestational limit for TB, varying from country to country. In approximately one-third of the countries in Europe, there is a legal gestational limit for TP, while TP is not legally available in other countries, such as Uruguay [15]. In our country, termination of pregnancy is a special medical intervention for which the pregnant woman freely decides until the end of term in the 12th g.w. The procedure for approving and performing TP in case of detected CM, according to the law on termination of pregnancy of the Republic of North Macedonia, can be carried out even after the 12th g.w of pregnancy until 22nd g.w. after a written request is obtained from the pregnant woman/the guardian, and a statement of consent to accept the implementation of the intervention for TP, or after a decision of a first-level committee if TP is needed over the 22nd g.w. [24]. Termination of pregnancy is a serious and difficult decision for parents. Early diagnosis is of essential importance for this procedure both from a legal and ethical point of view.

Aim

To analyze the incidence, distribution, and characteristics of severe fetal malformations (FM) in terminated pregnancies at the Clinic for Gynecology and Obstetrics in the “Remedika Hospital-Skopje, North Macedonia and to better manage termination of pregnancy (TP) at our Clinic. To determine the most significant demographic characteristics of pregnant women diagnosed with FM.

Materials and methods

We retrospectively evaluated the pregnancies with major congenital anomalies, which were terminated from 12 to 22 gestation week at the Clinic for Gynecology and Obstetrics in the “Remedika Hospital- Skopje, in the period between January 2019 and December 2021. The necessary data about the mother, obstetrical characteristics, and indications were taken by using the electronic system (BIRPIS) and maternity diaries of our hospital. Cases such as unwanted pregnancies, dead fetuses in the uterus, and premature rupture of the membranes at the time of admission to the hospital were excluded from this study. Major congenital malformations were defined as any structural abnormalities, or birth defects associated with physical or cosmetic damage to the fetus determined by factors acting largely before conception or during pregnancy. Demographic characteristics, clinical characteristics, associated risk factors, and type and distribution of fetal anomalies by organ systems were analyzed. Age, pregnancy and parity, gestational week of pregnancy, method of conception (spontaneous/assisted reproductive technologies), chorionicity (singleton/mul-

tiple), and if available, karyotype assessment of pregnancy were analyzed. The results obtained regarding cases with congenital anomalies were grouped systematically, and their incidence and distribution were compared with the literature. The inclusion criteria of CM, their severity, and their classification, were according to the EUROCAT guidelines, a computer algorithm implemented by EUROCAT for the classification of cases of congenital anomalies followed by a manual review of the cases by geneticists, which is based on the International Classification of Diseases version 10 (ICD-10). Terminated cases were classified as chromosomal, genetic and ecological, isolated, and multiple congenital anomalies. Patients with more than one involved system were recorded as multiple abnormalities. All pregnant patients who are followed in our institution are offered a screening test that is carried out according to the instructions of the International Association for Ultrasound in Obstetrics and Gynecology (ISUOG), in the first trimester between the 11th and 13+6th gestational week and fetal screening for ultrasonography abnormalities between the 18th and 22nd gestational weeks.Fetal echocardiography is performed as part of the fetal screening in the second trimester. Karyotyping of the fetus by chorion biopsy, amniocentesis, or non-invasive prenatal test (NIPT) in necessary cases was applied after obtaining informed consent from the patient. All TP were performed after a submitted request for approval of TP with detailed informed consent from the patient and after obtaining approval for TP by a medical ethics committee consisting of three specialists in obstetrics and gynecology.
Vaginal or intramuscular parenteral induction with prostaglandins, with or without oxytocin, is generally used as the main procedure in the second trimester for TB. The optimal dose and dosing interval are selected based on the gestational week, obstetric history, clinical guidelines, practice, examinations, and clinical condition. In cases that do not respond to prostaglandin or oxytocin stimulation, transcervical application of a Foley catheter was performed. After the expulsion of the fetus in a short-term i.v. anesthesia, manual and/or instrumental revision of the uterus was performed to remove the retained or partially retained parts of the placenta.
Congenital malformations were confirmed after termination of pregnancy by physical examination of the fetus or pathohistological autopsy findings or karyotyping from a tissue section.

Statistical analysis

The data obtained from the medical history were grouped and distributed accordingly in a database in Microsoft Excel. They were processed with the statistical software package SSPS 26. A descriptive analysis of data was made, with which certain conclusions were obtained, and part of the results are the basis for calculating further statistical research. Using the normality test, it was checked whether the sample was selected from a population with a normal distribution. Mean value standard deviation, and structure percentages were determined. The difference was determined by the difference test (Difference test). A p-value of less than 0.05 was considered statistically significant.

Results

In a period of three years (2019-2021) 27 pregnancy terminations were registered, of which 40.8% in 2019, and in 2020 and 2021, 29.6% each (Table 1).

Table 1. Presentation of patients' characteristics

Year			**Number**	**%**
2019			11	40.8
2020			8	29.6
2021			8	29.6
Age	**Average**	**Minimum**	**Maximum**	**SD**
	33.5	24	44	5.7
Anomalies				
Chromosome anomalies			17	63.0
Isolated anomalies			6	22.2
Multiple anomalies			4	14.8
Nationality				
Macedonian			22	81.5
Albanian			3	11.1
others			2	7.4
Parity				
first			14	51.9
fourth			1	3.7
second			7	25.9
third			5	18.5
Chronic diseases				
non			22	81.5
Myasthenia gravis			1	3.7

Hashimoto	3	11.1
Uterus didelfus, cervix duplex, septum vagine	1	3.7
Drugs during pregnancy		
vitamins	27	100.0
Euthyrox	3	11.1
Conception method		
IVF	7	25.9
spontaneous	20	74.1
Antenatal screening		
ultrasound	23	85.2
PRISCA I-high risk, US	2	7.4
PRISCA I-low risk, US	1	3.7
PRISCA I, low bHCG	1	3.7
Karyotypization		
Chorion biopsy	7	25.9
no	5	18.5
Amniocentesis	7	25.9
NIPT	8	29.6

The average age of patients was 33.5±5.7 years; two of the patients smoke.

A significantly large number of 17(63.0%) chromosomal anomalies were detected, $p<0.05$ (Difference test, p=.0024), followed by 22.2% isolated anomalies and 14.8% multiple anomalies.

According to nationality, 81.5% were Macedonians and 11.1% Albanians; the percentage difference was significant for $p<0.05$ (Difference test, p=.0000).

51.9% of patients had first parity, 25.9% had second parity, 18.5 third, and quarter only one patient. The percentage difference between the first parity versus the rest was significant for $p<0.05$

Chronic diseases were registered in 18.5% of patients, and 81.5% were without any chronic disease; the percentage difference was significant for $p<0.05$ (Difference test, p =.0500).

Comorbidity (submucous myoma) was registered in one patient.

During pregnancy, all patients took vitamins, and 11.1% took Euthyrox in addition to vitamins.

All patients underwent antenatal screening.

The following systematic malformations were registered Spina bifida, gastroschisis, meningomielocele, Tetralogia Fallot, hydrocephalus, meningocela lumbosacralis, agenesio corpus callosum, holoprosencephaly, Polydactilia bill extremitas, Pes equinovarus, while some of them were in conjunction with chromosomal anomalies.

Table 2. Presentation of karyotype, gender, weight and gestational week

Gender	**Nº**		**%**	
Female	10		37.0	
Male	13		48.1	
No data	2		7.4	
cannot be detected from NIPT	1		3.7	
Karyotypization				
Trisomy 21 (Down sy)	9		33.3	
Heterozygote of sequence NEK I	1		3.7	
Trisomy 18 (Edward sy)	3		11.1	
Contamination	1		3.7	
Not done	4		14.8	
Syndrome Tripple XXX (47 xxx)	1		3.7	
Trisomy 13 (Patau sy)	1		3.7	
Disomy XYY	1		3.7	
Deletion 5p (Cri-Du-chat sy)	1		3.7	
Deletion 10q26 sy	1		3.7	
no chromosomal abnormality	4		14.8	
	Average	**Minimum**	**Maximum**	**SD**
Weight	107.9	101	116	5.7
G.w. of termination	16.7	12	22	3.4

48.1% were males and 37.0% females; the percentage difference was insignificant for $p<0.05$. The sex of one fetus could not be determined. The average weight was 107.9±5.7 g, ranging from 101 g to 116 g. The average gestational week was 16.7±3.4, ranging from 12 to 22 gestational weeks (Table 2).

Table 3. EUROCAT Classification-Presentation of systemic malformations

Nervous sustem	No.
Neural tube defects - anenecephaly and similar, encephalocele, spina bifida	2
Hydrocephalus	1
Arhinencephaly/holoprosencephaly	3
Agnesiocorpus callosum	1
Kade treba da stoi ovoj broj?	1
Abdominal wall defects	
Gastroschisis	2
Chromosomal	
Down Syndrome	9
Patau syndrome/trisomy 13	1
Edward syndrome/trisomy18	3
Tripple XXX syndrome	1
Disomy XYY	1
Deletion 5p (Cri-Du-chat syndrome)	1
Deletion 10q26 syndrome	1
Heterozygote of sequence NEK I	1

Table 3 includes the number and type of anomalies registered according to the EUROCAT classification. The most frequently registered chromosomal anomaly was Down syndrome, detected in 9 fetuses.

Discussion

Termination of pregnancy is a serious and difficult decision for parents. Early diagnosis is of essential importance for this procedure both from a legal and ethical point of view. The inclusion of social media in such popular medical topics and the opportunistic approaches of politicians create difficulties in routine practice. Physicians must be more careful in their practice and need supportive scientific recommendations and protocols from medical organizations to make bold decisions. We believe that considering the ethical, social, psychological, economic, and legal aspects of TP and its implementation in collaboration with families and doctors will be effective in developing standard approaches for this work [20]. The decision to choose TP is considered a private work of the couple. Couples may be fearful of the potential negative outcomes of even less severe CM so they are unwilling to take any risks, even if the likelihood of a negative outcome is low. In addition, the innovation and popularization of prenatal diagnostic technologies have led to a diagnosis in an earlier gestational period, accordingly, TP may be more acceptable when performed in earlier periods [17]. The current study showed that a significant part of TP between 12-22 gestational week, with an average gestational week of 16.7±3.4 of pregnancy for fetal anomalies, were due to genetic-chromosomal diseases, of which the most frequent one was Down syndrome, followed by isolated and multiple malformations. The majority of anomalies in the group of isolated malformations were central nervous system defects. This results are in accordance with previous studies [19]. Chromosomal abnormalities were identified in more advanced maternal age and in earlier weeks of pregnancy. We observed that isolated structural and multiple congenital anomalies were identified at younger ages and more advanced weeks of pregnancy. It has been reported that congenital abnormalities are the most common causes of TOP and among these abnormal conditions, malformations originating from the central nervous system are most frequently observed [17].

Ne se site reference citirani niz tekstot

Fali conclusion

Conflict of interest statement. None declared.

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MMP

Original article

INSOMNIA AMONG ADDICTS MITTENED TREATED WITH OPIOID AGONIST THERAPY

НЕСОНИЦА КАЈ ЗАВИСНИЦИ ТРЕТИРАНИ СО ОПОИДНИ АГОНИСТИ

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Abstract

Introduction. Methadone and buprenorphine are used to prevent illicit drug use and mitigate related risks and harms. However, many methadone maintenance treatment (MMT) patients experience sleep disturbances, while buprenorphine maintenance treatment (BMT) may initially cause sleep issues but can improve overall sleep quality over time. This study aimed to compare the severity of insomnia among MMT, BMT, and healthy control (HC) subjects.

Methods. The study included patients who had been on MMT or BMT for at least two years. HC subjects had no history of substance use. Exclusion criteria were dual disorders, neurological diseases, and pregnancy or breastfeeding. A non-standardized questionnaire was used for demographic characteristics, drug and medicine use, and the Insomnia Severity Index was employed to evaluate insomnia severity over the last two weeks. This cross-sectional study was conducted at the Department for Drug Dependence, University Clinic for Psychiaty in Skopje.

Results. The three groups did not differ significantly in terms of age, gender, or education. A significant difference was found between the groups in the total score of insomnia (p<.01**), with MMT patients experiencing more severe sleep problems than BMT and HC subjects. A higher percentage of MMT patients had subthreshold, moderate, and severe insomnia compared to the BMT group, with more cases of no clinically significant insomnia.

Conclusion. The results demonstrated that MMT patients exhibit more severe insomnia compared to BMT and HC subjects. The findings underscore the need for targeted interventions to address sleep disturbances in MMT patients.

Keywords: insomnia, opioids, maintenance treatment, methadone, buprenorphine

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Апстракт

Вовед. Метадон и бупренорфин се користат за превенција на нелегалната употреба на дроги и за редукција на асоцираните со нив ризици и штети. Сепак, многу пациенти на метадонска одржувачка терапија (ММТ) се соочуваат со нарушувања на сонот, додека одржувачката терапија со бупренорфин (БМТ) иако првично може да предизвика проблеми со сонот, по одреден временски период може да го подобри целокупниот квалитет на сонот. Оваа студија имаше за цел да ја спореди тежината на несоницата кај пациенти на ММТ, БМТ и здрави контролни субјекти (ЗК).

Методи. Во студијата беа вклучени пациенти кои биле на ММТ или БМТ во период од најмалку две години. Здравите контролни субјекти немаа историја на употреба на супстанции. Критериуми за исклучување беа двојни нарушувања, невролошки болести, бременост или доење. За демографските карактеристики, употребата на дроги и лекови беше користен нестандарден прашалник, а за проценка на тежината на несоницата во последните две недели беше користен Индексот на тежина на несоницата. Оваа пресек студија беше спроведена на Одделот за зависност од дроги, Психијатриска болница Скопје.

Резултати. Трите групи испитаници не покажаа значајни разлики во однос на возраста, полот или образованието. Беше утврдена значајна разлика меѓу групите во вкупниот резултат за несоница (p <.01**), при што пациентите на ММТ имаа посериозни проблеми со сонот во споредба со пациентите на БМТ и здравите контролни субјекти. Поголем процент од пациентите на ММТ имаа субпрагова, умерена и тешка несоница во споредба со групата на БМТ, која имаше повеќе случаи без клинички значајна несоница.

Заклучок. Пациентите на ММТ имаат потешка несоница во споредба со пациентите на БМТ и здра-

вите контролни субјекти. Наодите ја истакнуваат потребата од насочени интервенции за решавање на нарушувањата на сонот кај пациентите на ММТ.

Клучни зборови: несоница, опиоиди, одржувачка терапија, метадон, бупренорфин

Introduction

Insomnia is one of the most common sleep disorders among the general population, frequently seen in medical practices. Global studies show that 10% to 30% of people suffer from insomnia, with some reports indicating rates as high as 50% to 60% [1,2]. The consumption of alcohol or opioid drugs additionally increases the risk of sleeping problems and insomnia symptomatology. In relation to this, although short-term opioid use primarily helps people fall asleep faster, it reduces both sleep quality and total sleep duration. Initially, opiates have sedative effects, causing increased daytime sleepiness and shorter sleep latency. However, they also lead to sleep disruptions later in the night, including more frequent awakenings due to acute withdrawal effects [3]. Along with the previously stated, an acute opioid use further leads to more frequent changes in sleep states, increased awakenings, a rise in non-rapid eye movement (NREM) sleep, and decreases in total sleep duration, slow wave sleep, and rapid eye movement (REM) sleep [4]. Despite their sedative reputation, opioids can disrupt sleep quality when used chronically. Over time, users might build tolerance to some of the negative sleep effects, yet more severe insomnia can still occur.

Methadone and buprenorphine, long-acting synthetic opioids, are given to opioid-dependent patients in opioid maintenance therapy (OMT) to prevent illicit drug use and its associated risks [1]. However, many patients (75-84%) in methadone maintenance treatment (MMT) suffer from significant sleep disturbances, which can negatively impact daytime activities and increase the risk of drug relapse [5-7]. A recent study by Ignjatova *et al*. demonstrated that sleep disturbances and the use of alcohol, cannabis, and benzodiazepines were very common among patients undergoing methadone maintenance [8]. It was also indicated that female patients experienced significantly poorer sleep quality compared to males [8]. In line with this evidence, Zedler *et al*. reported that sleep disorders were highly prevalent among patients undergoing methadone maintenance treatment (MMT). The study found that these patients frequently experienced significant sleep disturbances, with a notable prevalence of insomnia [9]. Furthermore, an ever-increasing body of literature shows that poor sleep efficiency, decreased total sleep time, increased nighttime wakefulness, decreased REM and decreased slow wave sleep are frequent subjective sleep complaints of the methadone-maintained patients [10]. Patients undergoing methadone treatment frequently suffer from depression and anxiety disorders, which further negatively influence their sleep as well [8]. Having said that, it is clear that sleep disturbances among the MMT group are indeed of a significant concern, though the exact mechanisms underlying the disruption of the normal sleep patterns are still unclear.

Conversely, certain studies indicate that buprenorphine (BMT) may initially disrupt sleep but could enhance overall sleep quality with prolonged use. Evidence also suggest that buprenorphine might be more effective than traditional opioids in treating pain due to its reported pain-relieving effects and fewer side effects. For example, one case report demonstrated a successful reversal of central sleep apnea (CSA) by switching from methadone to buprenorphine [11]. Another also relevant study on buprenorphine treatment in heroin-dependent men indicated that it might alleviate sleep disturbances and normalize sleep patterns [12]. On the contrary, other research demonstrate that individuals with opioid use disorder (OUD) receiving buprenorphine experience statistically significant symptoms of insomnia. Moreover, the results from a cross-sectional observational study also implied that buprenorphine/naloxone might induce significant CSA and hypoxemia [13]. Data from studies also suggests that individuals undergoing methadone and buprenorphine maintenance treatment frequently experience insomnia and excessive daytime sleepiness, with women reporting these sleep disturbances more often than men [9]. Consistently, White *et al.*, based on the results of their study inferred that insomnia is common in this population and may influence treatment effectiveness, highlighting the need of personalized treatment approaches that address both sleep disturbances and substance use [14]. Having this conflicting evidence in mind, it can be noted that one conclusion regarding the relationship between buprenorphine and insomnia cannot be made and more research is needed.

A better understanding of the relationship between sleep disturbances and substance-use behaviors and the mechanism behind it, is needed, since it could aid in developing new, personalized treatment approaches for individuals with OUD and concurrent insomnia. Therefore, the aim of current study was to compare the severity of insomnia among MMT, BMT and healthy control (HC) subjects.

Materials and methods

Participants

All of the participants met the ICD-10 criteria for opiate addiction and were between 32-56 years of age. Inclusion criteria for both groups were undertaking methadone (MMT) or buprenorphine (BMT) for a minimum

of 2 years and stabilized on their current dose for at least six months. The inclusion criteria for healthy control subjects were no current or lifetime history of drug or alcohol use. Exclusion criteria were administered to all participants, and included a history and present of dual disorders (addiction and other mental disorder) as well as neurological disease and self-reported current pregnancy or breastfeeding. The MMT group consisted of 28 males and 2 females, with a mean age of 44.8±4.87 years. The BMT group included 28 males and 2 females, with a mean age of 41±6.31 years. Finally, the control group was consisted of 30 healthy control subjects, recruited from a local community. This group included 28 males and 2 females, with a mean age of 41.37±7.32 years.

The study was approved by the Human Research Ethics Committee, Ss. Cyril and Methodius University in Skopje, Faculty of Medicine in Skopje (No:03-3951/9) and a signed informed consent was obtained from all participants.

Not standardized questionnaire was used for collecting demographic characteristics, history and current use of drugs and medicines. ISI (Insomnia severity index) was used to evaluate the severity of insomnia in the last 2 weeks. The ISI questionnaire is consisted of 7 items (questions) and for each item the participants rate the severity of their insomnia problem(s) at the scale from 0-4. The items are evaluating different aspect of both nighttime and daytime components of insomnia: the severity of difficulties with falling asleep, staying asleep, and waking up too early; satisfaction with current sleep patterns; impact on daily activities; how noticeable the sleep problem is; and the distress level it causes. All scores from the seven questions are than added in one total score. When it comes to the scoring of the scale, A 5-point Likert scale (0 - none; 4 -very severe) is used to rate each item, with total scores ranging from 0 to 28. The interpretation of the scores is as follows: from 0 to 7 - no clinically signifycant insomnia; 8-14 - subthreshold insomnia; 15-21-clinical insomnia (moderate severity) and from 22 to 28 - severe clinical insomnia.

Study Design and Outcomes

This cross-sectional study was conducted in the Department for prevention and treatment of drug abuse and dependence, University Clinic for Psychiatry in Skopje. The primary aim for the current study was to compare differences between MMT, BMT and healthy controls (HC) in the severity of insomnia. Outcomes were analyzed for the treatment and healthy control group.

Statistical analysis

Descriptive and analytical statistical techniques were employed to analyze the results. The descriptive statistics methods used to summarize the data included arithmetic mean (average), and standard deviation. Amplitudes and latencies of the components were computed for each condition and each subject separately. One-way ANOVA was used for assessing statistical significance of the differences between groups (MMT, BMT and HC). Moreover, chi-square (x^2) test was also used in order to test the null hypothesis and make a valid conclusion. Due to page length limit, in the present study only the significant effects and interactions between groups are presented.

The levels of probability of realization of the null hypothesis according to the international standards of biomedical sciences was 0.05 and 0.01. The stars mean the level of significant difference between the groups (**p<0.01, *p<0.05).

Results

All three groups did not differ in age, gender and education (p<.05). Demographic characteristics of the participants together with the treatment duration and polydrug use are illustrated in Table 1. According to statistical analyses, the methadone group received a statistically significantly longer treatment than the buprenorphine group (p <.01).

Table 1. Demographic characteristics, treatment duration and polydrug use

	Age	Female	Male	Education (years)	Treatment duration (month)	Polydrug use (lifetime)
MMT	42.2	2	28	11.3	151.3	30/0
BMT	42	2	28	11.3	77.3	30/0
HC	41.4	2	28	11.5	0	0
p	n.s	n.s	n.s	n.s	<.01**	n.s

Table 2. Average number of used substances in lifetime period/last year /month

Group	Lifetime			Last year			Last month		
	M	SD	p	M	SD	p	M	SD	p
MMT	2.67	±1.18	n.s	0.33	±0.55	n.s	0.23	±0,5	n.s
BMT	2.73	±1.74	n.s	0.43	±1.3	n.s	0.17	±0,46	n.s

As we can see from Table 2, regarding the two treatment groups, there is no significant difference in the use of multiple substances during lifetime, in the last year nor in the last month (p >.05).

As previously stated, in order to determine the differrences among the groups in severity of insomnia, one-way ANOVA was conducted. The analysis revealed that there were statistically significant differences in the total score of ISI questionnaire across the MMT, BMT and the control group. In other words, there was a significant effect of the opioid agonist therapy on the ISI total score, with a F-ratio value of 7.56 and a p-value of .0009 (p<.01**). According to the mean values of the three groups, MMT (10.03±8.56); BMT (4,47±5.15) and HC (4,47± 4.82), it can be noted that participants in the MMT group experienced more severe insomnia symptoms when compared to participants of the other two groups (Table 3). Moreover, the results revealed a statistically significant difference between methadone (MMT) and buprenorphine (BMT) patients (p=003**), although these differences were not observed between BMT and the control group (p=1).

Furthermore, statistical analysis was also conducted in order to examine the differences between the three groups across the seven items of the ISI questionnaire separately. Regarding the first three items: difficulty falling asleep, difficulty staying asleep, and problems waking up too early, there were statistically significant differences between the MBT group and the other two groups (BMT and controls) (p<0.5*). In other words, people undertaking methadone had statistically significantly higher scores on these questions when compared to the BMT and control group. Correspondingly, the MMT group also reported more dissatisfactions in their sleep pattern (p<.01**), more noticeable symptoms of sleep problems (p<.01**), greater worries connected to the sleep problem (p<.01**) and stated bigger level of interference of these problems within their daily functioning (p < .01**), (Table 3).

Table 3. Means scores, standard deviations and p value for ISI

Item ISI	MMT M±SD	BMT M±SD	Controls	p
1. falling asleep	1.43±1.59	0.6±0.93	0.77±0.9	.018* .019 *
2. staying asleep	1.47±1.43	0.8±1.06	0.8±0.96	.04 *
3. early awakening	1.37±1.35	0.8±1.13	0.67±0.88	.04*
4. satisfaction	1.83±1.32	0.9±0.84	0.67±0.88	.00058**
5. noticeable	1.2±1.16	0.4±0.67	0.5±0.86	.0019**
6. worry	1.37±1.38	0.37±0.76	0.37±0.72	.0001**
7. interference	1.37± 1.45	0.6±0.77	0.37±0.72	.0008**
Total ISI score	10.03±8.56	4.47±5.15	4.47± 4.82	.0009**

Additionally, the participants from each of the three groups were further subdivided into four categories based on their insomnia severity score (0-7-no clinically significant insomnia; 8-14-subthreshold insomnia; 15-21-clinical insomnia (moderate severity); and 22-28 - severe clinical insomnia). As shown in Figure 1, where the number of patients in different score categories is presented, the participants in the HC and BMT group reported way less clinically significant symptoms of insomnia (HC-n=26; BMT-n=21), when compared to the MMT group (n=15). In order to compare the three groups in the insomnia severity levels, a chi-square test was also conducted. The chi-square statistics was 9.43, with a corresponding p-value of 0.0089, indicating statistically significant differences in insomnia severity among the groups at p < 0.01 level.

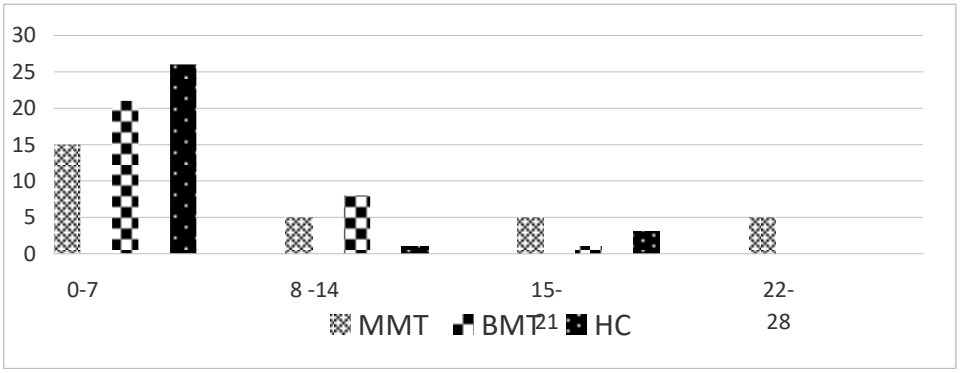

Fig. 1. Insomnia differences among groups

Discussion

The one-way ANOVA analysis conducted to examine

the differences in the severity of insomnia among participants undergoing methadone maintenance therapy (MMT), buprenorphine maintenance therapy (BMT), and a control group (HC) revealed significant findings, suggesting that participants in the MMT group experienced more severe insomnia symptoms compared to the other groups. Additional statistical analyses of the individual items of the ISI questionnaire shed light on specific sleep-related issues experienced by participants in each group, indicating more severe sleep difficulties in participants undergoing methadone treatment. To further examine the relationship between treatment modality and insomnia severity, a chi-square test was also conducted. The chi-square statistics of 9.43, with a corresponding p-value of 0.0089, indicated a statistically significant differences in insomnia severity among the groups ($p<0.01$ level). This result reinforces the findings from the ANOVA, emphasizing the significant impact of opioid agonist therapy, particularly methadone, on insomnia severity.

The findings of this study align with previous research indicating that methadone maintenance therapy is associated with higher rates of sleep disturbances compared to buprenorphine and control groups. For example, Zheng *et al*., found that individuals on methadone therapy reported significantly more sleep-related problems compared to those on buprenorphine [15]. Similarly, Peles *et al*., reported higher rates of insomnia among methadone-treated patients [7]. However, some studies have presented contrasting results. A study by Dunn *et al*., found no significant difference in sleep quality between methadone and buprenorphine groups, suggesting that factors other than the type of opioid agonist therapy might play a role in influencing sleep quality [16]. These discrepancies highlight the need for further research to clarify the relationship between different opioid maintenance therapies and sleep disturbances.

Limitations, Implications and Future Directions

Despite the significant findings of this study, several limitations should be acknowledged when interpreting the results. One limitation is the relatively small sample size, which may affect the generalizability of the findings. A larger sample could provide more robust data and improve the accuracy of the results. Furthermore, the study utilized a cross-sectional design, which limits the ability to infer causal relationships between opioid agonist therapy and insomnia severity. Finally, the use of self-reported measures, such as insomnia severity index (ISI), gives the potential for reporting biases. Participants may underreport or overreport their insomnia symptoms based on their perceptions and experiences. Objective measures of sleep quality could provide more accurate assessments.

The findings of this study have important implications in clinical practice and future research. The significant differences in insomnia severity among the groups suggest that methadone maintenance therapy is associated with more severe insomnia symptoms compared to buprenorphine maintenance therapy and the control group. This highlights the need of targeted intervenetions to address sleep problems in patients undergoing methadone treatment.

Future research should explore the underlying mechanisms contributing to the higher severity of insomnia in the MMT group and investigate potential strategies to mitigate these effects. Additionally, longitudinal studies could provide further insights into the long-term impact of different opioid agonist therapies on sleep quality and overall well-being.

Conclusion

In conclusion, this study demonstrates the significant impact of opioid agonist therapy, particularly methadone, on insomnia severity. Addressing sleep issues in this population is crucial for improving treatment outcomes and enhancing the quality of life in individuals undergoing opioid maintenance therapy.

Conflict of interest statement. None declared.

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MMP

Original article

200W THULIUM YAG LASER TRANSURETHRAL VAPORESECTION OF THE PROSTATE - FIRST 20 CASES IN REPUBLIC OF N. MACEDONIA WITH A 6-MONTH FOLLOW-UP

200W THULIUM YAG ЛАСЕРСКА ТРАНСУРЕТРАЛНА ВАПОРЕСЕКЦИЈА НА ПРОСТАТА - ПРВИ 20 СЛУЧАИ ВО РС. МАКЕДОНИЈА СО 6-МЕСЕЧНО СЛЕДЕЊЕ

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Abstract

Introduction. Benign prostatic obstruction (BPO) is the most common urologic condition in male population over age of 50. Transurethral Resection of the Prostate (TURP) has long been considered a reference (gold standard) technique for the surgical management of LUTS/BPO for prostates with volume below 80ml and open prostatectomy for prostates with volume over 80ml. In order to reduce the morbidity, surgical lasers and different laser techniques have emerged. One such is the Thulium laser transurethral vaporesection of the prostate (ThuVARP), first introduced in 2005. In addition, the recent introduction of the 200W Tm:YAG high power laser generator provide more effective prostate tissue ablation.

Methods. A total of 20 patients with BPO, between July 2022 and January 2023 were treated for a first time with Thulium laser transurethral vaporesection of the prostate (ThuVARP) at University Clinic for Urology in Skopje, RN Macedonia. A 200W latest generation high power Tm:YAG laser generator was used with an end-firing 800nm optical fiber introduced in the prostate through a 26F laser sheath, through which the laser beam was transferred to the prostate tissue via direct contact.

Results. We report the perioperative outcomes, voiding parameters change and perioperative complications on a group of 19 patients who managed to complet the 6-month follow-up after ThuVARP surgery. Significant improvements were seen in the voiding parameters (IPSS, QoL score, Qmax, PVR) at 3 and 6 months following surgery (improvement in IPSS -82,7%, QoL score -70,0%, Qmax +174% and PVR -89,8% at 3 months and IPSS -86,7 %, QoL score -72,1%, Qmax +155% and PVR -93,2% at 6 months postoperatively from baseline values respectively). Mean prostate volume was reduced for 54.0%, from initial 68.1±25.31ml to 31.3±15.5ml at 6 months postoperatively. Perioperative outcomes showed low mean decrease in Hb 9.3± 9.2 g/L with no need of transfusions, short catheterization time and hospital stay of only 2.4±0.9 days, but slightly longer average operative time of 79.7±28.6 min. Our outcomes were compared with those of other studies related to this technique.

Conclusion. Our findings suggest that ThuVARP is an effective and safe procedure for treatment of BPO. It offers advantages in intraoperative safety, minimal blood loss, very short catheterization time and hospital stay but needs a longer operation time.

Keywords: BPH, BPO, Thulium, laser, transurethral, vaporesection, prostata, ThuVARP

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Апстракт

Вовед. Бенигната простатична опструкција (БПО) е најчеста уролошка состојба кај машката популација на возраст над 50 години. Трансуретралната ресекција на простата (TURP) подолго време се смета за референтна техника (златен стандард) во хируршкиот третман на БПО кај простати со волумен под 80ml, а отворената простатектомија кај простати со волумен над 80ml. Со цел намалување на перипоративниот морбидит во третманот се воведе и хируршкиот ласер и неколу различни ласерски техники. Една од таквите е Тулиум ласерската трансуретралната вапоресекција на простатата (Thulium laser transurethral vaporesection of the prostate -ThuVARP), за прв пат изведена во 2005 година. Дополнително, воведувањето на Tm:YAG ласерскиот генератор со висока моќност од 200W обезбеди уште поефикасна аблација на простатичното ткиво а со тоа и поефикасен ласерски третман на БПО.

Методи. Вкупно 20 пациенти со БПО, во периодот од Јули 2022 година до Јануари 2023 година, на Универзитетската клиника за урологија во Скопје, Р.С. Македонија за прв пат беа третирани со тулиум ласерска трансуретрална вапоресекција на простата (ThuVARP). Користевме најнова генерација Tm:YAG ласерски генератор со висока моќност од 200 W и оптичко влакно од 800 nm за пренос на ласерскиот зрак, кое преку ласерска кошулка со промер од 26F ендоскопски беше пласирана во простатата каде во директен контакт се вршеше аблација на ткивото.
Резултати. Презентираме резултати од периоперативен исход, промена на параметрите на мокрење и периоперативните компликации кај од 19 од 20 оперирани пациенти, кои поминаа 6-месечно постоперативно следење. Утврдивме значајни подобрувања во параметрите на мокрење: максимален проток (Qmax), остаточна урина (PVR), интернационален простатичен симптом скор (IPSS) и квалитет на живот (QoL score) во 3-тиот и 6-тиот месец постоперативно. (подобрување на IPSS -82,7%, QoL score -70,0%, Qmax +174% и PVR -89,8% во 3-ти и IPSS -86,7 %, QoL score -72,1%, Qmax +155% и PVR -93,2 во 6-ти постоперативен месец соодветно во однос на предоперативните вредности). Средниот постатичен волумен беше намален за 54.0%, од предоперативните 68.1±25.31ml на 31.3±15.5ml во 6 тиот месец постоперативно. Периоперативните индикатори покажаа ниско просечно намалување на Hb за 9,3±9,2 g/L, без потреба од трансфузија на крв, кратко време на катетеризација и престој во болница од само 2,4±0,9 дена, но и подолго просечно оперативно време од 79,7±28,6 мин. Добиените вредности ги споредивме со истите од неколку студии кои ја обработуваат идентичната оперативна техника.
Заклучок. ThuVARP е ефикасна и безбедна процедура во третманот на БПО. Истата нуди висока периоперативната безбедност, отсуство на ТУР синдром, минимална загуба на крв, кратко време на катетеризација, краток престој во болница, но и истовремено релативно подолго времетраење на операцијата.

Клучни зборови: БПХ, БПО, тулиум, ласер, трансуретрална, вапоресекција, простата, ThuVARP

Introduction

Benign prostatic hyperplasia (BPH) is the most common urologic condition in male population over the age of 50 [1]. Approximatelly 50-60% of men aged >60 years present with BPH [2]. It often leads to a certain level of urinary obstruction referred to as Benign Prostatic Obstruction (BPO) and presents with symptoms termed as Lower Urinary Tract Symptoms (LUTS). These symptoms cause certain level of impairment of patient quality of life (QoL) and in more advanced stages, when left untreated or therapy fails, BPO can lead to serious complications as urinary retention, urinary tract infection (UTI), calculosis, stasis and acute or chronic renal failure. Vast majority of BPO patients depending on the symptoms intensity are treated either conservatively with watchful waiting or pharmacologicaly with medications (Alpha - blockers, 5-Alpha Reductase Inhibitors 5-ARI). A smaller share that initially present with moderate to severe LUTS or fail pharmacologic therapy, receive surgical treatment. Based on its ubiquitous availability, as well as good efficacy, Transurethral Resection of the Prostate (TURP) has long been considered as the reference (gold standard) technique for the surgical management of LUTS/BPO for prostates with volume below 80ml and open prostatectomy for prostates with volume over 80ml [3]. In the latest guideline of the European Association of Urology (EAU Guidelines 2024) both techniques still remain a current standard/first choice option in the surgical treatment of BPO. However, they both are associated with considerable morbidity. Even after decades of techniqual imporovement, the overall morbidity rate after TURP remains as high as 11.1% [4]. Therefore in the past decades various other minimaly invasive techniques have been developed with the aim of providing a safe and effective alternative to TURP [3]. One such technique is the Thulium laser transurethral vapresection of the prostatae (ThuVARP), first introduced in 2005 by Xia et al. under the original name Thulium laser resection of the prostatae - Tangarine Technique (TmLRP-TT). This as well is the first time that Thulium laser has been used into urological soft tissue surgery [5]. In 2007, the first report on Tm:YAG laser prostatectomy using the technique of VapoResection with a 70-Watt Tm:YAG laser was published by Bach *et al*. [6]. As latest generation of surgical laser, unlike it predecessors it can emit radiation beside pulse in continuous mode, which enables superior vaporizing capacity compared to any other laser. It provides precision cut and advanced haemostatic abilities. In addition, the improvement in Tm:YAG laser generator to power of 200W from initial 50W, makes it a very reliable tool for transurethral treatment of BPO [5,7,10].

Material and methods

A total of 20 patients with manifest BPH (BPO) were treated with Tm: YAG laser vaporesection of the prostatae (ThuVARP) in our department between July 2022 and January 2023.
Before treatment, all patients provided a complete medical history (IPSS questionnairy) and underwent a physical examination, including DRE, transabdominal

ultrasound of the prostate, urine analysis, PSA measurement, blood chemistry studies, and postvoiding residual urine (PVR) as well as Qmax measurements.

A 200W Thulium: YAG, 2013nm continuous wave laser (ROCAMED Hemera Laser) was used at maximum power as an energy source. An 800nm end-firing optical core multiuse laser fiber was introduced through a 26 F continuous-flow laser resectoscope (Richard Wolf, Knittlingen, Germany) with normal saline as irrigation. All operations were performed by 2 urologists experienced in endoscopy who previosly had received a standard ThuVARP training. The vaporesection of the prostate was performed under direct vision using the bare-ended fiber in a contact mode. The term vaporesection describes the simultaneous vaporization and resection of prostate tissue and is closely related to the high vaporization capacity of the thulium laser. Gas bubbles indicate vaporisation activity. Within vaporesection the degree of vaporization is controlled by the speed of laser fiber movement through the tissue. Operation begins by marking the proximal end of the veromontanum. Two incisions at 5 and 7 o'clock, at the level of the bladder neck are performed and if present the median lobe is vaporesected with transverse movements of the fiber, followed by vaporesection of the lateral lobes. The latter is performed in one or more steps, depending on the size. Lateral lobe resection starts proximally at the bladder neck and proceeds distally towards the verumontanum with each lobe level being vaporesected in alternating order. Lateral lobes are resected with combined circumferential, longitudinal and transverse movements of the laser fiber (Figure 1). They are always performed in a retrograde fashion towards the bladder neck and in depth until the prostate capsule is reached. It is of prime importance the vaporesected prostate chips to be small enough for an easy retrieval through the resectoscope at the end of the procedure (Figure 2).

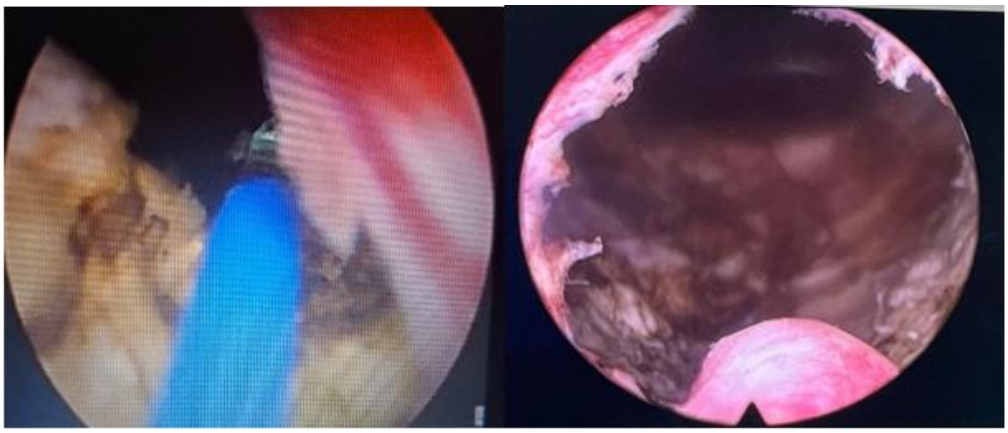

Fig. 1. Left - Vaporesection of the left lobe. Right - Look from the level of verumontanum at the end of the procedure. All lobes vaporesected.

After removing the laser resectoscope, a 3-way 20 or 22 F foley catheter is inserted for continuous bladder irrigation. When a clear urine is established, usually the first postoperative day, the irrigation is terminated and after the urine becomes fully clear, the next (second) postoperative day the catheter is removed and if a spontaneous micturion is confirmed the patient is discharged from the clinic. All 20 operations finished as ThuVARP, with no need for conversion to TURP. In general, the ThuVARP technique simulates the conventional TUR P technique with the difference of using a laser instead of electric current and an optical fibre instead of a loop.

Assessed perioperative outcomes were the operative time, the time of catheterisation and hospitalization, the decrease in haemoglobin, and the blood transfusion rate. The voiding outcomes: IPSS- International Prostate Symptom Score, QoL-quality of life, Qmax-maximum flow rate, and PVR-post void residual were measured

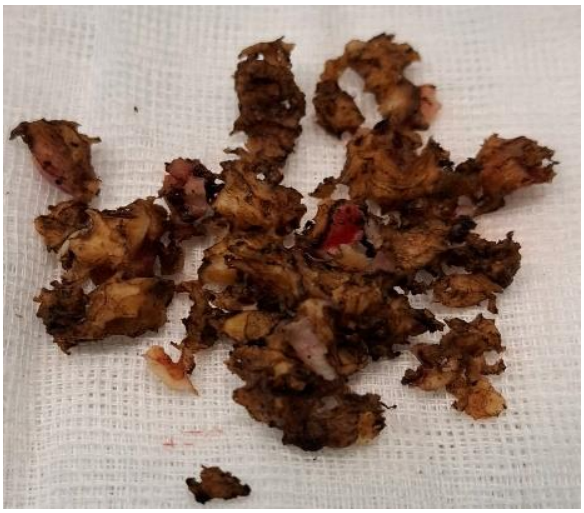

Fig. 2. Vaporesected prostate tissue for histologic evaluation. The thin coagulation rim of necrotic tissue of <1mm does not impair adequate histologic diagnosis

preoperatively and reassessed in the 3rd and 6th month postoperatively. PSA was reassessed in the 6th month. The first reassesment was scheduled 3 weeks after discharge for urinculture and potential perioperative complications and adverse effects.

Results

Baseline characteristics, perioperative data and voiding data with 6-months follow-up of 20 patients with manifest BPH treated with Tm: YAG laser vaporesection are summarised in Table 1. Data are presented as mean ±SD (range). Patients mean age was 69.1±6.62 years, the mean prostate volume 68.1±25.31 ml and mean PSA 3.78±3.78 ng/ml. Baseline IPSS was 24.83±2.2, QoL score 4.66±0.65, Qmax 5.27±3.3 ml/s, and PVR 147.8±88.4 ml. Eight patients had urinary catheter because of history of acute urinary retention with failed previous voiding attempts or chronic urinary retention with high quantity of residual urine. During follow-up only one patient was lost due to rapidly developing malignant disease. Voiding parameters: IPSS, QoL, Qmax, and PVR, had improved significantly compared to their pre-operative values for -82.7%, -70.0%, +174% and -89.8% at the 3rd postoperative month and -86.7%, -72.1%, +155% and -93.2 at the 6th postoperative month respectively. Prostate volume and PSA as well improved after surgery, being reduced at the 6th month for 54.0% and 49.7% respectively. Among perioperative parameters, operating time was 79.7±28.6 min, Hb decrease 9.3±9.2 g/l, catheterisation time 2.4±0.9 days and hospital stay 2.4±0.9 days.

Table 1. Baseline characteristics, perioperative outcomes and voiding data with a 6-months follow up

Perioperative data	Mean ± SD (range)				
No. of pts.	20				
Age	69.1 ± 6.62 (58-79)				
Operating time (min)	79.7 ± 28.6 (35-145)				
Hb decrease (g/l)	9.3 ± 9.2 (1-22)				
Catheterisation time (days)	2.4 ± 0.9 (1-4)				
Hospital stay (days)	2.4 ± 0.9 (1-4)				
Voiding data	**Baseline, (Pre-operative)**	**3 months**	**Improve (%)**	**6 months**	**Improve (%)**
IPSS	24.83 ± 2.2 (21-29)	4.3 ± 4.8 (1-22)	-82.7	3.3 ± 4.8 (0-22)	-86.7
QoL	4.66 ± 0.65 (4-6)	1.4 ± 1.1 (0-4)	-70	1.3 ± 1.5 (0-6)	-72.1
Qmax (ml/s)	6.52 ± 2.4 (3.5-10.6)	17.9 ± 10.1 (5.1-41.4)	174	16.6 ± 8.9 (5.1-41.4)	155
PVR (ml)	147.8 ± 88.4 (10-330)	15.1 ± 20.1 (0-60)	-89.8	10 ± 20.1 (0-60)	-93.2
Prostate V (ml)	68.1 ± 25.31 (30-120)	30.2 ± 14.9 (13.1-68)	-55.6	31.3 ± 15.5 (12.2-65)	-54
PSA (ng/ml)	3.78 ± 3.78 (0.9-7.5)	/	/	1.9 ± 1.5 (0.5-5.3)	-49.7

Data are mean ±SD (range). IPSS, international prostatic symptom scores; QoL, quality of life; Qmax, maximum urinary flow rate; PVR, post-voiding residual volume; PSA, prostate-specific antigen; prostatae V, volumen with transabdominal ultrasonography; Hb, hemoglobin concentration;

In **Table-2.** perioperative data and postoperative voiding outcomes at the 6th month of the entire group of all 20 patients were compared with the outcomes in other similar studies. They all showed comparable results [5,8,9].

Table 2. Comparison of perioperative and voiding data follow-up among different studies.

Study	No. of pts	Follow up (months)	Age	Preoperative Prostate V (ml)	Operating time (min)	Hb decrease (g/l)	Catheter (days)	Hospital stay (days)	Postoperative			
									IPSS	QoL	Qmax (ml/s)	PVR (ml)
Our results	20	6	69.1 ± 6.6	68.1 ± 25.3	76.7 ± 28.6	9.3 ± 9.2	2.4 ± 0.9	2.4 ± 0.9	3.3 ± 4.8	1.3 ± 1.5	17.9 ± 10.1	10 ± 20.1
Xia 2008	52	6	68 ± 7.7	59.2 ± 17.7	46.3 ± 16.2	9.2 ± 8.2	1.9 ± 1.1	4.8 ± 1.1	4.0 ± 2.4	1.1 ± 1.1	24.5 ± 9.2	7.1 ± 6.6
Szlauer 2008	56	9	72.9 ± 7.7	50.0 ± 28.8	60.0 ± 34.8	13.3 ± 1.8	1 ± 0.7	5 ± 2.4	8.6 ± 6.5	1.4 ± 1.2	19.3 ± 7.9	57 ± 46.1
Hashim 2020	204	12	70.8 ± 7.8	35 (25-50)*	/	6(1-13)*	2(1-5)*	2 (1.2-2.4)*	6.4 ± 6.8	1.2 ± 1.7	20.2 ± 16.9	/

Data are mean ± SD; *Data are median ± IQR

Table 3. Two patient groups with prostate volume below and above 80 ml with baseline characteristics, perioperative outcomes and voiding data with 6-months follow-up

Perioperative Data	Prostate volume ≤80 ml					Prostate volume >80 ml				
No. of pts.	14					5				
Age	69.1±6.4					69±7.8				
Operating time (min)	70.1±20.6					97.5±38.3				
Hb decrease (g/l)	9.0±10.2					3.5±17.4				
Catheterisation time (days)	2.2±0.9					2.8±1				
Hospital stay (days)	2.2±0.9					2.8±1				
Voiding data	Pre-operative	3 months	Improve (%)	6 months	Improve (%)	Pre-operative	3 months	Improve (%)	6 months	Improve (%)
IPSS	24.2±1.7	3.3±2.5	-86	2.6±2.2	-89	28.0±1.4	6.7±7.8	-76	5.0±8.3	-82
QoL	4.7±0.7	1.3±1.0	-72	1.4±1.5	-70	4.5±0.7	1.7±1.4	-62	1.0±1.5	-78
Qmax (ml/sec)	7.1±2.2	20.5±10.9	189	17.3±9.9	144	3.9±0.5	11.9±3.9	205	15.1±6.3	287
PVR (ml)	130.3±74.3	11.2±17.4	-91	6.1±7.6	-95	235±134.4	28.8±25.3	-88	23.8±29.3	-90
Prostate V (ml)	54.6±13.4	23.5±7.1	-57	25.8±13	-53	99.5±16.6	45.6±17.3	-54	44.1±13.4	-44
PSA (ng/ml)	3.8±3.3	/	/	1.6±1.1	-58	3.7±5.0	/	/	2.6±2.1	-30

Data are mean ± (SD). IPSS, international prostatic symptom scores; QoL, quality of life; Qmax, maximum urinary flow rate; PVR, post-voiding residual volume; PSA, prostate-specific antigen; prostatae V, volumen with transabdominal ultrasonography; Hb, hemoglobin concentration

In table 3 two subgroups of patients with prostate volume below 80ml and above 80ml were presented and compared. Their baseline characteristics, perioperative outcomes and voiding data with 6-months follow-up were comparable, as well as comparable with those in the main group.

Table 4. Perioperative and postoperative complications

Perioperative and postoperative complications	**n (%)**
Intraoperative bleeding and transfusion	
TUR syndrome	
Re-operation	
Re-cateterisation	
Transitory iritative symptoms	0%
UTI (urinary tract infection)	%
Transitory (urgent) incontinence	%
Permanent (stres) incontinence	
Postoperative bleeding with re-catheterisation	0%
Urethral stricture	
Bladder neck contracture	%

Perioperative and early postoperative complications within a 6-month follow-up were registered in 7 patients (35%), sumarized in Table 4. No intraoperative complications occurred. There was no significant intraoperative bleeding and need of transfusion or and a need of re-operation. No TUR syndrome was encountered. Two patients presented with transitory iritative symptoms, one had UTI. No permanent (stress) incontinence was encontered, and only one case of transitory urgent incontinence. Two patients experienced perioperative bleeding in the second and third postoperative week, respectively. Within a 6 months follow-up one patient was confirmed bladder neck contracture.

Discussion

BPH is not a life-threatening disease, but it certainly has crucial impact on patients' quality of life [14].

Lower urinary tract symptoms are strongly associated with ageing, and therefore are likely to increase with future demographic changes This imposes great preassure on the health system in terms of medical staff burden as well as high costs and financial impact. TURP even though still a gold standard, remains a technically demanding procedure with a learning curve of up to 100 procedures and associated risk of complications [3]. According to a large multicentric Bavarian study conducted on a 10654 patients, it is associated with an overall immediate morbidity of 11.1%, as blood transfusion rate of 2.0-9.5%, failure to void (5.8%), surgical revision (5.6%), and TUR syndrome (1.4%) [4].

All of this generates a need for developing and introducing new minimaly invasive procedures with less morbidity and shorter perioperative period in terms of less perioperative bleeding, hospital stay and catheter time. Lasers were introduced in urology in the late 90' and ever since have been in a constant development and tendency for a wider use [11,12]. The latest Guideline of the European Association of Urology (EAU Guidelines 2024), recommends 3 transurethral ablative techniques that include lasers as energy source: resection, enucleation and vaporization performed with Holmium (Ho:YAG), Thulium (Tm:YAG), Diode, Potassium-Titanyl-Phosphate (KTP-Green light) and Lithium Borat (LBO) laser as only recommended for BPO treatment. Thulium laser has been introduced into urological soft tissue surgery in 2005 [5]. It emits laser energy in a continuous wave fashion at a wavelength of 2013nm. As the particular wavelength is very close to the absorption peak of water, the laser energy is fully absorbed in the surface layers of the prostatic tissue and only a fraction would penetrate into deeper layers. This provides thulium laser with the shallowest tissue penetration capacity among all lasers, and penetration depth of only 0,2 nm. In the same time, it creates a very thin coagulation and necrotic tissue zone thus providing high surgical safety [15]. The high density of absorbed energy at the tissue surface is transferrred into great amount of heat reaching high temperatures of over 100 degrease Celsius leading to instant tissue vaporization, but only in the tiny surface tissue. The high vaporization ability combined with the very small penetration depth, establish the thulium laser as a very effective and safe tool for removing the prostate tissue without damaging the surrounding structures as the urinary sphincter and prostatic capsule. While resecting, a simultaneous strong vaporizing process is always underway, thus a combined process called vaporesection is established only and exclusively to the thulium laser. Beside vaporesection (ThuVARP), thulium laser can be used in 3 other ablative tehniques as vaporization (ThuVAP), vapoenucleation (ThuVEP) and enucleation (ThuLEP) [6].

The ThuVARP proves to be is effective and safe technique. In our series a significant improvement was seen in voiding parameters (Qmax, PVR, IPSS and QoL score) and prostate V and PSA at 3 and 6 months following surgery. (Table 1) Improvements of -82.7%, -70.0%, +174% and -89.8% in 3 months and -86.7%, -72.1%, +155% and -93.2 in 6 months postoperatively from baseline values were observed for Qmax, PVR, IPSS and QoL score respectively. Perioperative outcomes showed low mean decrease in Hb 9.3±9.2 g/l with no need of blood transfusions. Catheterisation time and hospital stay lasted only 2.4±0.9 days, at a cost of a slightly longer average operative time of 79.7±28.6 min.

The ablative effect of the thulium laser vaporesection can be evaluated either by TRUS measurement of pre- and postoperative prostate volume or by a pronounced decrease in the tissue marker PSA, which can be used as a surrogate parameter for prostate tissue volume reduction [8]. At 6 months we found 49,6% decrease in PSA and 54 % decrease in residual prostate volume measured with Transabdominal US, proving a high ablative effect of the ThuVARP technique. Having that in consideration we came to a conclusion that even high volume prostates (above 100ml) could be treated safely and effectively with ThuVARP. To evaluate this, patients were divided in two subgroups with prostate volume below and above 80 ml. Besides longer operative time of 97.5±35.3 vs 70.6 ±20.6 min all other perioperative and voiding outcomes between the different subgroups remained comparable (Table 3).

When compared with different series from other studies (Table 2) comparable results were observed. In our series with a mean prostatic weight of 68 ml, the mean operative time was 76 minutes when compared it with the series of Xia 2008, Szlauer 2008 and Hashim 2020 with a mean prostatic weight of 59ml, 50ml and 25ml the operative time was 46min and 60 minutes respectively. The mean postoperative catheter time was 2,4; 1,9; 1 and 2 days respectively for the same series which is as well comparable. The mean hospital stay was 2,4; 4,8; 5 and 2 days. Regarding the postoperative voiding results, comparable results of postoperative values of Qmax, PVR, IPSS and QoL were also observed among the different series.

Perioperative and early postoperative complications within a 6-month follow-up were sumarized in (Table-4**)** and were of low grade (Clavien-Dindo scale), Two patients presented with transitory iritative symptoms which were relieved spontaneously. One patient had UTI in the first days after surgery and was treated accordingly with antibiotics. No permanent (stress) incontinence was encontered, only one case of transitory urgent incontinence. Only two patients experienced perioperative bleeding in the second and third postoperative week, respectively. In the first case it was caused by UTI, and in the second by a careless heavy physical activity from the patient in the early postoperative

stages. No intraoperative complications were reported. Because of saline irrigation, there was no risk of TUR syndrome even at longer operation time. Within 6 months' follow-up one patient was confirmed bladder neck contracture after complaining for dysuria.
ThuVARP in contrast to other techniques with vaporizing effect, has an ability to retrive tissue for histologicall analysis. Another advantage of this technique is that it has a relatively short learning curve of around 15-20 cases for na experienced urologist at TURP.

Conclusions

Our findings suggest that ThuVARP is an effective and safe procedure for treatment of BPO. It offers advantages in intraoperative safety, no TUR syndrom, minimal blood loss, very short catheterization time and hospital stay but needs a longer operation time.

Conflict of interest statement. None declared.

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Original article

CORRELATION BETWEEN HISTOLOGICAL FINDINGS AND CYTOLOGICAL FINDINGS AND HPV STATUS IN PATIENTS WITH HSIL - RETROSPECTIVE STUDY

КОРЕЛАЦИЈА ПОМЕЃУ ХИСТОЛОШКИТЕ НАОДИ И ЦИТОЛОШКИТЕ НАОДИ И СТАТУСОТ НА ХПВ КАЈ ПАЦИЕНТИ СО ХСИЛ – РЕТРОСПЕКТИВНА СТУДИЈА

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Abstract

Introduction. Cervical intraepithelial neoplasia (CIN) and invasive cervical cancer are most commonly caused by human papillomavirus, which causes malignant transformation of cervical epithelial cells. The aim of this study was to investigate the association between different HPV types and histological changes of the cervix in patients in our hospital.
Methods. In the period from January 2022 to December 2023, an analysis of 100 samples was made with histological findings confirmed by biopsy from the University Clinic for Gynecology and Obstetrics in Skopje. The relationship between HRHPV and high-grade CIN and CIS, as well as the age-dependent prevalence of single HPV infection, were examined.
Results. In both CIN2, CIN3 and CIS group, HPV16, 18, 31, 33 and 58 were detected as the top 5 high-risk human papillomavirus (hrHPV) types. HPV16 was the predominant genotype in CIN2, CIN3 and CIS, with 44.23%, 60.53% and 90% respectively. The prevalence of HPV16 was most common in all age groups. The peak incidence of CIN2 was observed from 31-40 and 41-50 years (28.85%), and CIN3 from 21-30 (28.95) and 51-60 years (23.68), and CIS from 31-40 (40%) and 41-50 years of age (30%).
Conclusion. If circumstances permit, women between the ages of 21 and 60 are advised to undergo normative screening for high-grade CIN. Patients who test positive for HPV16 should be prioritised for opportunistic screening. Patients infected with other forms of HPV should also be treated seriously if they are ladies 61 years of age or older. The most prevalent genotypes in our patients were HPV16, 18, 31, 33 and 58. Therefore, a vaccine including these dominant genotypes may be crucial for preventing cervical cancer.

Keywords: CIN, HPV, malignant transformation

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Апстракт

Вовед. Цервикална интраепителна неоплазија (ЦИН) и инвазивниот карцином на грлото на матката најчесто се предизвикани од хуман папиломавирус, кој предизвикува малигна трансформација на цервикалните епителни клетки. Целта на оваа студија е да се истражи поврзаноста помеѓу различните типови на ХПВ и хистолошките промени на грлото на матката кај пациентите во нашата болница.
Методи. Во периодот од јануари 2022 до декември 2023 година направена е анализа на 100 примероци со хистолошки наоди потврдени со биопсија од Гинеколошко-акушерската клиника во Скопје. Беше испитуван односот помеѓу ХРХПВ и ЦИН и ЦИС со висок степен, како и преваленцата на единечна ХПВ инфекција зависна од возраста.
Резултати. И во групата ЦИН2, ЦИН3 и ЦИС, ХПВ16, 18, 31, 33 и 58 беа откриени како топ 5 високоризични типови на хуман папиломавирус (хрХПВ). ХПВ16 беше доминантен генотип во ЦИН2, ЦИН3 и ЦИС, со 44,23%, 60,53% и 90% соодветно. Преваленца на ХПВ16 беше најчеста кај сите возрасни групи. Врвна инциденца на ЦИН2 беше забележена на 31-40 и 41-50 години (28,85%) и ЦИН3 од 21-30 (28,95%) и 51-60 години (23,68%) и ЦИС 31-40 години (40%) и 41-50 години (30%).
Заклучок. Ако околностите дозволуваат на жените на возраст меѓу 21 и 60 години им се советува да подлежат на нормативен скрининг за висок степен на ЦИН. На пациентите кои се позитивни на ХПВ16 треба да им се даде приоритет на опортунистички скрининг. Пациентите инфицирани со други форми на ХПВ, исто така треба сериозно да се третираат ако се дами на возраст од 61 година или постари. Најраспространети генотипови честопати беа ХПВ 16, 18, 31, 33 и 58. Затоа вакцината што ги вклучува овие доминантни генотипови може да биде клучна за спречување на рак на грлото на матката.

Клучни зборови: ЦИН, ХПВ, малигна трансформација

Introduction

Human papillomavirus, or HPV, is the most prevalent sexually transmitted virus in the world and a major contributor to disease and fatalities [1]. In 2020, cervical cancer accounted for 604,000 new cases and 342,000 deaths worldwide, making it the fourth most frequent cancer among women [2]. Chronic hrHPV infection results in the integration of viral DNA into the host squamous epithelium cells' genome, which triggers the production of viral oncoproteins and moves cervical epithelial cells towards precancerous lesions and ultimately malignancies [3-5].

The International Agency for Research on Cancer (IARC) designated HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 as Group 1 carcinogens, and HPV66 and HPV68 as additional HPV genotypes that have been categorised as "high risk" because of their great carcinogenic potential [6-7]. It is crucial to comprehend the prevalence and type distribution of HPV in cervical lesions and cancer, particularly in precancerous lesions, due to the variations in pathogenicity and different HPV genotypes. The World Health Organisation (WHO) authorised a global strategy in January 2019 with the goal of eradicating cervical cancer as a public health issue. The strategy placed the world on track to eradicate cervical cancer by outlining the primary objectives and established milestones to be met by 2030 [8]. For decades, cervical cytology screening has been considered an effective cancer detection method to prevent the progression of cervical carcinoma. Although cytological screening has shown high specificity, its relatively low sensitivity and interobserver subjectivity can lead to missed diagnosis [9-11]. In contrast, HPV screening has a higher sensitivity but a lower specificity for detecting precancerous or cancer forms [12]. Many countries have used the DNA-based Hybrid Capture 2 (HC2) HPV tests and Cobas 4800 HPV tests as the sole screening tool for primary cervical cancer in women aged 25 years or older 11-13 years, with significant sensitivity improved [13-15]. However, DNA-based HPV tests cannot distinguish transient viral infection from persistent infection [16].

Statistical analysis

Statistical analysis of data obtained in this study was done with the statistical program SPSS for Window 23.0. The obtained data are shown in tables. Categorical (attributive) variables are shown with absolute and relative numbers.

Chi-square test and Fisher's exact test were used to compare the qualitative variables. Statistical significance was defined at $p < 0.05$ level.

Results

A total of 100 respondents from the University Clinic for Gynecology and Obstetrics in Skopje participated in the study. They were 20 to 71 years old, and the average age was 42.7±12.5 years. Female patients aged 31-40, and those of 41-50 years old predominated (26% and 25%, respectively).

The most common histopathological finding was CIN2 (52%), followed by CIN 3 (38%) and CIS (10%).

The average age of patients with CIN2, CIN3 and CIS was 42.9±11.8, 42.4±13.9 and 43.2±11.7 years, respectively, and there was no statistically significant difference (Analysis of Variance F=0.02 p=0.98).

Female patients with HP findings of CIN2 were mostly aged 31-40 and 41-50 years, with representation in both age groups individually of 15(28.85%); female patients with HP finding CIN3 were mostly aged 51-60 years - 9(23.68%); patients with HP finding CIS were mostly aged 31-40 years - 4(40%).

The tested difference in the distribution of patients aged less than 20 years, 21-30, 31-40, 41-50, 51-60 and older than 60 years, and depending on the histopathological findings was not statistically significant (p=0.595).

Table 1. Age distribution of CIN2, CIN3 and CIS incidence

Age groups	N	Histopathological finding			p-level
		CIN 2	CIN 3	CIS	
<20	1	1(1.92)	0	0	
21 – 30	19	7(13.46)	11(28.95)	1(10)	
31 – 40	26	15(28.85)	7(18.42)	4(40)	
41 – 50	25	15(28.85)	7(18.42)	3(30)	p=0.595
51 – 60	20	10(19.23)	9(23.68)	1(10)	
≥ 61	9	4(7.69)	4(10.53)	1(10)	
Total	100	52	38	10	

p (Fisher's exact test)

A negative Pap test was most often obtained in patients with HP finding CIN2 (51.92%), followed by patients with HP finding CIN3 and CIS (28.95% and 20%, respectively).

For p=0.035, a statistically significant difference was confirmed in the distribution of patients with a positive and negative Pap test, depending on the histopathological findings. Patients with CIN2 significantly more often than patients with CIS had a negative Pap test (p=0.029).

Table 2. Correlation between HPV positivity and negativity of PAP test with histological CIN

PAP test	N	Histopathological finding	p-level

		CIN 2	CIN 3	CIS	
Positive	60	25(48)	27(71.05)	8(80)	Pearson Chi-square *p=0.035
Negative	40	27(51.92)	11(28.95)	2(20)	

*sig p<0.05

Patients with HP findings of CIN2, CIN3 and CIS did not differ significantly in terms of the result of the Pap test (p=0.835).

The most common Pap finding in all three groups of HP finding was HPV (36%, 29.63% and 50%, respectively). This was followed by Pap finding CIN1 in the groups with HP finding CIN2 and CIN3 (32% and 25.93%, respectively), and CIN1, CIN2, CIN3 and ASC-H in 12.5% of patients individually in the group with HP finding CIS.

CIN1 Pap findings were insignificantly more frequent in HP patients than CIN2 findings (32%); CIN2 Pap findings were insignificantly more frequent in HP patients than CIN3 findings (22.22%); CIN3 Pap findings were insignificantly more frequent in HP patients than CIS findings (12.5%); HPV findings on Pap were insignificantly more frequent in patients with HP than CIS (50%); ASC-H findings on Pap were insignificantly more frequent in patients with HP than CIS (12.5%); CIS findings on PAP had only one patient with HP than CIN3.

Table 3. Correlation between cytological and histological CIN lesion

PAP test	N	Histopathological finding			p-level
		CIN 2	CIN 3	CIS	
Cin 1	16	8(32)	7(25.93)	1(12.5)	
Cin 2	12	5(20)	6(22.22)	1(12.5)	
Cin 3	3	0	2(7.41)	1(12.5)	
Hpv	21	9(36)	8(29.63)	4(50)	p=0.835
ASC-H	4	2(8)	1(3.7)	1(12.5)	
AGC	3	1(4)	2(7.41)	0	
Cis	1	0	1(3.7)	0	
Total	100	25	27	8	

p (Fisher's exact test)

Distribution of isolated HPV types is shown in Table 4. In this cohort of patients, HPV type 16 was most often isolated, with a prevalence of 55%, followed by HPV type 31, with a prevalence of 15%.

A statistically significant difference in the frequency of isolated HPV types was demonstrated only for type 16 (p=0.017); HPV 16 was most frequently observed in patients with HP findings of CIS (90%), followed by patients with HP findings of CIN3 and CIN2 (60.53% and 44.23%, respectively).

Table 4. Distribution of HPV genotypes in CIN

Type of HPV	N	Histopathological finding			p-level
		CIN 2 n=52	CIN 3 n=38	CIS n=10	
16	55	23(44.23)	23(60.53)	9(90)	*p=0.017
31	15	10(19.23)	5(13.16)	0	P=0.36
33	7	4(7.69)	3(7.89)	0	P=1.0
35	1	0	1(2.63)	0	P=0.48
18	7	3(5.77)	4(10.53)	0	P=0.5
51	2	1(1.92)	1(2.63)	0	P=1.0
52	4	3(5.77)	1(2.63)	0	P=0.76
54	3	1(1.92)	2(5.26)	0	P=0.69
45	4	3(5.77)	1(2.63)	0	P=0.76
40	1	1(1.92)	0	0	P=1.0
58	7	4(7.69)	1(2.63)	2(20)	P=0.12
59	4	3(5.77)	1(2.63)	0	P=0.76
56	6	3(5.77)	2(5.26)	1(10)	P=0.68
39	3	2(3.85)	1(2.63)	0	P=1.0
70	2	2(3.85)	0	0	P=0.6
66	2	0	2(5.26)	0	P=0.33
73	4	2(3.85)	1(2.63)	1(10)	P=0.55
53	5	4(7.69)	0	1(10)	P=0.16

p (Fisher's exact test), *sig p<0.05

Discussion

According to a study by Massad *et al*. (2001), on the basis of histological results of cytological findings,

30% of ASCUS findings were really histologically negative, 47% were associated with lumps, and 18% reflected CIN 1, 3% CIN 2 and 3% CIN 3.

According to histopathological findings in the study by Mahmuda Naznin *et al*., out of 1000 participants, 31.0% had either cervical carcinoma (5.3%), cervical intraepithelial neoplasia-I (CIN-1), CIN-II, or CIN-III. According to cytological findings, 25.3% had either cervical carcinoma (4.6%), low-grade squamous intra-epithelial lesion (LSIL), or high-grade squamous intra-epithelial lesion (HSIL). The frequency of HPV-positive cases was 24%. The correlation of cervical carcinoma detection between histopathological and HPV-DNA tests and between cytological and HPV-DNA tests was found to be statistically significant.

In the study by Stoler MH and Schiffman M, HSIL was confirmed in small percentages in the ASC-US and LSIL results. Based on data from the ASC-US LSIL Triage study, Sherman *et al*. concluded that CIN3 lesions found after LEEP excision were smaller (<10 mm) than those expected for microinvasive carcinoma (63.5 mm). In this study CIN3 lesions detected after a less severe cytological result than HSIL tend to be small. The small CIN3 result also has a slightly increased risk of being related to a false negative HPV test.

Conclusion

In conclusion, the age-dependent distribution indicated that women aged 21 to 60 had a higher prevalence of high-grade CIN; hence, if circumstances allow, a routine screening of women aged 21 and above is advised. Other forms of HPV infection should also be treated seriously in women over the age of 61. HPV16 was especially active in the formation of cervical premalignant lesions and malignant lesions in women between the ages of 21 and 60. Based on the statistics from our clinic, patients who test positive for HPV16 should be prioritised for opportunistic screening. The most prevalent genotypes in high-grade CIN were often HPV16, 18, 31, 33, and I-58; vaccinations that cover these key genotypes may be very beneficial in preventing cervical cancer. With a modest sample size and a retrospective analysis, the current study provided additional validation and confirmation.

Conflict of interest statement. None declared.

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MMP

Original article

SITUS INVERSUS TOTALIS IN A NEWBORN WITH CONGENITAL HEART DISEASE

SITUS INVERSUS TOTALIS КАЈ НОВРОДЕНЧЕ СО КОНГЕНИТАЛНА СРЦЕВА МАЛФОРМАЦИЈА

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Abstract

Introduction. Situs inversus totalis (SIT) is rarely reported in newborns. Isolated or associated with other congenital abnormalities, most often with congenital heart malformations (3-9%), SIT can often be an accidental finding.
Case report. We report a term-newborn with SIT and complex congenital heart defect, diagnosed prenatally by fetal ultrasound. SIT was confirmed with plane film X-ray (liver on a left side, spleen on right side). Heart ultrasound was done and revealed a complex cardiac malformation (CHM) - dextrocardia, single ventricle, tricuspidal valvular atresia, hypoplastic aortae, ASD II, PDA. The baby was transferred to a heart surgery center where the neonate was treated but unfortunately passed away.
Conclusion. SIT with CHM is a rare condition in neonatal period. Although a myriad of congenital malformations can be accompanying, isolated SIT is the most common. SIT and CHM is a condition challenging for surgical treatment.

Keywords: situs inversus totalis, newborn, congenital heart malformation

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Апстракт

Вовед. Situs inversus totalis (SIT) е ретка кондиција кај новороденчиња. Може да биде изолиран или асоциран со вродени абнормалности, најчесто со вродени срцеви малформации (3-9%), но често може да биде и случаен наод.
Приказ на случај. Доносено новороденче со SIT и комплексна вродена срцева мана, пренатално дијагностицирана со ултразвук. Со бебиграм се потврди SIT и се детктираше: црн дроб на левата страна, слезината на десната страна. Ехокардиографски се потврди комплексна срцева малформација-декстрокардија, single ventricle, трикуспидална валвуларна атрезија, хипопластична аорта, ASD II, PDA. Новороденчето се префрли во кардиохируршки центар, се изврши хирушка интервенција, но поради комлексноста на срцевата мана за жал почина.
Заклучок. SIT во комбинација со конгенитална срцева мана е ретка состојба во неонаталниот период. Иако мноштво вродени малформации можат да бидат придружни, но изолираниот SIT е најчест. SIT и конгенталните кардиопатии се состојби кои се вистински предизвик за изведување на хируршки третман.

Клучни зборови: situs inversus totalis, новороденче, вродени срцеви малформации

Introduction

Situs inversus totalis (SIT) is a rare congenital abnormality. The abdominal and thoracic organs are positioned as a mirror-image transposition [1,2]. SIT is categorized as solitus, inversus, and ambiguous; solitus is the normal arrangement of the organs, situs inversus totalis is a mirror image of the normal position of internal organs [2], while situs ambiguous or heterotaxy is the random arrangement of internal organs [3].
There is a lengthy history of description of SIT, from Aristotle (BC. 384-322) who described this condition in animals [4] to Fabricius (1600 a.d.) who reported SIT in humans [5]. The first X-ray report was the transposition of the viscera in 1897 by Vehsemeyer [6].
It has been found that some conditions are risk factors for the development of SIT. Among them, the most important are: family history of heart defects, family history of noncardiac anomalies, maternal diabetes, paternal smoking, antitussive use, and low socioeconomic status [7].
Dextrocardia occurs when the heart fails to migrate to the left chest. In situs inversus totalis the heart tubes are rotated to the left and the placement of the heart and other internal organs is a mirror image of the normal arrangement. A chain of signaling molecules has been implicated in influencing organ rotation and migration. „Sonic hedgehog" (Shh) is a protein that affects the expression of two transforming growth fac-

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tors, called Nodal and Lefty [1,8]. A number of genes, more than 100, are associated with laterality, including genes for primary ciliary dyskinesia (PCD) [1].
We present a term-newborn with a congenital heart defect.

Case report

A 27-year-old patient with first regularly controlled pregnancy was hospitalized at the University Clinic for Gynecology and Obstetrics in Skopje in February 2024. A prenatally verified complex cardiac anomaly (AVSD-atrioventricular septal defect, single ventricle, stenosis valvulae mitralis) was US diagnosed as well as situs inversus totalis. Family history was uneventful. A term boy in 38+3 week of gestation, with birth weight of 3470 g, Apgar score 2/6/7 in the first, fifth and tenth minute was born by elective caesarean section. After primary resuscitation with ambu ventilation with 100% oxygen, the baby was transferred to the NICU. A plain film X-ray was done and situs inversus totalis (dextrocardia, liver-left positioned, spleen on the right) was confirmed (Figure 1). Due to acidosis (pH=7.09, pCO_2=69.1, pO_2=41.6,

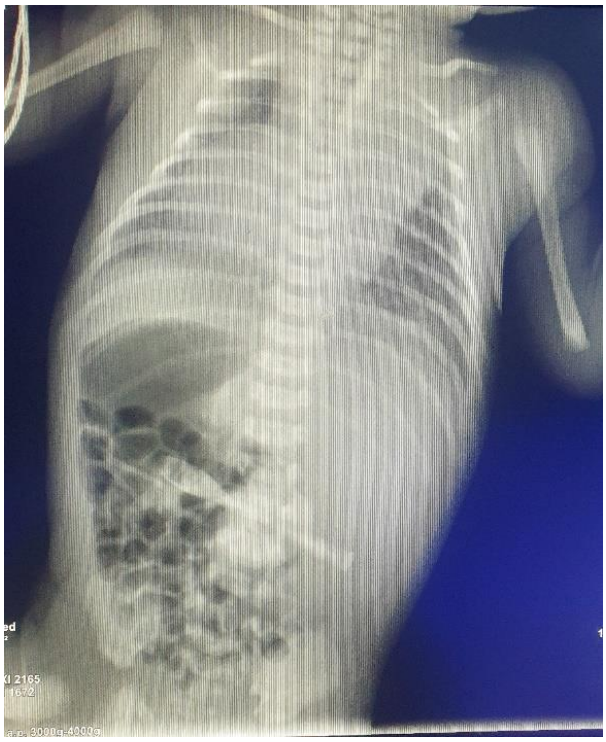

Fig. 1. Situs inverus totalis with complex congenital heart anomaly

HCO_3=20.6, BE=-10.4, sO_2=73.2%) the baby was intubated and put on conventional mechanical ventilation (SIPPV+VG). A pediatric cardiologist was consulted and a heart ultrasound was performed. A complex heart malformation was diagnosed (dextrocardia, single ventricle, tricuspidal valvular atresia, hypoplastic aorta, ASD II, PDA). The newborn was transferred to a cardiac surgery center. Surgery was performed, but unfortunately, due to the complexity of the heart anomalies, the newborn died at the age of 6 days.

Discusion

The incidence of situs inversus totalis is estimated to be 1:6,500 to 1:25,000 [1], with a male-to-female ratio of 3:2 [8].
The first suspicion of situs inversus totalis can be raised after a careful physical examination, ECG, as well as with imaging techniques. Typical findings are dextrocardia, left-sided liver and right-sided spleen [9-11], confirmed by electrocardiography inversion of electrical waves [12]. Computed tomography (CT) or magnetic resonance imaging (MRI) are useful imaging techniques that provide a detailed description of situs anomalies well before delivery [13]. SPECT/CT labeled with 99mTc is used to differentiate between polysplenia and abdominal masses [14].
The diagnosis of SIT is rare in the neonatal period. SIT is most often incidental during radiographic evaluation [15]. In our patient, the diagnosis of SIT and complex congenital heart malformation were detected in the uterus. We confirmed SIT with plain film X-ray (dextrocardia, left-placed liver and right-placed spleen) and heart ultrasound (dextrocardia with complex congenital heart disease).
The fact that the patient has a diagnosis of situs inversus totalis is an important finding [16]. The diagnosis of SIT is especially important in emergency surgical situations. Acute abdominal emergencies, such as cholecystitis, acute appendicitis or spleen injury, the manifestation of symptoms and signs is unusual [17,18]. Sometimes technical modifications are needed in surgical interventions. Patients with SIT can also develop malignant or benign neoplasms [19,20], and accurate diagnosis is required for localization and treatment. In patients with SIT, organ transplantation is more complicated [21].
Most people with situs inversus live normal lives [12]. SIT can be isolated or associated with other congenital abnormalities. The most common is intestinal malrotation, which affects 40-90% of patients [22]. Other malformations are duodenal atresia, biliary atresia, gastrochisis, congenital coronary abnormalities, ventricular septal defect, congenital heart disease [23,24]. SIT is also a part of some syndromes, such as Kartagener's syndrome (situs inversus totalis, abnormal paranasal sinuses and bronchiectasis) [25] and Ivemark's syndrome (SIT and asplenia) [26]. SIT has been shown in 20% of patients [27]. The rate of congenital heart disease is estimated to be ~0.6% in situs solitus (normal anatomy), 3-9% in situs inversus totalis, and almost 80% in situs ambiguous (1). SIT with dextrocardia and congenital heart defect has been observed in 3-5%. The most common congenital heart

defect in SIT is transposition of the great vessels [28]. Situs inversus totalis with left heart is a rare condition [29] and is mostly associated with congenital heart disease [30]. Our patient was the newborn with a rare congenital heart defect associated with SIT-single ventricle, tricuspid valvar atresia, hypoplastic aortae. Due to the complexity of the heart defect, despite cardiosurgical interventions, the newborn died.

Conclusion

Situs inversus totalis is a complex disorder in embryological morphogenesis. Efforts should be done to discover associated congenital anomalies and the possibility of life-threatening complications should always be kept in mind. A multidisciplinary approach is important in all stages of diagnosis and monitoring the patients. It is mandatory to inform clinicians of the anatomical mirroring to prevent complications during some interventions.

Conflict of interest statement. None declared.

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ММР

Original article

STRESS AND ITS ROLE IN THE OCCURRENCE AND MANIFESTATION OF PSYCHOLOGICAL AND PSYCHIATRIC SYMPTOMS IN PEOPLE WITH SKIN DISEASE

СТРЕСОТ И НЕГОВОТА УЛОГА ВО ПОЈАВА И МАНИФЕСТАЦИЈА НА ПСИХОЛОШКИ И ПСИХИЈАТРИСКИ СИМПТОМИ КАЈ ЛИЦА СО КОЖНА БОЛЕСТ

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Abstract

Introduction. Although skin diseases are mostly "non-life-threatening", because of their obviousness-they can be "life-destroying". A skin disease carries an association of something contagious and is something that is socially unacceptable due to public disregard and superstition. Because of this, people with skin malformations often feel socially unacceptable and psychologically devastated. This is because skin diseases entail their own wide range of emotional difficulties: stress, discomfort, impaired self-image, reduced self-esteem, anxiety, mood swings, reduced quality of life. of life, poor therapeutic response to dermatological treatments, and even suicidal risk.
The research was done in order to trace the impact of stressful perceived skin disease on the prevalence of psychiatric symptoms and psychiatric morbidity in patients with a diagnosed dermatological disease.
Methods. The study is a clinical, prospective study that was conducted at a University Dermatology Clinic. The examined group consisted of 70 subjects diagnosed with a dermatological disease according to ICD 10.
Results. The results of this research confirmed the association of skin disease with the presence of psychogical manifestations and psychiatric symptoms as a consequence of skin changes.
Conclusion. Stress triggers psychopathology symptoms as well as the onset or exacerbation of dermatological diseases. The research shows that the subjective experience of stress is much more important than the stress itself and the situation that caused the stress.

Keywords: stress, stressful situation, emotional difficulties, psychiatric symptoms

Апстракт

Вовед. Иако кожните заболувања најчесто се „живо тонезагрозувачки“, поради нивната воочливост истите можат да бидат „животоуништувачки“. Кожната болест носи асоцијација за нешто заразно и е нешто што е социјално неприфатливо поради јавното игнорирање и суеверие. Поради тоа и лицата со кожни малформации често се чувствуваат социјално неприфатливо и психолошки опустошено. Тоа е затоа што кожните заболувања со себе повлекуваат сопствена широка палета на емоционални потешкотии: стрес, неудобност, нарушена слика за себе, намалена самодоверба,анксиозност, променливо расположение, намален квалитет на животот, слаб тераписки одговор на дерматолошките третмани, па дури и суицидален ризик. Истражувањето беше изработено со цел да се утврди влијанието на стресогено перцепираната дерматолошка болест во појавата и манифестацијата на психијатриски симптоми и и психијатриски заболувања кај пациенти со дијагностицирана кожна болест.
Методи. Клиничката проспективна студија беше спроведена на Универзитетската Клиника за Дерматологија. Испитуваната група ја сочинуваа 70 пациенти дијагностицирани со кожна болест според критериумите на ICD 10.
Резултати. Резултатите од истражувањата ја потврдија асоцираноста на кожната болест со психолошки манифестации и психопатолошки симптоми кај испитаниците како одговор на постоечките кожни промени.
Заклучок. Стресот не само што ја тригерира појавата на психопатолошки симптоми кај пациентите со кожна болест туку негативно влијае врз појавата и егзацербацијата на кожната болест. Истражувањето покажа дека субјективното доживување на стресот има многу поголемо влијание отколку самиот стрес како таков и ситуацијата која истиот го предизвикала.

Клучни зборови: стрес, стресна ситуација, емоционални потешкотии, психијатриски симптоми

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Introduction

Although skin diseases are mostly "non-life-threatening", because of their obviousnessthey can be "life-destroying". A skin disease carries an association of something contagious and is something that is socially unacceptable due to public disregard and superstition. Because of this, people with skin malformations often feel socially unacceptable and psychologically devastated. This is because skin diseases entail their own wide range of emotional difficulties: discomfort, disturbed self-image, reduced self-esteem, anxiety, mood swings, reduced quality of life, poor therapeutic response to dermatological treatments, and even suicidal risk. For example, patients with psoriatic changes face a problem in social adaptation due to the feeling that everyone around them is looking at them. In period adolescence, skin changes such as acne vulgaris cause growing anxiety and represent a potential handicap in the development of relations with the opposite sex. The adolescent may become withdrawn, isolated from the environment or aggressive and uncooperative [1]. Many of the patients with skin diseases face sweatscots in employment, especially in those professions where appearance is important.

Stress and other psychological factors trigger the appearance or exacerbation of dermatological diseases [2]. Each individual has a stress-sensitive organ that is defined by genetic and environmental factors. Panconesi [3] suggested that dermatological diseases activated or aggravated by emotional stressors are called "dermatology stress disorders". Stress, which plays a role in dermatological diseases, is categorized as:

1. environmental factors that cause stress;
2. subjective experiences in specific situations and
3. biological response to stress [4].

The thesis that specific diseases occur in specific stressful situations is no longer valid. Research shows that the subjective experience of stress is much more important than the stress itself and the situation that caused the stress [5].

Somatic diseases occur in the organs innervated by the autonomic nervous system and are the result of long-term physiological changes caused by unconscious, repressed contents, that is, specific unconscious conflicts result in psychosomatic disease [6].

Biological responses to stress are strictly individual. In a state of stress, vasoactive peptides, lymphokines and chemical mediators are secreted. This leads to the development of an inflammatory process as a result of their influence on the immune system [7].

The role of stress, not only as a factor in the occurrence, but also in the exacerbation of dermatological chronic diseases, dermatitis atypical, eczema, psoriasis, acne vulgaris [8] confirmed in many studies [9] despite the fact that most of the authors use acceptable methodological standards for stress measurement.

In series of studies [10] found only weak evidence for an association between stressgenetic events and the onset of skin disease-alopecia areata, or the exacerbation of psoriasis and vitiligo. Most of these studies suggest that poor social support and individual differences may play a key role in modulating susceptibility to skin disease. Namely, it is not uncommon for an individual to biasly perceive stress leading to a dissociation between subjective and physiological responses to stress.

Poor social support, which is a very important factor associated with health, as well as a protective factor for health, is also associated with the exacerbation of psoriatic plaques and vitiligo, as well as the onset of alopecia areata. The apparent importance of social support is underscored by recent findings that psychological distress is more strongly associated with poor social support than clinical status and physical symptoms in patients with skin disease [11]. A large number of studies suggest that individual differences can and do play a cardinal role, perhaps much more than stressful events, per se, in increasing vulnerability to skin disease.believe that stress is inherent not only to the environment or the individual separately, but results from their mutual relationship [12]. Stressful events and situations have no impactwe of the inert object. Individual emotions, thoughts and behavior contribute to the initiation and maintenance of stress. Individual factorial differences affect the selection and modeling of the stressful situation. The role of individual variation has been suggested by many studies, emphasizing that some of the dermatological patients are stress reactors while others are not. It is interesting that individual differences depend on whether some of the dermatological patients will perceive the disease itself as stress, while others will not. The diversity is determined by the different defense capacities, the use of appropriate defense mechanisms with which the individual would defend against and cope with the disease perceived and experienced as stress [13].

Detailed studies in patients undergoing analytical psychotherapy insist on the fact of the existence of narcissistic fragility in patients who manifest somatic illness. Namely, these patients who have poor self-esteem and self-image are much more sensitive to how they are perceived by others. They are hypersensitive to the slightest look, movement or sentence and in constant search for interest, confirmation and love from others. Such patients tend to suppress hostile feelings due to fear of losing love from others. Narcissistic fragility can also explain the different description of the severity of the disease reported by the patient on the one hand, versus the specialist on the other hand.

In their research, epidemiologists A. Picardi and D. Abeni [14] talk about the role of stress in skin conditions and the need for stress to be considered in the

context of personality characteristics and its social and emotional connection.

Objectives of the research

To trace the impact of stressful perceived skin disease on the prevalence of psychiatric symptoms and psychiatric morbidity in patients with a diagnosed dermatological disease.

Material and methods

Study design

The study is a clinical, prospective study that was conducted at a University Dermatology Clinic. Subjects diagnosed with a dermatological disease according to ICD 10 were included in the research.

Sample selection and characteristics

Subjects with the following dermatological diseases were included in the sample: Vitiligo, Urticarija, Angio Edema, Dermatitis atopica, Alopecia areata.

Study population

The examined group consisted of 70 subjects diagnosed with a dermatological disease and to whom the set of questionnaires was applied once, at the beginning of the research.

Inclusion criteria:

a) persons with a diagnosed dermatological disease,
b) duration of illness > 6 months,
c) age from 20-55 years,
d) outpatient or hospital treatment,
e) persons with signed consent to participate in the study.

Exclusion criteria:

a) acute and chronic systemic disease,
b) diagnosed psychiatric disorder, mental retardation, neurological disease, addiction to alcohol or narcotics, pregnancy, breastfeeding,
c) duration of illness < 6 months,
d) age under 20 and over 55 years,
e) persons who will not agree to participate in the study.

SCL-90-R [21]- scale for evaluation of psychopathological psychological problems

The SCL-90-R scale is one of the most commonly used instruments for research purposes. It was designned in the early 1970s by Decrogatis, Lipman, Covi, and Rickels in order to better define the measured psychopathology and psychological stress and to create a suitable measurement instrument for monitoring psychopathological status. The SCL-90-R scale measures current psychological symptoms. It is considered that persons with established 6th grade education can access testing. The scale does not apply to dementia, comorbid conditions, mental retardation and acute psychoses. It takes 12-15 minutes to fill the instrument, and the instructions 2-5 minutes [15-17].

One of the main advantages of the scale is that, in addition to the short time needed to complete it, it also enables a multidimensional profile of symptoms, which significantly increases the quality of the measurement compared to a one-dimensional scale. Multidimensional examination of this type allows measurement not only of individualsthe individual psychopathological symptoms but also their mutual comparison.

Individual dimensions and indices of the SCL-90-R compared with standard clinical scales showed significant intercorrelations.

The scale consists of 90 questions to which the respondent answers in a way that, on a 5-point scale (from 0-not at all, to 4-expressed), determines the degree of discomfort that caused the described symptom.

The SCL-90-R scale is defined to measure nine primary symptom dimensions and three global stress indices. The obtained individual scores are calculated as follows: for each dimension, the "value" of the intensity of discomfort is calculated, then the values of all responses for the individual dimension are summed and divided by the number of responses. It is calculated from the value of individual dimensionsthe three indices of the scale.

Primary dimensions of the SCL-90-R scale:

The nine primary dimensions of the stress symptom are: somatization, obsessive complusciousness, sensitivity in interpersonal relations, depression, anxiety-knowledge, enmity, phobic, paranoid ideas, psychosis.

Additional topics:

In the SCL-90-R-scale, seven questions remain undefined under the primary dimensions of stress. They are singled out as a separate group of questions that are clinically significant and contribute to the evaluation of the SCL-90-R-scale.

SCL-90-R scale indices:

The indices are constructed to provide better flexibility in the assessment of the respondent's psychopathological status caused by stressful situations.

General Difficulty Index (GSI):

It is the best indicator of the current severity of the disorder. It is obtained by dividing the total number of responses (from 0-4) on all dimensions of the scale by the total number of responses.

Positive Stress Symptoms Index (PSDI):

It defines the exaggeration or minimization of stress

symptoms by the respondent. It represents the total sum of values from the individual dimensions of the scale. It is interpreted as a measure of symptom intensity.

Total positive symptoms:
It represents the total number of symptoms listed by the respondent, and is defined as a measure of the number of symptoms. It is obtained by dividing the total sum of responses (0-4) obtained from all dimensions of the scale by the total number of positive responses (response 0 is excluded).
The PTS and PSDI indices also enable detection of possible dissimulation by the respondent. Empirical research suggests that male respondents with PTS<3 and female respondents with PTS<4 intentionally conceal symptoms in order to be acceptedtend to be unemotional, stable and well socially integrated. When PTS>50 in male respondents or>60 in female respondents, there is high confidence of their tendency to dramatize the answers and present a worse and more difficult situation.

Results

At the beginning of this section, the data obtained by processing and analyzing 70 subjects, patients with a diagnosed dermatological disease, aged from 21 to 59 years, with an average age of 41.2±10.7 years, are shown. The gender structure of the respondents consisted of 31 (44.29%) male patients and 39 (55.71%) female patients (Table 1, Figure 1): According to the scale for descriptive assessment of psychopathological symptoms and their intensity in the majority of respondents, the presence of paranoidness -32(45.71%), obsessive-compulsive symptoms -28(40%), depression - 22(31.43%), and in a smaller number of respondents, symptoms of phobia were detected -2(2.86%) (Table 2, Figure 2).

Table 1. Demographic characteristics of the respondents

Variable	n (%)
Sex	
men	31(44.29)
women	9(55.71)
Age	
N (70) mean ± SD (41.2±10.7) min-max (21-59)	
Education	
1	12(17.14)
2	36(51.43)
3	4(5.71)
4	18(25.71)

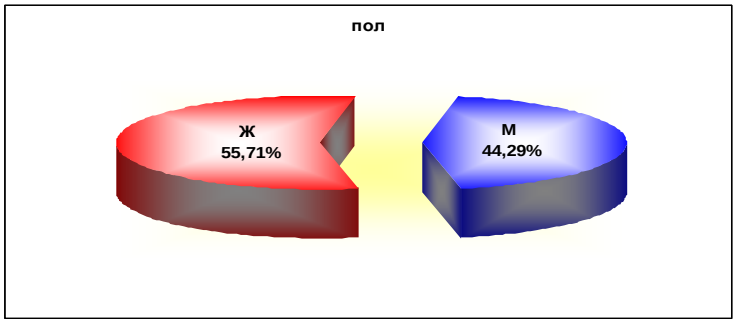

Fig. 1. Graphic representation of the gender distribution of respondents

Table 2. Distribution of the scales of the Symptom Check list - 90

Variable	SCL – 90	
	Absent n (%)	Present n (%)
som	60(85.71)	10(14.29)
oc	42(60)	28(40)
is	61(87.14)	9(12.86)
dep	48(68.57)	22(31.43)
anx	49(70)	21(30)
hos	55(78.57)	15(21.43)
phob	68(97.14)	2(2.86)
par	38(54.29)	32(45.71)
psy	70(100)	0

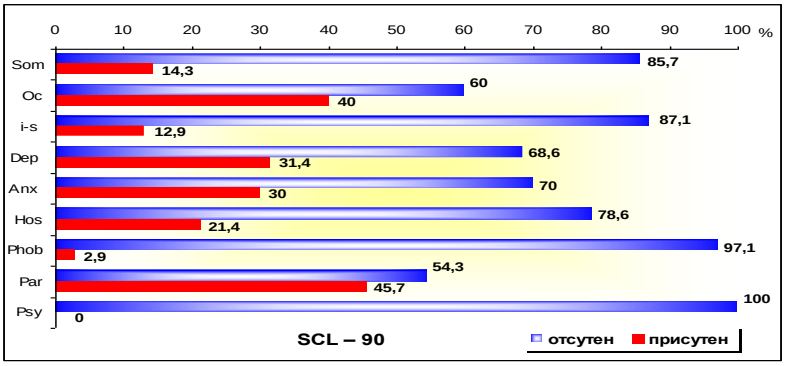

Fig. 2. Graphic representation of the scales of the Symptom Check list - 90

Discussion

Subjects with skin disease experience significantly more stressful life events and more unpleasant subjective experiences in relation to life events than the general population. For example, patients with chronic urticaria had more anxiety and depression than patients with fungal infections. Experiencing stress-skin disease, in these respondents is significantly related to psychopathological symptoms. The study confirmed the existing hypotheses that skin disease causes the emergence and development of psychiatric comorbidities manifested by psychological difficulties, psychopathological symptoms and reduction in social functioning. Our results also confirmed the hypothesis from the literature that the stressor (skin disease) is positively associated with psychiatric comorbidity [18]. The results of our study confirmed the claim that skin disease and psychiatric disorders often go together.

Recognition, identification of comorbid mental disorders, psychyatric symptoms and psychological manifestations as well as the application of appropriate psychological interventions, can positively influence the severity and course of the skin disease.

Although basic in the treatment of dermatological diseases is the standard treatment on them, in a large number of cases, it is insufficient by itself to minimize the emotional and socio-professional impact of the dermatosis. The same imposes the need for a simultaneous and combined psychotherapy treatment that will enable the patient's own insight and recognition of comorbid psychological difficulties and symptoms, as well as overcoming the tendency to avoid certain, anxiety-generating situations (new profession, partner, social groups and relations).

Conclusion

There is a great deal of literature on the connection between the psyche and the skin. On the one hand, psychosocial factors seem to have a role in the pathogenesis and course of several skin diseases, and on the other hand, the psychopathological status occurs as a complication or consequence of the skin disease itself.

The results of this research confirmed the association of skin disease with the presence of psychological manifestations and psychiatric symptoms as a conesquence of skin changes.

Conflict of interest statement. None declared.

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Original article

UTERINE ARTERY DOPPLER AND SERUM LEVEL OF IMMUNOBIOMARKERS IN PREECLAMPSIA - OUR EXPERIENCE

ДОПЛЕР НА УТЕРИНА АРТЕРИЈА И СЕРУМСКО НИВО НА ИМУНИТЕ БИОМАРКЕРИ КАЈ ПРЕЕКЛАМПСИЈА - НАШЕ ИСКУСТВО

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Abstract

Introduction. Important mechanisms are known to be involved in the immunomodulatory pathways which are crucial for maintaining an adequate utero-placental circulation in pregnancy. Its disbalance brings to impaired tolerance, which leads to inflammation and autoimmune processes in preeclampsia.
Aim. The aim of this study was to find if inadequate uteroplacental hemodynamic was associated with improper feto-maternal immune adaptation. The risk of developing preeclampsia can be predicted by combining use of uterine artery flow and cytokine values. The aim was to show their combination as a predictive indicator of preeclampsia in the second trimester of pregnancy.
Methods. This study enrolled 96 pregnant patients in the second trimester (patients were between the 14th and 20th gestational weeks). Their history data, routine foetal ultrasound, bilateral uterine artery Doppler ultrasound and cytokines were evaluated. All patients were followed up till the end of pregnancy. Half of the pregnant women consisted the study group (N=48), which had presence of notch of the uterine artery. In the control group (N=48), there was an absence of uterine artery notch. In all patients, Doppler of the uterine artery, pulsatility index (PI) and resistance index (RI) were made and determined. The pro-inflammatory cytokines (TNF-α, IL-1α, IL-2 and IL-6) and anti-inflammatory cytokines (IL-4 and IL-10) from patient's serum were analyzed.
Results and Discussion. In the study group (N=48), 32 patients had changes in the cytokine serum levels. Increased pro-inflammatory biomarkers (IL-6, TNF-α, IL-1α) were with sensitivity of 78 to 91.2%. According to this, high predictive value was found. Of these 32 patients, 21 developed preeclampsia. When the sensitivity of pro- and anti-inflammatory biomarkers together with the uterine artery Doppler ultrasound was combined, a sensitivity resulted in 81.5%. Multivariate regression analysis detected that IL-6 was the most significant predictive parameter. This result is similar to that presented in the study by Teran and Hentschke *et al.*
Conclusion. Using predictive tests is imporatnt to detect undeveloped preeclampsia in a timely manner that would prevent possible developmental complications. After abnormal Doppler results, cytokines should be investigated as a predictive method.

Keywords: preeclampsia, cytokines, immunobiomarkers, pregnancy

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Апстракт

Вовед. Важни механизми се вклучени во имуномодулаторните патишта, што е од клучно значење за одржување на адекватна утеро-плацентарна циркулација во бременоста. Нивниот дисбаланс доведува до нарушена толеранција, што доведува до инфламација и автоимуни процеси кај преeклампсијата.
Цел. Целта на оваа студија е да открие дали несоодветната утероплацентарна хемодинамика е поврзана со неправилна фетоматернална имунолошка адаптација. Ризикот од развој на преeклампсија може да се предвиди со комбинирање на употребата на протокот на утеринатa артерија и вредностите на цитокините. Целта е да се прикаже нивната комбинација како предиктивен индикатор како ризик за преeклампсија во вториот триместар од бременоста.
Методи. Оваа студија опфати 96 бремени пациентки во вториот триместар (пациентките беа помеѓу 14 и 20 гестациска недела). Беа евалуирани податоците од нивната историја, рутински ултразвук на фетусот, билатералниот доплер на утеринатa артерија и вредностите на цитокините. Сите пациентки биле следени до крајот на бременоста. Кај сите пациентки беа вклучени Доплер на утеринатa артерија, индекс на пулсатилност (PI) и резистенс индекс (RI). Половина од трудниците кои ја сочинуваат испиту-

ваната група (N=48) имаа присуство на notch на утеринатa артерија. Кај пациентките од контролната група (N=48) имаше отсуство на notch на утеринатa артерија. Проинфламаторните цитокини (TNF-α, IL-1α, IL-2 и IL-6) и антиинфламаторните цитокини (IL-4 и IL-10) беа анализирани од серумот на пациентките.

Резултати и дискусија. Во испитуваната група (N=48), 32 пациентки имале промени во серумските вредности на цитокините. Зголемените проинфламаторни биомаркери (IL-6, TNF-α, IL-1α) беа со сензитивност од 78 до 91,2%, резултат со висока предиктивна вредност. Од нив, 21 развија прееклампсија. Кога сензитивноста на про и антиинфламаторните биомаркери заедно со утериниот артериски Доплер беше комбинирана, сензитивноста резултираше со 81,5%. Од мултиваријатната регресиона анализа откриено е дека IL-6 е најзначајниот параметар за предикција. Овој резултат е сличен на студијата на Теран и Хенчке и колегите.

Заклучок. Користењето на предиктивни тестови е важно за навремено откривање на неразвиена прееклампсија што би ги спречило можните развојни компликации. По абнормални Доплерови резултати, вредностите на цитокините треба да се испитаат како метод за предвидување.

Клучни зборови: прееклампсија, цитокини, имунобиомаркери, бременост

Introduction

Maternal immunological tolerance in pregnancy towards the semi-allogenic fetus is crucial for maintaining a normal pregnancy. Immune imbalance may lead to a higher risk of developing pregnancy complications such as preeclampsia. Preeclampsia is a multisystem disorder that occurs in 3 to 7% of pregnancies [1], and it is the most common cause of maternal and perinatal morbidity and mortality worldwide. According to American College of Obstetricians and Gynecologists (ACOG) [2], preeclampsia is defined as hypertensive disorder after 20 gestational weeks with presence of proteinuria at previously normotensive women, or absence of proteinuria but with other clinical manifestations expressed. There are several important mechanisms known that are involved as immunogenic and immunomodulatory pathways crucial for maintaining balance, and their loss leads to weakened tolerance, strong inflammation and autoimmunity, thus describing preeclampsia [3].

The vascular layers of the myometrium are properly invaded by the extravillous trophoblast to precede uterine spiral artery remodulation. The process is dependent on the balance in the produced immunological biomarkers from the deciduas. SFlt-1 (soluble fms-like tyrosine kinase-1 factor) is expressed by the foetal tissue (trophoblast) and maternal tissue (endothelium) [4]. In preeclampsia, it is well known that exacerbation of clinical symptoms is a result of increased levels of pro-inflammatory and decreased level of anti-inflammatory cytokines [5].

The activity of the antigen presentation is weakened, therefore the immune tolerance towards the fetus is inadequate [6]. It is reflected in the shallow nidation of the extravillous trophoblast [7,8]. Because of the immunological changes during nidation at the level of extravillous trophoblast according to findings in the literature, there are antiangiogenic and pro-inflammatory factors released in circulation as a result of poor placental perfusion [9]. This imbalance leads to ischemia that leave consequences due to a multiorgan dysfunction [10].

IL-6 together with TNF-α stimulates the production of endothelin 1, reactive oxygen species and antibodies, like a ROS and AT1-AA I, and IL-10 decreased values exacerbate hypertension and endothelial dysfunction [11].

Changes of uterine artery flow results in impaired uteroplacental circulation, an insufficient vascular arborisation in tertiary placental villi. The notch is examined, with a lower sensitivity value, but also PI and RI with higher sensitivity in relation to the prediction of vascular deviations.

According to literature data, preeclampsia which is developed before 34 g.w. is mostly dependent on the placental insufficiency, whereas after 34 weeks of gestation the maternal etiological factors are more expressed.

Aim

The aim of this study was to find if inadequate uteroplacental hemodynamic was associated with improper feto-maternal immune adaptation. The risk of developping preeclampsia can be predicted by combining the use of uterine artery flow and cytokine levels. The aim was to show their combination as a predictive indicator for preeclampsia in the second trimester of pregnancy.

Material and methods

Pregnant patients were recruited successively for this prospective cohort study. They were between 14 to 20 weeks of pregnancy, a total number of 96 patients. The study was performed at the University Clinic for Gynecology and Obstetrics in Skopje, RN Macedonia in a period of 12 months (the year 2019). An approved consent to participate in the study was signed by each patient. The study was approved by the Research Ethics Committee at the University Clinical Center in Skopje.

This study enrolled 96 pregnant patients in the second trimester (patients were between the 14th and 20th gestational weeks). Their history data, routine foetal ultrasound, bilateral uterine artery Doppler ultrasound

and cytokines were evaluated. All patients were followed up till the end of pregnancy. Half of the pregnant women consisted the study group (N=48), which had presence of the uterine artery notch. In the control group (N=48), there was an absence of uterine artery notch. In all patients, Doppler of the uterine artery, pulsatility index (PI) and resistance index (RI) were made and determined. The pro-inflammatory cytokines (TNF-α, IL-1α, IL-2 and IL-6) and anti-inflammatory cytokines (IL-4 and IL-10) from patient's serum were analysed.

Inclusion criteria were: single pregnancy, normotensive patient before pregnancy, live foetus - without malformation. Exclusion criteria were multiple pregnancy and stillbirth.

In patients, the data were obtained from patient history, family history and previous comorbidities. After an ultrasound assessment of the fetal biometry (14-20 g.w.) normal appearance of foetus was confirmed without ultrasound visible malformation, as well as placenta and amniotic fluid and umbilical cord. By Doppler method, Mindray Dc 7, Voluson 8, according to the ultrasound software, examined the flow of the uterine artery, where in addition to the presence of notch, the values of pulsatility (PI) and resistance (RI) indexes were measured (according to the reference values of the ultrasound software). Serum levels of pro-inflammatory cytokines (TNF-α, IL-1α, IL-2 and IL-6) and anti-inflammatory cytokines (IL-4 and IL-10) were examined using the ELISA methodology (Magnetix Luminex Assay multiplex kit) at the Institute of Immunobiology and Human Genetics of the Faculty of Medicince, Ss. Cyril Methodius University in Skopje. Patients were followed by ultrasound and other additional diagnostic procedures according to clinical protocol until delivery. The obtained data were statistically processed (STATISTICA 21, SSPS for Windows).

Results

Of a total number of 96 patients, regarding the history data (Table 1), statistical significance was found in the study group compared to the control group regarding history of previous pregnancy with preeclampsia, for was p<0.05 (16.67% *vs.* 4.17%). In the study group, 27.08% were smokers *versus* 10.42% in the control group (p-0.03).

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Table 1. Characteristics of patients

Characteristics of patients	Study group (48)	Control group (48)	P- value
Parity: nulliparous	28(58.33%)	21 (43.75%)	0.15
Multiparous	20 (41.67%)	27 (56.25%)	0.15
Diabetes	6 (12.50%)	3 (6.25%)	0.29
Smokers	13 (27.08%)	5 (10.42%)	0.03
Previous pregnancy with PE	8 (16.67%)	2 (4.17%)	0.04
BMI	24.5	2 2.2	0. 56
Systemic lupus erythematosus (SLE)	2 (4.17%)	0	0.15
Morbus von Willebrand	2 (4.17%)	0	0.15
Family history of PE	7 (14.58%)	2 (4.17%)	0.08

Regarding the results of the flow indexes, a significant result was obtained in terms of RI and PI values between the two groups for p-0.005 (Table 2). The mean PI value in the study group was 1.95, and 1.43 in the control group, showing a statistical significance. The mean RI value in the study group was 0.64, and in the control group 0.51, which demonstrated a statistical significance (p-0.007).

Table 2. Doppler evaluation (PI and RI)

Presence of notch		Number of patients	Average value	Стандардна девијација (SD)	Стандардна грешка (SE)	T	Df	P (2-tailed)
PI	study group	48	1.9585	0.15269	0.02204	11,959	94	0.005
	control group	48	1.4327	0.26359	0.03805		75.351	
RI	study group	48	0.6498	0.10558	0.01524	8,649		0.007
	control group	48	0.5094	0.03878	0.00560		59.455	

Increased resistance in PI and RI values above 1.75 and 0.68, respectively, and the presence of a diastolic notch were abnormal results.

Of the 48 pregnant patients from the study group, 32 had changes in cytokine levels. Pro-inflammatory biomarkers (IL-6, TNF-α, IL-1α) were elevated, and anti-inflammatory biomarker (IL-10) was decreased. There were changes in IL4 level in the study group, but no changes in the control group. Also, there were no changes in the minimum and maximum IL-2 levels, but little difference in the mean level.

The analysis of the cytokines showed that the result obtained for IL-6 represented the most significant predictive indicator in comparison with other cytokines.

Statistical analysis with Pearson's coefficient with correlation confirmed an increase in the pro-inflammatory biomarkers (IL-6, TNF-α, together with IL-6 and TNF-α in correlation IL-1α with p <0.001).
By using ANOVA test and logistic multivariate regression analysis, IL 6 had highest influence as a pro-inflammatory cytokine (described in statistical procedures 1, 2 and 3).

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Statistical procedure 1. Sum value

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	0.452	0.204	0.160	0.46

a) Predictors : (Constants), IL - 2, IL - 4, IL - 6, IL - 10, T N F – α

Statistical procedure 2. ANOVA for analysis of cytokine variations in preeclampsia

Model	Sum of Squares	Df	Mean Square	F	P
Regression	4.882	5	0.976	4.61	0.001
Residual	19.024	90	0.211		
Total	23.906	95			

Dependent variable: patients with preeclampsia; Predictors (Constant): IL-2, IL-4, IL-6, IL-10, TNF-α

Statistical procedure 3. Result of the Logistic multivariate regression analysis

Model		Unstandardized Coefficients B	Unstandardized Coefficients Std. Error	Standardized Coefficients Beta	T	P
1	(Constant)	1.817	0.360		5.044	0.000
	TNF- α	0.008	0.041	0.020	0.197	0.844
	IL-6	-0.072	0.016	-0.432	-4.351	0.000
	IL-10	0.002	0.002	0.122	1.279	0.204
	IL-4	-0.010	0.008	-0.124	-1.313	0.192
	IL-2	-0.017	0.033	-0.050	-0.519	0.605

Mutual interaction of the pro-inflammatory cytokines in the study group showed a sensitivity of 78% to 91.2% in detecting the risk of preeclampsia. The combined usage of the Doppler method with immunobiomarkers resulted in: sensitivity of 81.5% (69.2-90.2%), specificity of 45.7% (32.2-60.1%), negative predictive value of 67.7% (50-81%) and positive predictive value of 63.8% (52-74%), which was a reliable predictive indicator.
The anti-inflammatory cytokines resulted in high sensitivity (95%) but low specificity (25%) for IL-10. IL-4 had no valuable range changes.
Of the 48 patients in the study group, 32 had elevated levels of pro-inflammatory and decreased levels of anti-inflammatory cytokines; in 16 patients there were no changes in the levels. In the third trimester, 21 patients (43.75%) developed preeclampsia. Of these, six patients (12.5%) had preterm birth (mean of 34.4 gestational weeks), *versus* the control group (38.3 gestational weeks). Complications had occurred in one patient having eclamptic seizure (2.08%), one patient had HELLP syndrome and pulmonary oedema (2.08%). Four patients had abruption of the placentas intrapartum (8.33%) and three foetuses had IUGR (6.25%). Six patients did not have complications (12.5%). In the same group with the presence of notch and elevated cytokines, three patients had gestational hypertension (6.25%) and three had gestational diabetes (6.25%), 5 resulted false positive. In those with presence of notch and normal cytokine range, two patients had SLE (4.17%), two had M. Von Willebrand (4.17%) and 12 resulted false positive (25%). In the control group, three patients had gestational hypertension (6.25%), two had gestational diabetes (4.17%) and two foetuses were diagnosed with IUGR (4.17%). There were 41 patients (85.42%) without complications.

Discussion

Preeclampsia is a multifactorial disorder which includes maternal, genetic, immunological, environmental, oxidative stress and angiogenic factors.
According to Mannisha Kar *et al.* [12] and ISSHP guidelines [13], multiparametric approach is required for detection of the risk for developing preeclampsia. Also, maternal factors are important in prediction preeclampsia such as previous pregnancies with preeclampsia and those who had been smokers.
Doppler measurement had sensitivity from 34 to 76%. Implementation of biomarkers are increasing the sensitivity of detection of patients which will develop preeclampsia in the second trimester [14,15].
The values obtained for flow indexes (PI above 1.75 and RI above 0.68) correspond to those from ISUOG where cut-off values are proposed for each trimester.

Between 14th and 20th gestational weeks, studies emphasize that a score of 1.75 for PI and 0.68 for RI indicates a risk of developing preeclampsia. According to Plasencia, PI in the first, as well as in the second trimester, a sensitivity of 77% for early preeclampsia and 27% for late preeclampsia were detected [16] The value of 95 percentile for PI was associated with a risk of developing more serious complications as we found in our study [17].

Goma detected PI value greater than or equal to 1.75 representing a sensitivity of 99%, and by using cytokines, he measured a sensitivity of 88.6% and specificity of 100% detection rate.[18] This corresponds to the findings in our study. Of all pro-inflammatory cytokines, single sensitivity of IL-6 was 85% [19].

The results of the combined usage of the uterine artery Doppler ultrasound together with pro-inflammatory and anti-inflammatory cytokines showed sensitivity of 81.5%, and the mutual correlation of the pro-inflammatory cytokines was 78 to 91.2%. This as a predictive tool in the second trimester, from the 14th to the 20th gestational week, which is applied in patients who are prone to develop preeclampsia after 28 weeks of gestation in the third trimester.

Teran [20] and Hentschke *et al.* [21] verified an increase in IL-6 in preeclampsia. Also, IL-6 analyzed with multivariate regression analysis was the most significant predictive parameter. In line with the results of this study, we should be more vigilant in monitoring these patients. The risk is detectable according to FMF in the first trimester of pregnancy [22] and the patients shoud be given Aspirin (120-160mg) as soon as we confirm the risk [23]. The final target is appropriate time for admission in tertiary care facility.

Conclusion

Usage of predictive test in the early second trimester for preeclampsia will help an appropriate monitoring of patients who have a risk of developing preeclampsia. If abnormal Doppler result is obtained, especially in patients with a known risk of preeclampsia, we suggest levels of cytokines, especially IL6, to be measured. Thus, we can prevent unfavourable outcome of development of preeclampsia and its complications.

Different therapeutic modalities and predictive methods can improve the overall health of both, the mother and the foetus. Taking into account that preeclampsia is a multifactorial disorder, the investigations for the disease never stop. Preeclampsia will be a field of research in the years to come. Our study is a little contribution to this issue, with the results obtained in our patients.

Conflict of interest statement. None declared.

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Case Report

BLEPHAROXANTHOGRANULOMA: RARE OCULAR MANIFESTATION OF XANTHOGRANULOMA NECROBIOTICUM

БЛЕФАРОКСАНТОГРАНУЛОМ: РЕТКА ОКУЛАРНА МАНИФЕСТАЦИЈА НА КСАНТОГРАНУЛОМА НЕКРОБИОТИКУМ

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Abstract

Introduction. Blepharoxanthogranuloma is a rare ocular manifestation of necrotizing xanthogranuloma, often associated with systemic conditions like monoclenal gammopathy. This case study presents the clinical progression and treatment methods for this rare condition, highlighting the importance of multidisciplinary approach and long-term monitoring.
Aim. The purpose of this study is to better understand the clinical course and management approaches for blepharoxanthogranuloma, a rare ocular manifestation of necrotizing xanthogranuloma that is frequently often associated with systemic diseases such as monoclonal gammopathy. This will emphasize the value of multidisciplinary cooperation and ongoing observation.
Methods. This case study follows a 56-year-old woman whose skin lesions initially appeared in 2013 and whose diagnosis of necrotizing xanthogranuloma was confirmed by biopsy in 2015. Hematological analysis in 2022 found bone marrow plasma cell infiltration; the level of immunoglobulin G (IgG) was found to be 47.5 g/L. Systemic treatment with Decortin and Ciprilon was initiated, followed by lenalidomide and dexamethasone. In 2022, the paraorbital lesions improved, but the infraorbital suppuration still persisted. The ulcer on the left eye was fully epithelialized by 2022, however there was a 2-3 mm purulent patch in the right infraorbital area. The monitoring of treatment response underscored the need for a multidisciplinary approach.
Results. The patient underwent monitoring and regular follow ups for a duration of four years, having regulary treatment with topical, intralesion and systemic corticosteroids. Our ophthalmological examination in 2024 revealed posterior capsule cataracts and paraocular scar lesions. Both eyes' corrected visual acuity was 20/63 BCVA, necessitating cataract surgery. Multiple periocular scarring lesions were seen on both sides during an eye checkup in 2024, showing that the illness process is persistent. Even while some lesions successfully epithelialized and showed signs of partial healing, further monitoring indicated that therapy was still necessary due to persisting problems.
Conclusions. This case contributes to the limited literature on blepharoxanthogranuloma, highlighting the complexities of its management and shows the importance of long-term monitoring to prevent complications. Blepharoxanthogranuloma management requires a multidisciplinary approach involving dermatologists, hematologists, and ophthalmologists. Continuous monitoring is crucial for optimizing patient outcomes and enhancing our understanding of this rare ocular condition.

Keywords: blepharoxanthogranuloma, necrotizing xanthogranuloma, monoclonal gammopathy, multidisciplinary approach, continuous monitoring

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Апстракт

Вовед. Блефароксантогрануломот е ретка окуларна манифестација на некротизирачки ксантогранулом. Често е поврзан со системски состојби како што е моноклонална гамопатија. Оваа студија на случај има за цел да ја прикаже клиничката прогресија и методите на лекување за оваа ретка состојба, нагласувајќи ја важноста на мултидисциплинарниот пристап и долгорочното следење на состојбата.
Цел. Целта на овој приказ на случај е подобро да се разберат клиничкиот тек и пристапите за управување со блефароксантогранулом, ретка окуларна манифестација на некротизирачки ксантогранулом кој често се поврзува со системски заболувања како што е моноклоналната гамопатија. Со овој приказ сакаме да ја нагласиме важноста за мултидисциплинарната соработка и тековното набљудување.

Методи. Овој приказ на случај следи 56-годишна жена чии кожни лезии првично се појавиле во 2013 година. Дијагнозата е поставена со биопсија на некротизирачки ксантогранулом во 2015 година. Хематолошката анализа во 2022 година откри инфилтрација на плазма клетки на коскената срцевина; беше откриено ниво на имуноглобулин G (IgG) е 47,5 g/L. Иницран бил системски третман со Декортин и Циприлон, проследен со леналидомид и дексаметазон. Во 2022 година, параорбиталните лезии се подобриле, но инфраорбиталната супурација сè уште опстојувала. Следењето на одговорот на третманот ја нагласува потребата за мултидисциплинарен пристап.
Резултати. Пациентот беше подложен на мониторинг и редовно следење во времетраење од четири години, со редовен третман од локални, интралезиски и системски кортикостероиди. Нашиот офталмолошки преглед во 2023 година откри катаракта на задната капсула и параокуларни лузни лезии. Корегирана визуелна острина на двете очи беше 20/63 НКВО, поради што беше потребна операција на катаракта. Повеќекратни периокуларни лузни лезии беа забележани на двете страни за време на прегледот на очите во 2024 година, што покажа дека процесот на болеста е постојан. Дури и додека некои лезии успешно се епителијализираа и покажаа знаци на делумно заздравување, понатамошното следење покажа дека терапијата е сè уште неопходна поради постојаните проблеми.
Заклучок. Овој приказ на случај придонесува во ограничената литература за блефароксантогранулом, нагласувајќи ја сложеноста на неговото менаџирање и ја покажува важноста на долгорочното следење за да се спречат компликации. Управувањето со блефароксантогрануломот бара мултидисциплинарен пристап кој вклучува дерматолози, хематолози и офталмолози. Континуираното следење е од клучно значење за оптимизирање на резултатите на пациентот и за подобрување на нашите знаења за оваа ретка окуларна состојба.

Клучни зборови: блефароксантогранулом, некротизирачки ксантогранулом, моноклонална гамопатија, мултидисциплинарен пристап, континуирано следење

Introduction

Necrobiotic xanthogranuloma (NXG) is a rare and chronic systemic disorder characterized by the infiltration of inflammatory cells and lipid-laden macrophages (xanthoma cells) within the dermis resulting in the formation of granulomatous lesions. These lesions usually located on the face, trunk, periorbital area, and extremities. Because of its rarity and potential systemic association, palpebral xanthogranuloma involving the eyelids poses diagnostic and treatment challenges. There are very few cases of blepharoxanthogranuloma, a subtype of necrotizing xanthogranuloma, documentted in the medical literature. Due to their rarity, doctors may have difficulty diagnosing and treating them because they are not familiar with the clinical presentation and suitable treatment approaches. Adult orbital xanthogranulomatous diseases are rare entities and encompass a group of disorders with varying manifesttations that are poorly understood. [4]Taken as a group, there are non-Langerhans histiocytic disorders (type II) that are diagnosed histologically by the presence of foamy histiocytes, Touton giant cells, and varying degrees of fibrosis [4].
Our case study focuses on the middle-aged woman's xanthogranuloma of the eyelids, including its clinical course, diagnostic assessment and tretatment. Though its precise cause is unknown, paraproteinemias-in particular, multiple myeloma and monoclonal gammopathy of unknown significance (MGUS)-are frequently linked to non-X-linked hematological disorders (NXG). On the other hand, hematological abnormalities are not always necessary for NXG to occur.
Ocular involvement is prevalent and can result in major side effects like restricted eye movement, proptosis, ptosis, and visual impairment [1]. NXG lesions can develop ulcers and cause pain in addition to ocular symptoms. This can result in secondary infection and necrosis. The size of the lesions typically increases over time or with the next recurrences. A multidisciplinary approach involving dermatologists, ophthalmologists, rheumatologists, and hematologists is frequently necessary for the diagnosis of NXG.

Materials and methods

Woman age 55 in 2012, during a routine blood test, elevated ESR (66 mm/1h) and leukopenia (WBC= 2.3x103/L) were found. March 2013 - Hematologic investigations were performed: Elevated Total protein =92 and IgG=26.6 g/L; Paraprotein; Urine electrophoresis was negative for Bence Jones protein; Dg: Paraproteinemia. In November 2014 serum protein electrophoresis was performed, and it demonstrated monoclenal spike in the gamma globulin region. Total protein 87g/l, Paraprotein 17.7 % (15.4 g/l). Immunoelectrophoresis also showed IgG kappa monoclonal gammopathy (Figures 1 and 2).

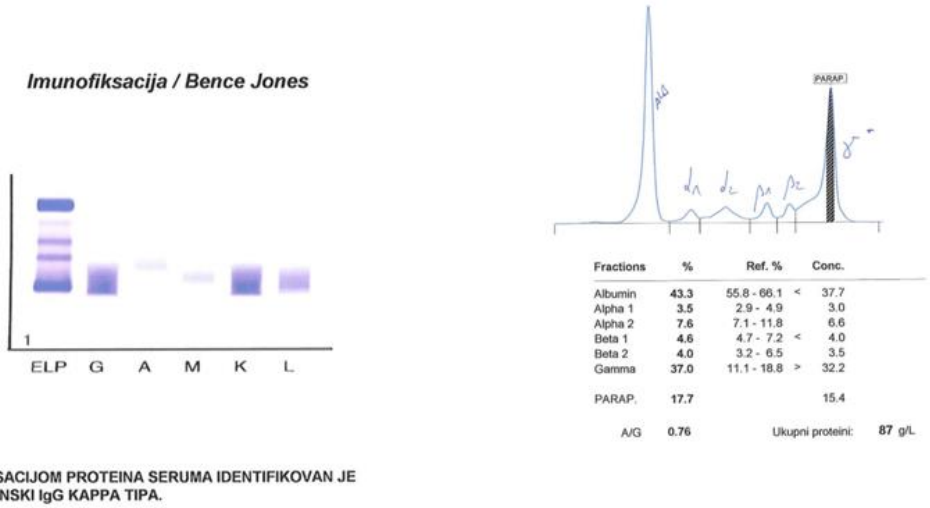

Fig. 1 and 2. Results of serum protein immunofixation

From May 2015 untill today - She is regularly followed (every two months) at the Department of Hematology, where was concluded the following diagnosis: Dg: Gamapathia monoclonalis IgG kappa type, MGUS (monoclonal gammopathy of uncertain significance). Since August 2016, once a month for a duration of 3 days, a condition appears accompanied by an elevated body temperature of 38.0 C, with characteristic migraine headaches, pain in the eyes, and fatigue. Since (21.12.2016 untill 02.02.2017) she was treated with high doses of corticosteroids Prednisolone results were with insignificant reduction of IgG, but without the above mentioned symptoms. Since then (28-08-2017 untill 20-09-2017) new treatment was prescribed: Prednisolone (Decortin) 15 mg/day. From 21.09.2017 to 03.03.2018 Decortin 10mg/day was prescribed, and finally, there was a reduction of IgG from 49.32 to 38.3 g/L. After the period when she was treated with Décortin 15 mg, there were visible flattering and lightening of the skin nodules on the legs and face, and 4 months without occurrence of elevated body temperature and headaches. From March 2018 till April 2021 she was regularly treated with Prednisolone (Decortin 5mg/day). Every 2 years, she had check-ups with sternal puncture (last performed December 2020 with the results: 8-10% plasma cells). December 2020, also performed CT/PET scan of the head, the chest, the abdomen, and the pelvis. From the results of the sternal puncture and CT/PET scan from December 2020, was concluded the development of Myeloma [5]. The patient initially presented with cutaneous manifestations in the summer of 2013, characterized by erythema on both lower extremities, which subsequently progressed to a darker, indurated texture over time. Concurrently, xanthomas emerged in the orbital regions.

Upon her first assessment at the Department of Dermatology in December 2013, the patient was diagnosed with Xanthelasma palpebrarum, denoting eruptive xanthomas in the lateral and zygomatic regions. Subsequent to this, new nodules developed on both lower limbs in November 2014.

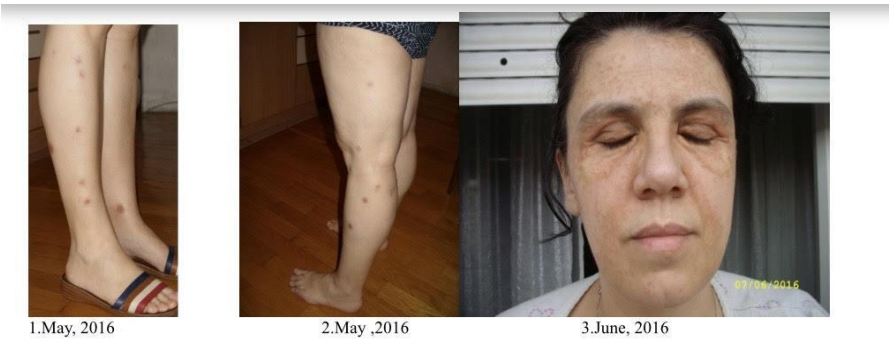

Fig. 3. Xanthomas on lower extremities and face

In March 2015, skin biopsies were obtained from a lower limb nodule, as well as the frontal and zygomatic regions of the face. The histopathological examination revealed a chronic, nonspecific granulomatous response characterized by inflammation, histiocytes, and multinucleated giant cells. Following extensive review and consultation with the scientific literature, an experienced skin pathologist confirmed the presence

of features consistent with Necrobiotic xanthogranuloma (NXG).
For the lower extremities, a local therapy regimen was initiated with Clobetasol propionate 0.05%. Despite application of the cream to the affected areas, notable improvement was not observed [4].
The patient did not report pain or ulceration associated with the skin changes. She maintained regular consultations with her Hematologist and kept her dermatologists informed about her condition every 4-6 months until 2019. During this period, the nodules on her legs gradually faded and nearly disappeared. However, in 2020, there was a progression of skin changes around the eyes, accompanied by the emergence of new nodules on the chest and upper arms. Due to the COVID-19 pandemic, her visits to the hematologists were less frequent. She was prescribed a daily dose of 5mg Decortin. Despite her general condition being relatively stable, she experienced frequent headaches, fatigue, and monthly fever episodes. Additionally, she developed bladder infection (Cystitis) and eye inflammation (Blepharitis).
From February to October 2021, there was a notable deterioration in the skin changes around her face and eyes, leading to swollen eyelids and increased orbital deposits [7].
The patient's hematologist initiated a Decortin regimen

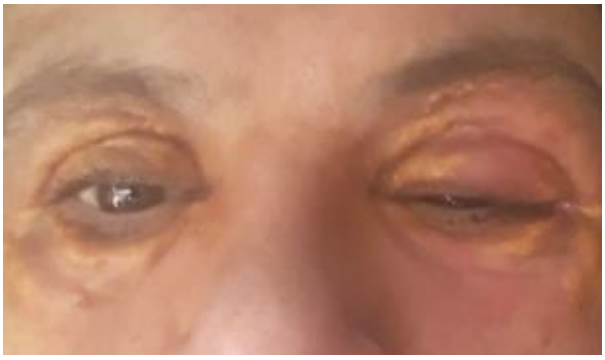

Fig. 4. Swollen eyelids and increased orbital deposits

of 30 mg daily for 7 days (April 17th to April 23rd, 2021), subsequently adjusting it to 20 mg daily from April 24th to May 24th, 2021. Following the patient's receipt of the first dose of the Covid vaccine on May 25th, 2021, the Decortin dosage was decreased to 15 mg. After the second vaccine dose on June 14th, 2021, the Decortin dosage was further reduced to 10 mg per day. During the treatment, the swelling on the upper eyelids visibly decreased, but the skin around the orbital area under both eyes started to darken (turning dark brown), and in early June 2021, it developed cracks and opened wounds.

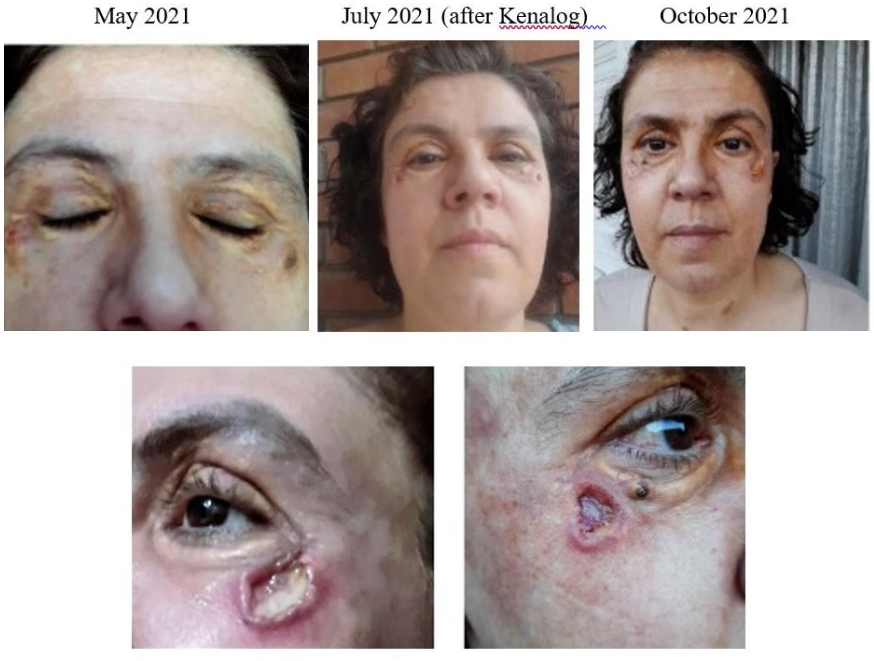

Fig. 5. Cracks and opened wounds

In June 2021, at the Dermatology Department, two doses of Kenalog (triamcinolone) at 20 mg each were administered to both eyes [6]. The initial dose was given on June 10th, 2021, followed by the second dose on July 6th, 2021. However, Kenalog did not produce a significant effect. By the end of September 2021, the wounds around the orbits under both eyes had worsened, leading to ulceration, with the left eye's wound being larger and deeper.

In October 2021, the Decortin dosage was escalated to 30 mg per day (administered as 3 tablets of 10 mg each), and then gradually tapered down. Additionally, she managed the wounds using Hydroclean Pads and Granulox spray, observing gradual closure. By January 2022, the right eye wound had healed, and the left eye wound had completely closed with scar formation. Concurrently, other xanthomatous lesions on the chest and upper arms showed partial improvement, characterized by fading and leveling. This improvement correlated with a reduction in Serum M-Gradient (Paraprotein) levels, from 2.37 g/dl on May 14th, 2021, to 2.03 g/dl on November 4th, 2021, and further to 1.84 g/dl in May 2022 (Serum protein electrophoresis was conducted).

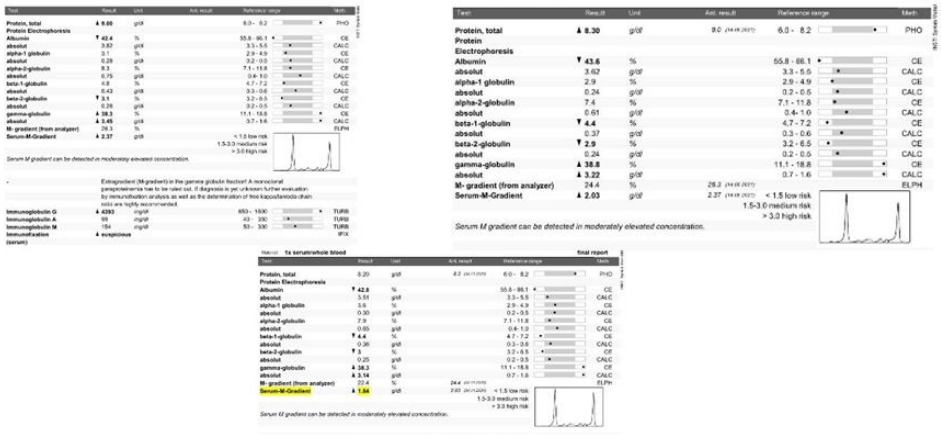

Fig.6. Results from serum protein electrophoresis

September 2022, the patient presented with a favorable general condition, marked by the absence of headaches, fatigue, and fever. However, notable changes were observed in the ocular region, characterized by the emergence of extensive yellow papules on both upper eyelids over the past 2 months, accompanied by discoloration and swelling. In October 2022, additional diagnostic procedures were conducted, including a sternum biopsy and a skin biopsy. The findings from these biopsies confirmed the diagnosis of Necrobiotic xanthogranuloma (NXG) along with monoclonal gammopathy (MGUS) [2].

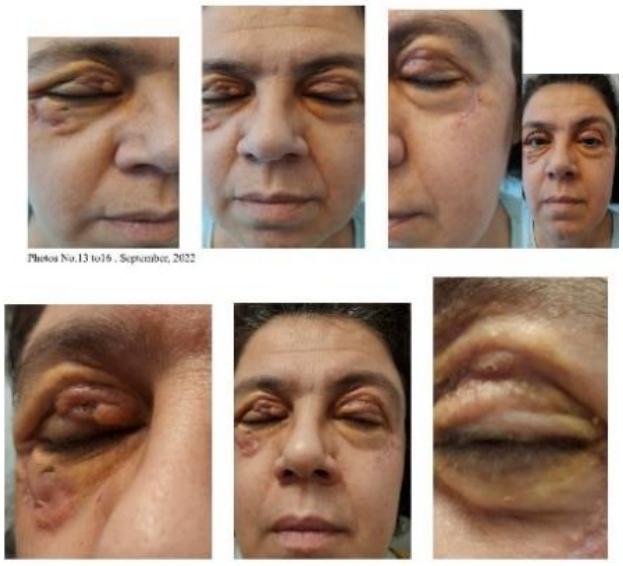

Fig.7. Extensive yellow papules on both upper eyelid

The ophthalmological examination revealed no significant eye abnormalities except for the presence of cataracts. In 2023, cataract surgery was successfully performed. The patient's ongoing systemic therapy involved prednisolone (Decortin 12.5mg/day) due to progressive skin changes on the eyelids noted towards the end of September. Multiple periocular lesions were noted on both sides during the ophthalmological examination, which indicated that the disease was persistent, further follow-up indicated that therapy was still necessary due to persistent manifestations.

Discussion

Blepharoxanthogranuloma represents an uncommon ocular manifestation of necrotizing xanthogranuloma that is often associated with systemic conditions such as monoclonal gammopathy [1]. Successful management requires a collaborative effort involving ophthalmologists, hematologists, and dermatologists. Treatment modalities may include immunomodulators, systemic corticosteroids, and surgical interventions aimed at addressing ocular complications. Long-term monitoring is crucial to prevent systemic complications and mitigate the risk of irreversible visual impairment.

Conclusion

Blepharoxanthogranuloma, a rare ocular manifestation of NXG, requires a comprehensive approach involving various medical specialties for accurate diagnosis and optimal management. Long-term monitoring and the-

rapeutic interventions are crucial to prevent irreversible complications.

Conflict of interest statement. None declared.

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MMP

Case report

HEART TUBEROUS SCLEROSIS IN PREGNANCY: A CASE REPORT

СРЦЕВА ТУБЕРОЗНА СКЛЕРОЗА ВО БРЕМЕНОСТ (ПРИКАЗ НА СЛУЧАЈ)

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Abstract

Introduction. Tuberous sclerosis, also known as tuberous sclerosis complex (TSC), is a rare genetic condition that mainly causes development of benign tumors in different parts of the body.
Case report. We present the case of a 22-year-old primigravida. At 21 weeks of gestation, while performing second trimester organ scan for fetal abnormalities, fetal cardiac rhabdomyoma (3×2.9 cm) (Figure 1) was found. Detailed antenatal anatomic survey using ultrasound ruled out angiolipoma of kidney and cerebral hamartoma. Prenasal edema and hyperechoic bowel were present. The patient was informed that her fetus was probably affected with tuberous sclerosis.
Discussion. Prognosis depends on the number, size and location of tumors. A wide spectrum ranging from normal life expectancy with mild symptoms to severe neurodevelopmental delay, epilepsy, autism and renal or pulmonary failure can be expected. Recurrence: Autosomal dominant: 50% if one of the parents is affected. De novo mutations (65% of cases): no increased risk.
Conclusion. Genetic counseling is recommended for couples who have a family history of tuberous sclerosis and who want to have children. Prenatal diagnosis is available for families with a known gene mutation or history of this condition.

Keywords: heart, pregnancy, tuberous sclerosis

Абстракт

Вовед. Туберозна склероза, позната и како комплекс на туберозна склероза (TSC), е ретка генетска состојба која главно предизвикува развој на бенигни тумори во различни делови од телото
Приказ на случај. 22-годишна примигравида, На 21-та недела од бременоста при изведување на скенирање на органи во вториот триместар за фетални абнормалности, откриен е фетален срцев рабдомиом (3×2,9 cm) (Слика 1). Детално антенатално анатомско истражување со помош на ултразвук го исклучи ангиолипом на бубрег и церебрален хамартом, преназален едем хиперехоично црево. Пациентката е информирана дека фетусот најверојатно има туберозна склероза.
Дискусија. Прогнозата зависи од бројот, големината и локацијата на туморите. Широк спектар кој се движи од нормален животен век со благи симптоми до сериозно задоцнување на невро-развојот, епилепсија, аутизам и ренална или пулмонална инсуфициенција. Повторување: Автозомно доминантно: 50% ако еден од родителите е засегнат. De novo мутации (65% од случаите): нема зголемен ризик.
Заклучок. Генетско советување се препорачува за парови кои имаат семејна историја на туберозна склероза и кои сакаат да имаат деца. Пренаталната дијагноза е достапна за семејства со позната генска мутација или историја на оваа состојба.

Клучни зборови: срце, бременост, туберозна склероза

Introduction

Tuberous sclerosis, also known as tuberous sclerosis complex (TSC), is a rare genetic condition that mainly causes development of benign tumors in different parts of the body. The tumors most often affect the brain, skin, kidneys, heart, eyes and lungs. In the past, it was believed that the typical presentation included seizure, mental retardation, and facial angiofibroma (adenoma sebaceum) (Vogt's Triad). This disorder has now wide variability of expression [1].
Tuberous sclerosis is diagnosed in most cases of multiple fetal cardiac rhabdomyomas and in 50% of single cases. Multiple echogenic nodules in the heart (rhabdomyoma, usually >20 weeks of gestation) and brain (cortical tubers and subependymal nodules, usually >30 weeks of gestation). In our case, it was diagnosed at 21 weeks by obstetric ultrasonography and fetal echocardiography [2].
Differential diagnosis: cardiac fibroma, which are single, large and often associated with pericardial effusion.
Tuberous sclerosis is found in 50% of cases of rhabdomyoma (in the other 50% of cases the cardiac tumor is an isolated finding). When there are multiple rhabdomyomas, the risk of tuberous sclerosis is >90%. Most rhabdomyomas cause no problems but some may cause

heart failure in the fetus or first year of life. Rhabdomyomas are believed to be responsible for the development of heart arrhythmia later in life, which is relatively common in TSC. Arrhythmia can be hard to spot in people with TSC, other than by performing routine ECG. For example, arrhythmia may cause fainting that is confused with drop seizures, and symptoms of arrhythmia such as palpitations may not be reported in an individual with developmental delay [3].
Associated abnormalities: The inheritance of TSC is an autosomal dominant trait with variable penetrance. Mutations in either the TSC1 or TSC2 gene are found in 90% of cases. It can be inherited from one parent with TSC or can result from a spontaneous genetic mutation. Children have a 50 percent chance of inheriting TSC if one of their parents has this condition. At this point, only one-third of TSC cases are known to be inherited. The tumors most often affect the brain, heart, skin, kidneys, eyes and lungs. However, prenatal diagnosis is confined to detection of the lesions in the heart and brain [4].
Prognosis: Arrhythmias, hydrops, and stillbirth in about 20% of cases.

Case Presentation

We report on the case of a 22-year old primigravida. At 21 weeks of gestation, while performing ultrasound for assessment of fetal growth and organ scan, fetal cardiac rhabdomyoma (3×2.9 cm) (Figure 1 and 2) was seen by fetal echocardiography. Detailed antenatal anatomic survey using ultrasound ruled out angiolipoma of kidney and cerebral hamartoma. Prenasal edema and hyperechoic bowel were present. The patient was informed that her fetus was probably affected with tuberous sclerosis. Amniocentesis was indicated and the obtained result confirmed tuberous sclerosis of the fetus. Due to the presence of heart regurgitation, axis deviation and pericardial effusion, the termination of pregnancy was recommended. Feticide was done and the induction of labor was done by application of 120 ml 33% NaCl; the patient delivered a stillbirth.

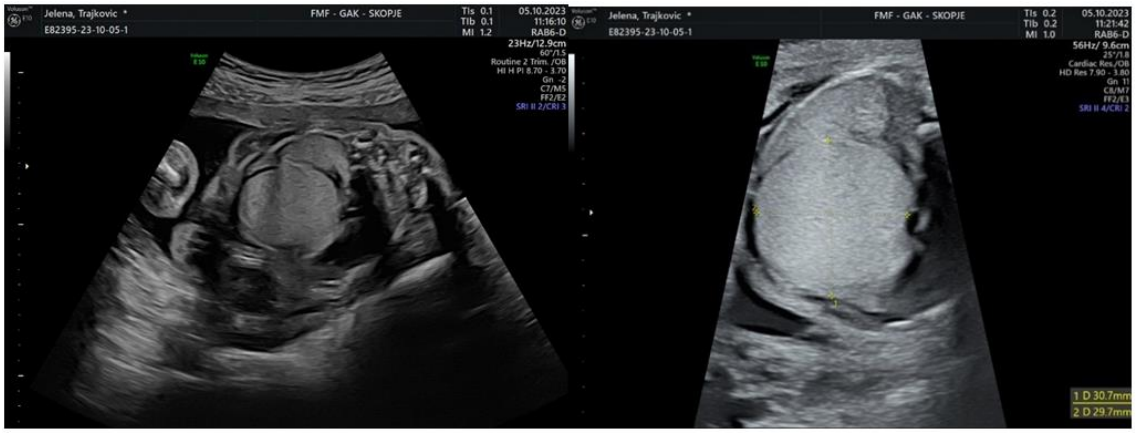

Fig. 1 and 2. Tubrosus sclerosus in heart

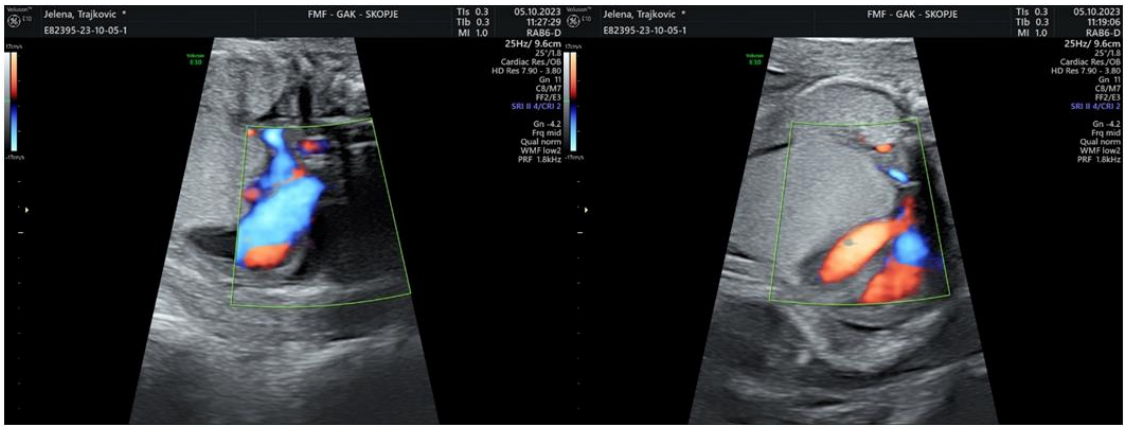

Fig. 3 and 4. Color Doppler ultrasound

A 22-year-old with live intrauterine fetus at 21 week of gestation showing cardiac rhabdomyoma. A: Ultrasound showing an echogenic mass (M) arising from the wall of the left ventricle (LV) (Figure 3 and 4), there is pericardial effusion (PE) present, normal right ventricle (RV) and interventricular septum (IVS), showing an isointense mass (M) arising from the left ventricle.

Discussion

The cardiac tumors usually regress in early life, whereas the brain tumors usually increase in size and number. Prognosis depends on the number, size and location of the tumors. A wide spectrum ranging from normal life expectancy with mild symptoms to severe neurodevelopmental delay, epilepsy, autism and renal or pulmonary failure can be expected.

Recurrence: Autosomal dominant: 50% if one of the parents is affected. De novo mutations (65% of cases): no increased risk [5].

When tuberous sclerosis complex is suspected or diagnosed in an unborn baby, it can be a time of worry, frustration and great distress for everyone involved. It may also lead to individuals and families making some incredibly difficult choices. During this confusing time, it is important to get the information that might help you take next steps [6].

Parents often talk about the stigma associated with ending a pregnancy and the difficulties talking about it, particularly to family members and children. Every situation is different, and the reasons for ending a pregnancy are unique to everyone [7].

In countries where second trimester abortion is allowed, parents are the only ones responsible for deciding the termination of the pregnancy, while in some European countries and in the Middle Eastern countries where abortion is prohibited, parents are forced against their will to continue the pregnancy and they face stillbirth or the consequences of this disease after birth [8].

Conclusion

Tuberous sclerosis is a rare genetic condition that mainly causes development of hamartomas. In tuberous sclerosis, a cardiac rhabdomyoma is the only sign that can be detected prenatally. A pregnancy complicated by fetal tuberous sclerosis deserves careful observation and the fetus should undergo prenatal fetal Doppler echocardiography and if possible magnetic resonance imaging for evaluation of other fetal structures including brain and renal parenchyma, so that parents can be counseled regarding its future prognostic implications [9]. Genetic counseling is recommended for couples who have a family history of tuberous sclerosis and who want to have children. Prenatal diagnosis is available for families with a known gene mutation or history of this condition.

Conflict of interest statement. None declared.

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MMP

Case report

RITUXIMAB IN TREATMENT OF A PATIENT WITH GRANULOMATOSIS WITH POLYANGIITIS – A CASE REPORT

РИТУКСИМАБ ВО ТРЕТМАН НА ПАЦИЕНТ СО ГРАНУЛОМАТОЗА И ПОЛИАНГИИТИС – ПРИКАЗ НА СЛУЧАЈ

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Abstract

ANCA-associated vasculitis (AAV) is a necrotizing vasculitis with few or no immune deposits that can affect predominantly small vessels. It can affect vessels in every organ and tissue of the body; the clinical manifestations of the disease are extremely variable. B-cells are of major importance in the disease pathogenesis as precursors of ANCA-producing plasma cells and, possibly, also as antigen-presenting and cytokine-producing cells. Therefore, rituximab, a monoclonal antibody drug causing partial B-cell depletion, has emerged as a powerful option in the treatment of AAV such as granulomatosis with polyangiitis. We present the case of a 25-year-old female diagnosed with granulomatosis with polyangiitis and treated with rituximab and high-dose corticosteroids.

Keywords: ANCA, vasculitis, rituximab, treatment, remission

Апстракт

ANCA-асоцираните васкулитиси (ААВ) се некротизирачки васкулити на малите крвни садови со малку или без присуство на имуни депозити. Тие може да го зафатат секој орган во телото и поради ова клиничките манифестации можат да бидат различни. Б-клетките се од есенцијално значење во патогенезата како прекурсори на плазма клетките кои ги произведуваат овие антитела, но и како антиген-презентирачки и клетки кои произведуваат цитокини. Поради тоа ритуксимабот кој е моноклонално антитело кое предизвикува делумна Б-клеточна деплеција претставува моќна опција во третманот на ААВ како грануломатоза со полиангиитис. Презентираме случај на 25 годишна жена со грануломатоза со полиангиитис лекувана со ритуксимаб и високи дози на кортикостероиди.

Клучни зборови: ANCA, васкулит, ритуксимаб, лекување, ремисија

Introduction

Granulomatosis with polyangiitis is an ANCA-associated small vessel vasculitis [1] which can affect multiple systems [2]. It is characterized by granulomas on tissue biopsy, usually affecting the upper and lower respiratory tract. Furthermore, nephritis first recognized by frank proteinuria is common. The disease can affect any organ in the body. This presents a challenge for establishing a timely diagnosis and starting effective treatment as soon as possible, as delay can be life threatening.

Case report

A 25-year-old female patient was hospitalized in the University Clinic for Rheumatology in March, 2020 presenting with vasculitis changes in the face, anemia, difficulty breathing, cough, fever, arthritis, weight loss and proteinuria. One month prior to hospitalization, she was hospitalized in the Clinic for Respiratory Diseases where a CT scan was performed. It showed changes in the lung parenchyma on both sides, predominantly in the subpleural spaces and from the middle to the basal parts, multiple irregular zones of consolidation, substrates, and granulomas (Figure 1 and 2). Proteinuria was 1.68g/24 hours, so active nephritis was suspected. Immunological tests showed positive cANCA (45.2U/ml) and pANCA (163/75U/ml), ANA Hep 2 was negative at 1:80. The patient satisfied the criteria for granulomatosis with polyangiitis according to the 2022 American College of Rheumatology/European

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Alliance of Associations for Rheumatology classification criteria for granulomatosis with polyangiitis [2].
The patient had a two-month history of fever, general weakness, weight loss, polyarthritis, peripheral vasculitis, lung granulomatosis, sores in the mouth and nose, proteinuria and a positive biological syndrome of anemia (Table 1). Based on these clinical signs the patient had a BVAS of 21 points. In order to start treatment as soon as possible it was decided not to biopsy lungs or kidneys.

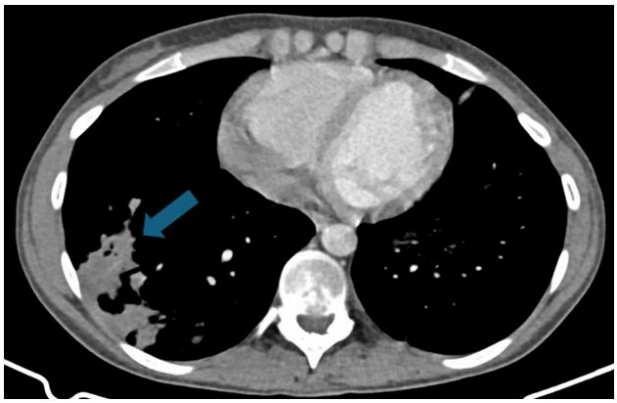

Fig. 1.

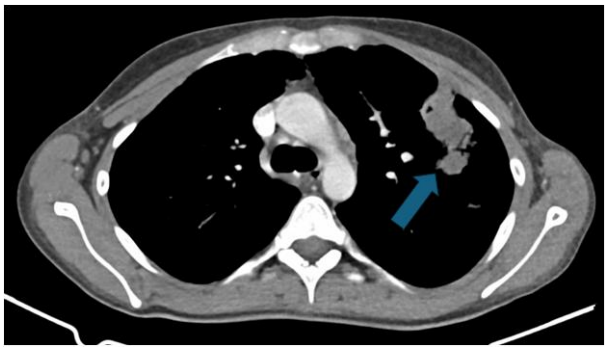

Fig. 2.

Fig. 1 and 2. CT scans predominantly in the subpleural spaces and from the middle to basal parts showing multiple irregular zones of consolidation, substrates, granules. Some of them are cavitating. The blue arrows are indicating cysts with substrates present, leading to a granulomatous disease.

Table 1. Laboratory tests before treatment with rituximab

	10.02.2020	**28.02.2020**
Sedimentation rate		74
Hemoglobin	56	84
Leukocytes	10.93	9.3
Platelets	475	699
Creatinine	125	77
CRP	202	
24-hour-proteinuria		1.68

The patient was treated with a high dose of corticosteroids (60mg/day), and rituximab was started, 500 mg i.v. once a week for four weeks. It was repeated every six months accordingly. Additionally, she was treated with anticoagulants and peripheral vasodilators.

A new chest computer tomography scan was performed in November 2020 showing the following: fresh parenchymal consolidation, but no focal and expansive changes: fibro-adhesive residual changes in addition to sequelae visible in the left anterior in the upper and middle lung parts towards the periphery; right posterior in the middle parts, a nodular change with lung opacity of 9 mm x 8 mm with surrounding fibro-adhesive changes in addition to the diff dg/differential diagnosis of repaired granulomatous change. No signs of hilar and mediastinal lymphadenopathy were registered and without bilateral, pleural and pericardial effusion. Normal hemodynamic presentation of the mediastinal vessels was seen (Figure 3 and 4). The last chest CT was performed in 2023 presenting the same findings.

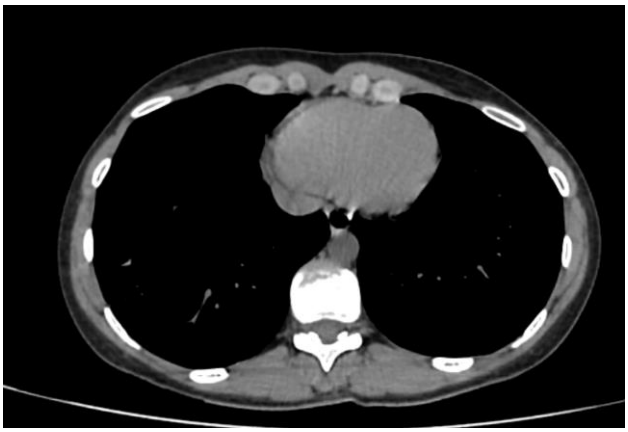

Fig. 3.

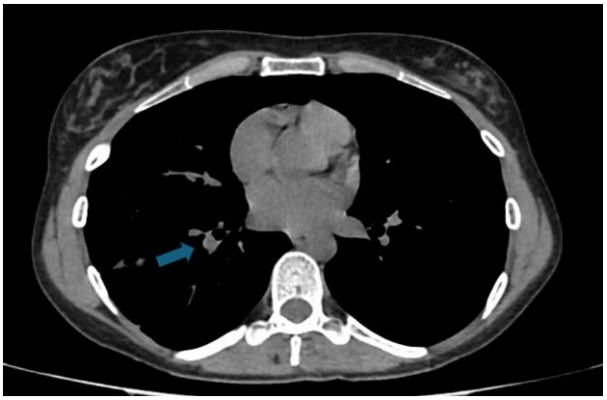

Fig. 4.

Fig. 3 and 4. CT scan showing fibro-adhesive residual changes in addition to sequelae visible in the left anterior upper and middle lung parts towards the periphery.

Table 2. Laboratory tests after treatment with rituximab

CRP	**0.6**	**Sedimentation rate**	**3**
24-hour-proteinuria	0.09	Erythrocytes	4.69
		Hemoglobin	154
		Leukocites	4.9
		Plateles	241

Blue arrow indicates a nodular change with a 9 mm x 8 mm dimension, with surrounding fibro-adhesive changes, leading to a differential diagnosis of healed granulomatous disease.
Treatment with one dose of 500 mg rituximab every 6 months continues, in addition to low dose corticosteroids after tapering (5 mg/day). The patient is in remission with BVAS=2.

Discussion

Wegener's granulomatosis is a necrotizing vasculitis usually associated with granulomatous inflammation of the respiratory tract and glomerulonephritis. Its treatment is difficult and challenging. Based on the clinical signs, lab results and imaging of our patient, a diagnosis for Wegener's granulomatosis was made. The goal of this treatment was to achieve remission and sustain it.
For remission induction in life-threatening or organ-threatening AAV, a combination of high-dose glucocorticoids with either rituximab or cyclophosphamide is recommended. Tapering of the GC dose to a target of 5 mg prednisolone equivalent/day within 4-5 months is recommended [3].
For patients with an active, severe disease the recommendation doses of rituximab are 375 mg/m2 once weekly, for 4 doses or 1 g once every 2 weeks for 2 doses, administered in combination with a systemic corticosteroids [4,5]
Maintenance therapy it is recommended at 500 mg once every 2 weeks for 2 doses, then 500 mg or 1 g once every 4 to 6 months [5-8]
Rituximab was shown as an effective treatment in achieving remission in our patient along with corticosteroids tapered.
In this patient a protocol of 500 mg rituximab administrated as an i.v. infusion once every 6 months was introduced.

Conclusion

It is critical to diagnose and start treatment in these patients as delay may only worsen the outcome. Our case shows that rituximab is an effective option for the induction and maintenance of remission in patients with AAV.

Conflict of interest statement. None declared.

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MMP

Case report

HYDROXYUREA-INDUCED CENTROFACIAL HYPERPIGMENTATION AND NAIL MELANONYCHIA IN A 69-YEAR-OLD MALE: CASE REPORT

ХИДРОКСИУРЕА-ИНДУЦИРАНА ЦЕНТРОФАЦИЈАЛНА ХИПЕРПИГМЕНТАЦИЈА И МЕЛАНОНИХИЈА НА НОКТИТЕ КАЈ 69 ГОДИШЕН МАЖ

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Abstract

????Nitu edna referenca ne e citirana vo tekstot????

Hydroxyurea, also known as hydroxycarbamide, is a chemotherapeutic agent commonly used to manage myeloproliferative disorders. Its mechanism of action involves inhibiting ribonucleoside diphosphate reducetase, thereby halting DNA synthesis during the S-phase of cellular replication. While hydroxyurea is generally well tolerated, long-term therapy can lead to mucocutaneous adverse effects, including skin hyperpigmentation and nail discoloration. These side effects, though benign, remain poorly understood due to limited case reports.

We present the case of a 69-year-old male diagnosed with myelodysplastic syndrome and treated with hydroxyurea at a dose of 1,000 mg per day for nine months. Three months after initiating therapy, the patient developed centrofacial hyperpigmentation, particularly in the nasal region, and melanonychia characterized by longitudinal brown-black bands on multiple fingernails and a few toenails most noticeable on the hallux. Alternate causes of hyperpigmentation, such as fungal or bacterial infections, systemic diseases, and nutritional deficiencies, were excluded. The patient exhibited no systemic symptoms, and his oral mucosa remained unaffected.

Given the benign nature of the lesions, no specific treatment or discontinuation of hydroxyurea was recommended. The patient was advised to continue therapy with regular follow-up. This case highlights the importance of recognizing hydroxyurea-induced mucocutaneous changes, differentiating them from serious conditions such as subungual melanoma, and balancing the risk-benefit ratio when considering therapy modifications. Further research is needed to better understand the pathophysiological mechanisms behind hydroxyurea-induced hyperpigmentation and explore potential management strategies for these adverse effects.

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Keywords: hydroxyurea, hyperpigmentation, melanonychia, myelodysplastic syndrome, chemotherapy side effect

Апстракт

Хидроксиуреа, исто така позната како хидроксикарбамид, е хемотерапевтски агенс кој често се користи за третман на миелопролиферативни нарушувања. Нејзиниот механизам на дејство се базира на инхибиција на рибонуклеозид дифосфат редуктазата, со што се запира синтезата на ДНК за време на S-фазата од клеточната репликација. Иако хидроксиуреата генерално добро се поднесува, долготрајната терапија може да доведе до мукокутани несакани ефекти, вклучувајќи хиперпигментација на кожата и дисколорација на ноктите. Овие несакани ефекти, иако се бенигни, остануваат слабо разбрани поради ограниченият број пријавени случаи.

Презентираме случај на 69-годишен маж со дијагноза на миелодиспластичен синдром, третиран со хидроксиуреа во доза од 1.000 mg дневно во период од девет месеци. Три месеци по започнувањето на терапијата, пациентот развил центрофацијална хиперпигментација, особено изразена во регионот на носот, и меланонихија, со надолжни кафено-црни линии на повеќе нокти на рацете и неколку на нозете, најзабележливи на палецот. Ги исклучивме сите можни причинители за хиперпигментација, како што се габични или бактериски инфекции, системски заболувања и нутритивни недостатоци. Пациентот не појави никакви системски симптоми, и немаше зафатеност на оралната мукоза.

Со оглед на бенигната природа на лезиите, не беше препорачано специфично лекување ниту прекин на терапијата со хидроксиуреа. Пациентот беше советуван да продолжи со терапијата со редовни контроли.

Овој случај ја истакнува важноста на препознавање на мукокутаните промени предизвикани од хидроксиуреа, разликувајќи ги од сериозни состојби како субунгвален меланом, и балансирање на соодносот помеѓу ризикот и користа при размислување за мо-

дификации на терапијата. Понатамошни истражувања се потребни за подобро разбирање на патофизиолошките механизми на хиперпигментацијата предизвикана од хидроксиуреа и за истражување на можни стратегии за справување со овие несакани ефекти.

Клучни зборови: хидроксиуреа, хиперпигментација, меланонихија, миелодиспластичен синдром, несакан ефект од хемотерапија

Introduction

Hydroxyurea, also referred to as hydroxycarbamide, is an antineoplastic and cytostatic agent first synthesized in 1869 by Dresler and Stein. Its antitumor activity was reported in the 1960s. The drug is primarily used to manage myeloproliferative disorders, such as acute and chronic myeloid leukemia. Additional indications include essential thrombocythemia, polycythemia vera, sickle cell disease, refractory hypereosinophilic syndrome, head and neck cancers, ovarian cancers, psoriasis (as a second-line systemic agent), and as an adjuvant in AIDS therapy.

Hydroxyurea exerts its pharmacological effect by selectively inhibiting the M2 subunit of ribonucleoside diphosphate reductase. This inhibition halts the conversion of ribonucleotides to deoxyribonucleotides, thereby interfering with DNA synthesis and arresting the cell cycle at the G1/S phase.

Consequently, this process sensitizes cells to radiation-induced damage.

Although hydroxyurea is generally well tolerated, prolonged therapy can result in a spectrum of mucocutaneous side effects, including eczema, xeroderma, skin atrophy, alopecia, and various forms of hyperpigmentation. Nail changes, including melanonychia, onycholysis, and brittle nails, have also been reported. Severe adverse effects such as nonmelanoma skin cancers and pre-malignant conditions, including actinic keratoses and Bowen's disease, have been documentted. Systemic effects may include hematological, gastrointestinal, pulmonary, and neurological manifestations.

Case Presentation

A 69-year-old male with histopathologically confirmed myelodysplastic syndrome was prescribed hydroxylurea at a daily dose of 1,000 mg for nine months as cytoreductive therapy. After three months of treatment, he observed gradually progressive hyperpigmentation localized centrofacial, muddy-brown hyperpigmentation particularly in the nasal region (Figure 1) and nail discoloration on multiple fingernails (Figure 2) and a few toenails most noticeable on the hallux (Figure 3). Nail pigmentation was characterized by longitudinal brown-black bands originating from the proximal nail plate and progressing distally, accompanied by periungual hyperpigmentation. No systemic symptoms, localized pain, or history of trauma were reported.

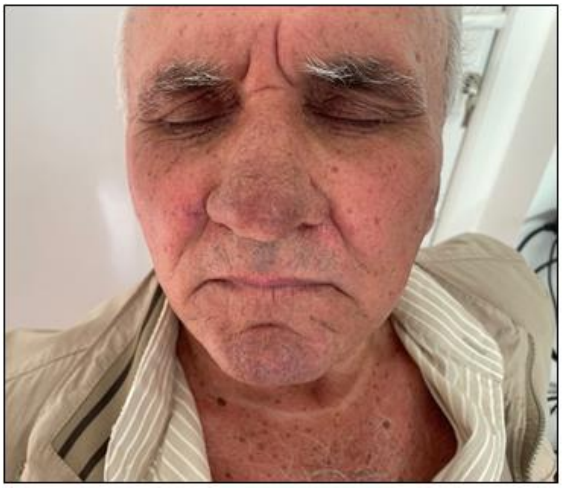

Fig. 1. Centrofacial muddy-brown hyperpigmentation

Fig. 2. Longitudinal melanonychia on the fingernails

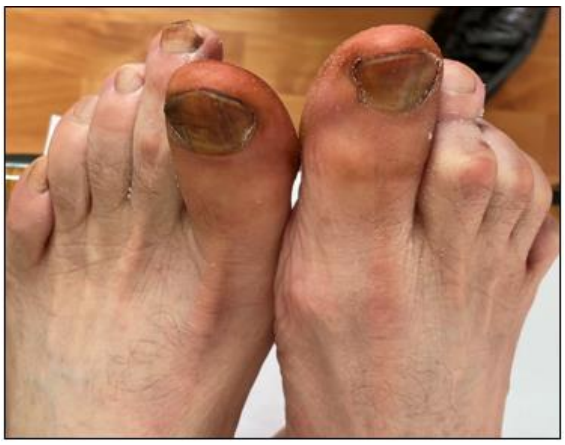

Fig. 3. Longitudinal melanonychia on the toenails

Chronic medications included nebivolol, clopidogrel, pantoprazole, diazepam, metformin, rosuvastatin, and hydrochlorothiazide. Hydroxyurea was the only recent addition to his treatment regimen. The patient's medical history included type 2 diabetes mellitus, hyper-

tension, and previous PCI stenting, among other conditions. He reported no personal or familial history of cutaneous malignancies.

A clinical examination revealed Fitzpatrick skin type IV and melanonychia with a longitudinal band pattern. Dermoscopic findings excluded melanoma or subungual malignancies. Alternate causes of hyperpigmentation, such as fungal or bacterial infections, thyroid disorders, Addison's disease, and nutritional deficiencies, were ruled out through comprehensive investigations.

The patient was counseled to continue hydroxyurea therapy, given the benign nature of the lesions, with regular follow-up at our University Clinic for Dermatology and Venereology in Skopje, Macedonia.

Discussion

Hydroxyurea-induced hyperpigmentation is a common side effect, while melanonychia is less frequently reported. Nail pigmentation can manifest as longitudinal bands, transverse bands, diffuse discoloration, or lunular hyperpigmentation, with variable onset after initiating therapy.

The mechanism of hyperpigmentation involves hydroxyurea's cytotoxic effects on rapidly dividing cells, photosensitization, melanin and iron deposition, and drug accumulation in the capillary-rich nail matrix, leading to melanocyte activation and melanin synthesis.

The clinical types of drug-induced hyperpigmentation can be classified as follows: Type 1, characterized by black-blue pigmentation in pre-existing scars; Type 2, involving black-blue pigmentation on the shins and forearms; and Type 3, presenting as diffuse muddy-brown discoloration in sun-exposed areas, as observed in our patient.

The pathologic causes of melanocytic activation are extensive and include regional, dermatologic, systemic, iatrogenic, and syndromic factors. Among iatrogenic causes, drug intake is a significant contributor to melanocytic activation in the human body. Various drugs have been implicated in this process, including bleomycin sulfate, busulfan, cyclophosphamide, dacarbazine, daunorubicin hydrochloride, doxorubicin, etoposide, 5-fluorouracil, hydroxyurea, imatinib, adrenocorticotropic hormone, amodiaquine, amorolfine, chloroquine, clofazimine, cyclosporine, fluconazole, fluorides, gold salts, ibuprofen, ketoconazole, melanocyte-stimulating hormone, minocycline, procarbazine, phenytoin, phenothiazines, psoralens, roxithromycin, steroids, sulfonamides, timolol, and zidovudine.

These drugs can result in subsequent longitudinal melanonychia. Drug-induced melanonychia typically affects multiple fingernails or toenails. However, in most cases, this condition gradually resolves once the patient discontinues the medication. Importantly, malignancy associated with drug-induced melanonychia is rare.

Differential diagnoses for melanonychia include onychomycosis, subungual melanoma, and drug-induced pigmentation. Unlike subungual melanoma, which typically affects a single nail and may show Hutchinson's sign, hydroxyurea-induced melanonychia usually involves multiple nails.

Discontinuation of hydroxyurea often resolves hyperpigmentation, but therapy adjustments must weigh risks and benefits. Further research is essential to understand the pathophysiology and develop alternative strategies to manage this side effect while maintaining therapeutic efficacy.

Conclusion

Clinicians should be aware of hydroxyurea's mucocutaneous side effects to facilitate prompt recognition and management. Accurate diagnosis is essential to differentiate benign drug-induced changes from malignant conditions like subungual melanoma.

Further research is needed to elucidate the mechanisms of hydroxyurea-induced hyperpigmentation and melanonychia, enabling better management of these side effects without compromising therapeutic efficacy.

Conflict of interest statement. None declared.

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

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

Извадокот на англиски јазик мора да е со содржина идентична со содржината на извадокот на македонски јазик.

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Дискусијата треба да ги истакне импликациите од добиените резултати, споредени со постојните сознанија за испитуваниот проблем. Заклучоците треба да не бидат подолги од 150 зборови.

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

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

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Адреса на Редакцијата Даме Груев бр. 3 Градски Ѕид блок II, 1000 Скопје,
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Известување за рецензентите за ММП

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