

ISSN 2671-3497 (Online)

INTERNATIONAL JOURNAL

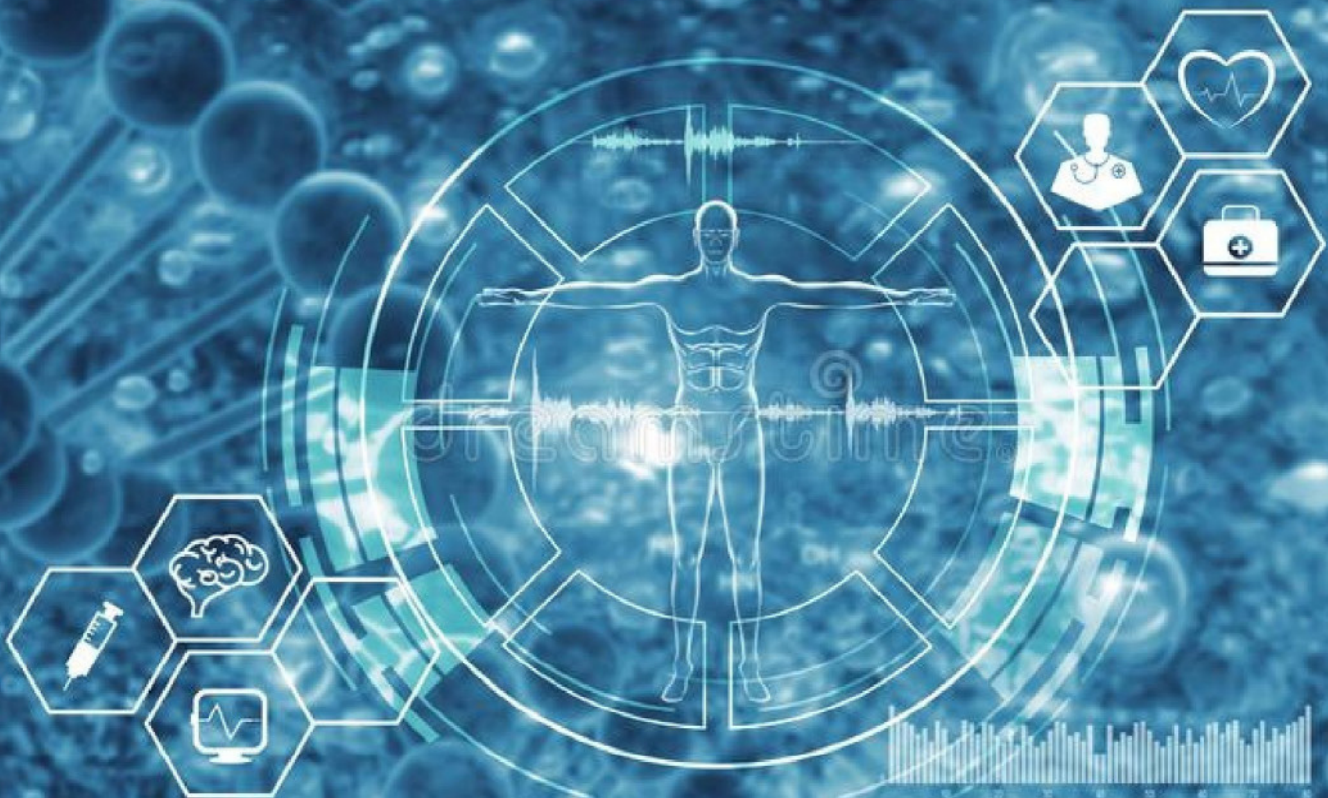
Institute of Knowledge Management

M E D I S



Vol. 3 Issue 3

MEDICAL SCIENCES & RESEARCH



**MEDIS – International Journal of Medical
Sciences and Research**

Volume 3, Issue 3, September 2024.

IMPRESSUM

**International Journal of Medical Sciences and Research
(MEDIS IJMSR)
(Volume 3, Issue 3 September 2024.)**

**Editor in chief:
Prof. d-r Robert Dimitrovski**

**Publisher:
Institute of Management and Knowledge
Address: Gjuro Gjonovikj, 11/4 , Skopje 1000, Macedonia
Phone: +389 70 207 370, + 381 63 700 4281**

**<http://medisij.com>
E-mail: editor@medisij.com**

**For publisher:
Prof. d-r Robert Dimitrovski**

**Print:
GRAFOPROM Bitola**

**Circulation:
50 copies**

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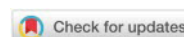
CORRELATION OF HYPOTHALAMIC-PITUITARY-ADRENAL AXIS ACTIVITY WITH CHRONIC COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES

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Abstract: For the successful prevention of chronic diabetic complications, it is crucial to identify novel etiopathogenetic factors that contribute to their development. We evaluated the association of hypothalamus pituitary adrenal axis activity (HPA) with the presence of chronic diabetic complications and glycemic control in 107 patients with type 2 diabetes and 29 healthy subjects, matched for age and sex. The study included 107 type 2 diabetic patients and 29 healthy control subjects who were hospitalized at the Internal Medicine Clinic of the University Clinical Center Tuzla. Patients with diabetes were evaluated for chronic complications and divided into two groups according to the presence (group 1, n = 57) and absence (group 2, n = 50) of complications. We determined the parameters of the HPA axis as follows: a level of 08 h cortisol and ACTH and a level of 09 h cortisol after a short dexamethasone test (DEX cortisol) and compared those among the groups. We determined the parameters of glycemic control and compared them with the parameters of the hypothalamus pituitary adrenal axis. In group 1, the values of cortisol were 454 (368–561), ACTH 12.6 (8.7–23), and DEX cortisol 37.5 (23–52), significantly higher compared to group 2 [320 (230–387), 7.9 (3.3–16.4), 26 (22–36), $p < 0.05$, and higher compared to healthy subjects [312 (233–342), $p = 0.001$, 12 (6–16.7), $p = 0.1$, 24 (19–29), $p = 0.126$, respectively]. Evaluating the parameters of glycemic control, we found a higher HbA1C in group 1, 7.9 (6.55–9.45) compared to group 2, 7.5 (5.97–10), $p = 0.498$, while correlation analyses showed a significant positive relationship between HbA1C and cortisol ($R = 0.242$, $p = 0.012$). **CONCLUSION:** Patients with type 2 diabetes have HPA axis dysfunction. Higher cortisol levels are associated with poor glycemic control and the presence of diabetic complications. To better understand the etiology and provide practical solutions for addressing this issue, additional studies are required.

Keywords: Diabetes type 2, chronic complications, cortisol, dexamethasone, ACTH

Field: Medical Sciences and Health

1. INTRODUCTION

The incidence of diabetes has increased during the past few decades, practically everywhere in the world. The primary cause of mortality and disability among individuals with diabetes are chronic micro- and macrovascular complications (International Diabetes Foundation, 2016). Although hyperglycemia is the most important factor in the etiology and pathogenesis of diabetic complications, other factors also play a significant role. Those other mechanisms in the development of chronic complications are being investigated with increasing interest. Glucocorticoid secretion in Cushing's syndrome is a known pathogenetic mechanism in the development of the metabolic deterioration, such as insulin resistance, hypertension, hyperlipoproteinemia, diabetes, obesity. The question arises whether higher, but below clinical radar, cortisol values could represent the link between the metabolic deterioration and the development of chronic complications in patients with type 2 diabetes. Several studies have recently found hypercortisolemia in patients with type 2 diabetes (Steffenson, 2019). Chiodini (2007) and Reynolds (2010) found that in patients with type 2 diabetes with chronic complications, the hypothalamic pituitary adrenal axis (HPA) is disrupted, and cortisol secretion levels are associated to the presence and number of chronic complications. The mechanism behind the link between chronic complications and HPA axis activity has yet to be determined. To further research this topic, we investigated the relationship between HPA axis activity with chronic complications, clinical characteristics, metabolic and glycemic control in patients with type 2 diabetes.

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2. PATIENTS AND METHODS

Participants

The prospective observational case-control study included 107 patients with type 2 diabetes in study group and 29 healthy subjects in the control group. All subjects were hospitalized at the Tuzla University Clinical Center, Internal Medicine Clinic. The study group was divided into two subgroups according to the presence/absence of chronic complications. Group with chronic complications (group 1) consisted of 57 patients with complications. The group without chronic complications (group 2) consisted of 50 patients. The inclusion criteria were: age at the time of diagnosis > 30 years; BMI ≥ 20 and ≤ 40 kg/m². Exclusion criteria: acute complications of diabetes in the last 3 months, acute illnesses in the last 3 months; previously established functional disorders of the adrenal glands and pituitary gland. Twenty nine nondiabetic patients were selected as control subjects according to the above-mentioned selection criteria (control group). The control subjects were admitted to the hospital for evaluation as potential donors for kidney transplantation. The Ethical Committee of University Clinical Centre Tuzla approved of the study protocol. Participation in the study was contingent on individual consent.

Methods

Waist circumference, body weight, body height was measured for all patients. RIA method was used to determine the cortisol and ACTH parameters. A low-dose overnight dexamethasone suppression test was performed by taking 1 mg of dexamethasone orally at 11 pm and determining the cortisol level at 9 am. A normal response cortisol < 50 nmol/L (Chiodini, 2005). Good glycemic control was defined with values of HbA1c < 7%, fasting blood glucose 3.9–7.2 mmol/L, blood glucose 2h after a meal < 10 mmol/L. Poor glycemic control is defined as HbA1c > 7%, fasting glucose > 7.2, glucose 2h after a meal > 10 mmol/L (American Diabetes Association, 2019). Neuropathy was evaluated by measuring the diabetic neuropathy score (Feldman, 1994); retinopathy by an ophthalmological examination of the eye fundus (Wong, 2011). Incipient nephropathy is proven by a serum microalbumin level of 30–299 mg/day; nephropathy with microalbumin > 300 mg/day (Kidney Disease: Improving Global Outcomes, 2012). The criteria for defining myocardial infarction were: previously established diagnosis of myocardial infarction; previously established diagnosis of angina; ECG findings of ischemia. Ischemic heart disease is defined in those patients who meet both MI and angina criteria. Cerebrovascular insult (CVI) ischemic or hemorrhagic is defined by the previously established diagnosis by the findings of computed tomography.

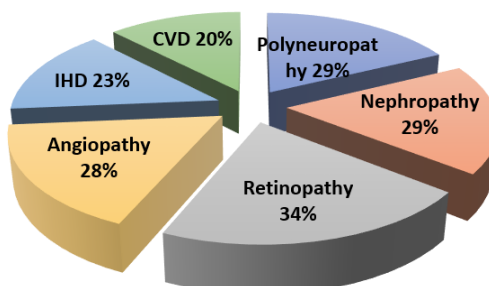
Statistical analysis

Statistical analysis was performed with the application software SPSS version 22, IBM Corp. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Descriptive statistics methods were used: measures of central tendency, measures of variability, and relative numbers. Analytical statistics: A) methods of checking general and specific assumptions for the performance of statistical procedures, B) methods for assessing the significance of the difference. For the analysis of categorical (nominal) variables, the Chi-square test of independence (2 x 2 or 2 x k) or Fisher's exact test was used in case of violated testing assumptions. The usual level of significance " $\alpha < 0.05$ " was chosen.

3. RESULTS

Evaluating the prevalence of certain diabetic complications, we found that in our sample prevalence for polyneuropathy was 29%, nephropathy 29%, retinopathy 34%, prevalence of patients with some form of ischemic heart disease was 23, peripheral angiopathy 28%, and cerebrovascular disease 20% (Graph 1)

Graph 1. Prevalence of chronic diabetic complications in the study groups



Source: Author Jusufović, S. et al. (2024), "Correlation of hypothalamic-pituitary-adrenal axis activity with chronic complications in patients with type 2 diabetes."

The clinical characteristics of the groups are shown in table 1. In the group of patients with complications treatment modality and duration of diabetes were equally distributed, while age was unequally distributed compared to patients without chronic complications. We found a higher age in the group of patients with complications (60.24 vs 46.89) (Mann-Whitney U test 069.500, Z -2.222, Wilcoxon W 2344.500, $p < 0.026$).

Table 1. Clinical characteristics of the patients among groups

		All patients (n=107)	Without complications (n=50)	With complications (n=57)	Healthy subjects (n=29)	P value
Sex	M	46 (43%)	22(44%)	24 (41%)	12(41%)	0.843
	F	61(56%)	28(56%)	33(58%)	17(59%)	
Age	Median Q1-Q3	55(49-62)	51(39-61)	56(53-62)	43(37-55)	0.026
Diabetes duration	Median Q1-Q3	22 (3-58)	22(4-58)	20 (3-61)	-	0.960
Treatment	Insulin	14	6	8	-	0.847
	OAD	28	13	15	-	
	Combined	65	31	34	-	
Diet	Diet	89	45	44	-	0.077
	No diet	18	5	13	-	

Legend: Parameters are expressed as n-absolute number, percentage value. Central value: Median Q1-Q3 – interquartile range; The Mann Whitney test and the Chi square test were used with a significance level of $p < 0.05$. Duration of diabetes expressed in months, Abbreviations: OAD- Oral antidiabetics

Source: Author Jusufović, S. at. all. (2024), "Correlation of hypothalamic-pituitary-adrenal axis activity with chronic complications in patients with type 2 diabetes."

The characteristics of metabolic comorbidities and glycemic control in the groups are shown in table 2. No statistically significant difference was found in the distribution of BMI, HLP and obesity in the entire sample. A higher prevalence of hypertension was found in the group of patients with chronic complications. Bipolar Chi-square matching test confirms this (Goodness-of fit Chi-Square =64.383, df-1) $p = 0.001$.

Table 2. The characteristics of metabolic comorbidities and glycemic control among groups

Diabetic patients					
		All patients (n=107)	Without complications (n=50)	With complications n=57	P value
HbA1c	Median Q1-Q3	7.8 (6.4-9.5)	7.5 (5.97-10)	7.9 (6.55-9.45)	0.498
Glycemic control	Good	58	34	24	0.007
	Poor	49	16	33	
BMI	Median Q1-Q3	29 (25-31)	29 (25-30)	29 (25-32)	0.272
HLP	Yes	79	38	41	0.633
	No	28	12	16	
Obesity	Yes	69	30	39	0.364
	No	38	20	18	
AH	Yes	95	42	53	0.001
	No	12	8	4	
Uncontrolled AH Controlled AH		50	22	28	0.596
		57	28	29	

Legend: Parameters are expressed as an n-absolute number. Pearson Chi-Square (Yates' Correction for Continuity) $\chi^2 = 0.291$, df-1, $p < 0.05$ was used. Abbreviations: BMI - Body mass index; HLP - hyperlipoproteinemia, AH - arterial hypertension, HbA1C - glycosylated hemoglobin.

Source: Author Jusufović, S. at. all. (2024), "Correlation of hypothalamic-pituitary-adrenal axis activity with chronic complications in patients with type 2 diabetes."

Biochemical parameters of HPA axis function from the whole diabetic and control group are summarized in Table 3.

Table 3. Comparison of HHA axis parameters between groups

		Diabetic patients (n=107)	Healthy subjects (n=29)	p value
Cortisol	Median (Q1-Q3)	387 (307-496)	307 (219-355)	0.017
ACTH	Median (Q1-Q3)	10.8 (4.6-22)	27 (23.5-42.25)	0.126
DEX cortisol	Median (Q1-Q3)	31 (22-51)	27 (24-42)	0.681
		Diabetic without complications (n=50)	Diabetic with complications (n=57)	p value
Cortisol 08h	Median Q1-Q3	320 (230-387)	454 (368-561)	0.001
ACTH	Median Q1-Q3	7.9 (3.3-16.4)	12.6 (8.7-23)	0.002
DEX cortisol	Median Q1-Q3	26 (22-36)	37.5 (23-52)	0.019
		Healthy subjects (n=29)	Diabetic without complications (50)	p value
Cortisol	Median (Q1-Q3)	312 (233-342)	320 (230-387)	0.45
ACTH	Median (Q1-Q3)	12 (6-16.7)	7.9 (3.3-16.4)	0.47
DEX cortisol	Median (Q1-Q3)	24 (19-29)	26 (22-36)	0.18
		Healthy subjects (n=29)	Diabetic with complications (n=57)	p value
Cortisol	Median (Q1-Q3)	312 (233-342)	454 (368-561)	0.001
ACTH	Median (Q1-Q3)	12 (6-16.7)	12.6 (8.7-23)	0.101
DEX cortisol	Median (Q1-Q3)	24 (19-29)	37.5 (23-52)	0.126
Legend: Parameters are expressed as Median Q1-Q3 – interquartile range. The Mann-Whitney test was used with a significance level of $p < 0.05$. Abbreviations: ACTH - adrenocorticotrophic hormone; DEX cortisol - cortisol after dexamethasone test.				

Source: Author Jusufović, S. at. all. (2024), "Correlation of hypothalamic-pituitary-adrenal axis activity with chronic complications in patients with type 2 diabetes."

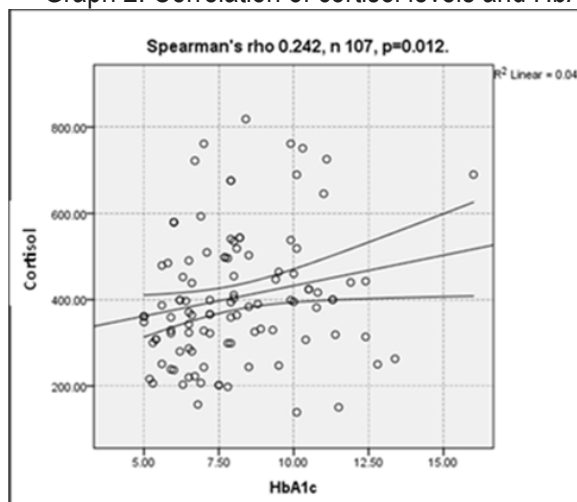
We found statistically significant higher cortisol levels in diabetic patients compared healthy subjects ($p = 0.017$), lower ACTH levels and higher DEX cortisol levels but without statistical significance. In diabetic patients with chronic complications we found statistically significant higher cortisol levels ($p = 0.001$), higher ACTH levels ($p = 0.002$) and higher DEX cortisol levels but without statistical significance. Levels of cortisol, ACTH, and DEX cortisol were comparable between the diabetic patients without complications and healthy subjects.

By comparing the HHA axis parameters of patients with complications and healthy subjects, we found a significantly higher value of cortisol in patients with complications ($p = 0.00012$). Levels of ACTH, and DEX cortisol were comparable between the two groups (HbA1c in the sample of patients with diabetes is 8.01 ± 2.16 percent. We found a higher mean rank in the group of patients with complications (55.90 vs 51.83).

Analyzing the factorial variable of the glucose control parameter, we found that 58 patients had good glucose control, and 49 patients had poor glucose control, with a statistically significant association of poor glucose control and the group with diabetic complications.

The correlation between cortisol and HbA1c measured on the same measuring scales was investigated using correlation analysis and shown in graph 1. The obtained Spearman's rho coefficient of non-parametric correlation is 0.242, $n = 107$, $p = 0.012$, explaining the significant positive relationship between these two variables, which means that more cortisol values follow higher HbA1c values (Graph 2).

Graph 2. Correlation of cortisol levels and HbA1C



Source: Author Jusufović, S. at. all. (2024), "Correlation of hypothalamic-pituitary-adrenal axis activity with chronic complications in patients with type 2 diabetes."

4. DISCUSSION

The activity of the HPA axis in patients with type 2 diabetes has been investigated as one of the factors in the pathogenesis of deterioration metabolic control in patients with type 2 diabetes (Joseph, 2015; Shengnan, 2023).

Our study aimed to examine the association of cortisol levels with the occurrence of chronic complications, with parameters of metabolic control and the degree of glycemic regulation in patients with type 2 diabetes.

We compared the parameters of HPA axis activity in patients with and without chronic diabetic complications, and healthy subjects. We further compared HPA axis parameters with glycemic control parameters and other metabolic dysfunctions, such as hyperlipoproteinemia, obesity and hypertension.

We examined the relationships between patients with type 2 diabetes and traditional risk factors for the emergence of chronic complications, including age, length of diabetes, type of treatment, and glycemic control.

We found a significantly higher age in patients with complications. According to the results of the study by Shamshingaram (2017) elderly patients with diabetes had a higher percentage of complications. In the study by Fei (2019) found older age as an independent risk factor for diabetic peripheral neuropathy.

We found a longer mean duration of the diabetes in the group of patients without complications, but the obtained result is not statistically significant. By analyzing treatment modalities, we did not find a significant association of different treatment modalities and BMI with chronic complications. Our result is in agreement with the previous study and with the meta-analysis results of Zhou et al. (27) who found no association of diabetic complications with BMI. In our study, the prevalence of hypertension was 88%. According to our results, hypertension and hyperlipidemia were more common in patients with complications, which is in agreement with the results of the UKPDS 50 study (28). It is important to note that in 53% of patients in our study, hypertension was uncorrected by therapy, which is in agreement with the study by Arambewela (2018). When we evaluated the prevalence of complications, our results were consistent with the results of studies on the prevalence of chronic complications (De Boehr, 2007).

By comparing the parameters of the HHA axis in patients with diabetes and healthy subjects, we found higher values of cortisol and DEX cortisol in patients with diabetes compared to healthy subjects, with no significant difference. Our results are in agreement with the study of Chiodini (2007) where the values of cortisol, DEX cortisol and ACTH were found in the normal range in the group of subjects with diabetes and in agreement with studies done on healthy subjects. By comparing the parameters of the HHA axis in the group of patients with chronic complications compared to healthy subjects and patients without complications we found significantly elevated cortisol values of patients with complications. Another significant result of our study is that we did not find significant differences in the values of the HHA axis parameters in the group of subjects without complications and healthy subjects. Our results are consistent with results of Roy (1998) who demonstrated elevated cortisol levels in patients with diabetic retinopathy and cardiovascular complications.

In our study, poor glycemic control is associated with higher prevalence of chronic complications, which is consistent with previous study results (Sharen, 2021). By correlating glycemic control and HHA axis parameters, we obtained a significant positive relationship between higher cortisol values and higher HbA1C values. This finding is consistent with previous studies (Chiodini, 2007; Joseph, 2015; Doing, 20212). In conclusion higher cortisol levels are associated with chronic diabetic complications. Additional studies are necessary to clear the pathophysiology of the dysfunction. If future studies establish a causal relationship between the HPA axis and diabetic complications, strategies to reduce cortisol could be developed for the prevention of complications.

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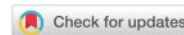
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THE CRITICAL ROLE OF DETECTION IN EFFECTIVE MELANOMA TREATMENT

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Abstract: The global incidence of skin cancer is continuously rising, particularly among the white population. Uncontrolled UV radiation exposure, combined with genetic factors, leads to various health risks, including wrinkles, pigment changes, and malignancies. This paper aims to highlight the increasing trend of skin melanoma and emphasize the necessity for ongoing education and preventive measures to detect potential changes early. Early diagnosis and disease assessment are crucial for successful treatment. High mortality rates are associated with late detection of malignant melanoma, making the development of new, more efficient detection methods essential. Additionally, efforts must be made to develop minimally invasive, safe, and effective therapies with fewer side effects. Lack of timely information for the population and the absence of continuous, targeted education for health personnel are significant factors contributing to the advanced-stage recognition and diagnosis of these diseases.

Keywords: skin cancer, melanoma, UV radiation, metastases, early diagnosis.

Field: Medical Sciences and Health

1. INTRODUCTION

Melanoma arises from malignant changes in melanocytes, primarily on the skin but also on mucous membranes in regions such as the head and neck, eyes, urogenital tract, and gastrointestinal tract (Grozdić Milojević et al., 2023). The development of melanoma skin cancer is predominantly attributed to exposure to ultraviolet (UV) radiation. Preventive measures include minimizing sun and tanning device exposure, using sunscreen, and wearing protective clothing like hats. The pattern and timing of UV exposure significantly influence melanoma development; frequent sunburns, especially in childhood, correlate with melanomas on the chest, back, and legs, areas intermittently exposed to UV radiation. Conversely, melanomas on the face, neck, and hands, which receive more consistent sun exposure, exhibit different characteristics (American Cancer Society, 2023).

Regularly monitoring moles for changes in size and texture enhances early detection of suspicious developments. Lighter skin tones pose the greatest risk for melanoma, with white individuals facing a lifetime risk of approximately 3% (1 in 33), compared to 0.1% (1 in 1,000) for black individuals and 0.5% (1 in 200) for Hispanics (American Cancer Society, 2024). Additional risk factors identified by Antonijević et al. (2018) include the presence of common and atypical nevi, skin type, family history of melanoma (found in 8-12% of patients), actinic damage, age over 65, history of sunburns and sporadic sun exposure, particularly during childhood, and geographic location.

In Germany and France, the two most populous countries in the European Union, 31.4 thousand and 16.4 thousand cases of melanoma skin cancer were reported in 2022, respectively. Italy followed with 12.5 thousand cases of this cancer type (Gagliardi, 2024). In England, there were over 8 thousand newly diagnosed melanomas in men and 7.7 thousand in women in 2021 (Gagliardi, 2023). According to the American Cancer Society, it is projected that in 2024 there will be 100,640 new cases of skin melanoma out of a total of 108,270 skin cancer cases, resulting in 8,290 deaths from melanoma (American Cancer Society, 2024).

Residents of Australia and New Zealand face the highest risk of skin cancer. In 2020, Australia recorded 37 cases per 100,000 inhabitants, while New Zealand had 32 cases per 100,000. Denmark followed closely with just under 30 cases per 100,000 inhabitants. New Zealand reported the highest mortality rate at 4.7 deaths per 100,000 inhabitants, followed by Norway (3.2) and Montenegro (3.0) (Fleck, 2024). Malignant melanoma is a deadly form of skin cancer, accounting for over 20,000 deaths in Europe annually, with nearly 100,000 new cases registered each year. Recent studies emphasize that early detection is the most crucial factor for improving survival rates in this disease.

(Fleck, 2024) In routine clinical practice, visual examinations are predominantly relied upon, but

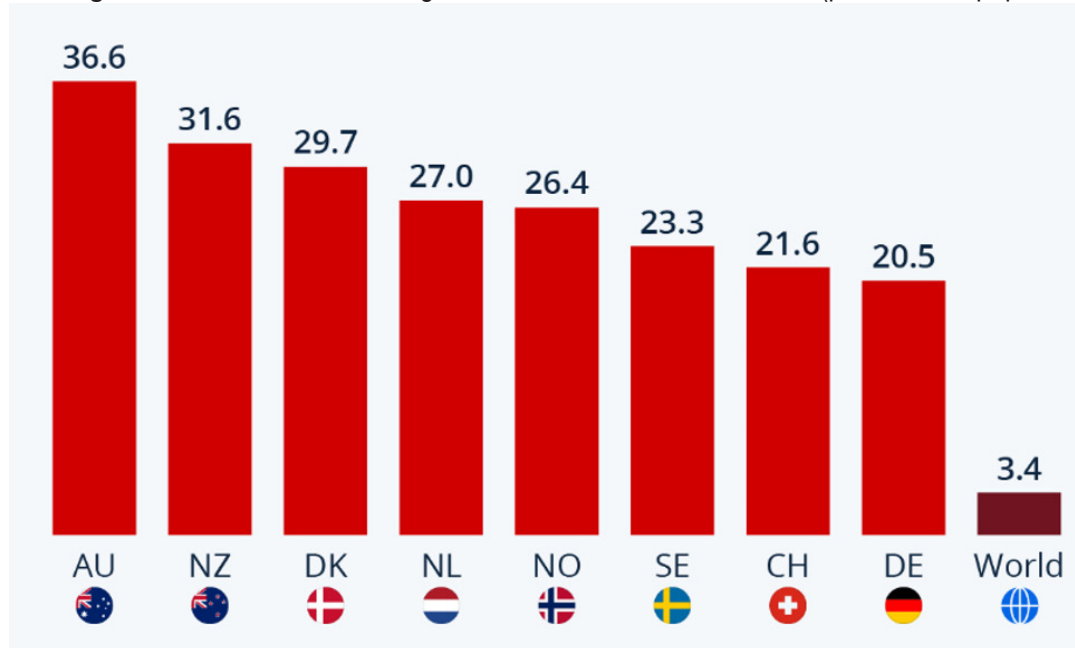
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their sensitivity in recognizing melanoma via dermoscopy is often less than 80%. Therefore, Abayomi-Alli et al. (2021) advocate for the enhancement of computer-assisted methods to improve the diagnosis of skin melanoma, potentially leading to higher survival rates.

UV radiation is epidemiologically and molecularly linked to the three most common types of skin cancer: basal cell carcinoma, squamous cell carcinoma, and malignant melanoma. Genetic factors also significantly influence the risk of UV radiation-induced skin diseases, with particular emphasis on polymorphisms of the melanocortin 1 receptor (MC1R) gene. These variants are associated with fair skin, increased UV sensitivity, and elevated cancer risk (D'Orazio et al., 2013).

Figure 1. Countries with the highest rates of skin cancer in 2020 (per 100.000 population)



Source: Fleck, 2024

2. LEADING RISK FACTORS

Approximately 80% of skin aging is attributed to sun exposure. Individuals using sunscreen with SPF 15 or higher demonstrate 24% less skin aging compared to those who do not use sunscreen. Sun damage accumulates over time: Table 1 illustrates the average cumulative sun exposure over a lifetime of 78 years.

Table 1. Average lifetime sun exposure

Age□	Accumulated sun exposure□	□
1-18□	23%□	□
19-40□	47%□	□
41-59□	74%□	□
60-78□	100%□	□

Source: Skin Cancer Foundation, 2024.

The depletion of the ozone layer has led to an increase in skin cancer cases. According to estimates from the World Health Organization, every 10% reduction in the ozone layer results in three million additional cases of non-melanoma skin cancer and 4,500 cases of melanoma skin cancer. The ozone layer acts as a barrier in the stratosphere, absorbing harmful ultraviolet radiation and thereby providing protection against skin cancer. These radiations can induce severe mutations and genetic alterations in skin cells, leading to uncontrolled cell growth (Vishwakarma et al., 2024).

Medenica (2008) emphasizes that skin cancer is potentially the most serious consequence of

excessive sun exposure, serving as a lasting reminder of past sun exposure behaviors. Therefore, it is crucial to adopt preventive measures from a young age to safeguard against sun exposure.

The World Health Organization has classified tanning beds as a Class 1 carcinogen. Countries like Brazil and Australia have banned the use of tanning beds since 2014. In Serbia and most European nations, tanning beds are prohibited for individuals under 18 years old, while older individuals are permitted use only with signed informed consent (Ministry of Health of the Republic of Serbia, 2019).

Table 2. Recommendations for protection against ultraviolet radiation and skin self-examination in adults

1.□	Avoid unnecessary sun exposure from 10 a.m. to 5 p.m. during the summer, from June to October, including cloudy days. Be especially cautious near water, sand, and snow, as these surfaces reflect UV rays, increasing their harmful effects.□	□
2.□	It is recommended to check the UV index via media or web applications before spending time outdoors during sunny periods of the year.□	□
3.□	Wear protective clothing, a hat, and UV-blocking sunglasses.□	□
4.□	Apply sunscreen with a high protection factor (SPF 50+) that protects against both UVA and UVB rays. Use it 30 minutes before sun exposure and reapply every two hours while outdoors.□	□
5.□	Skin self-examination is necessary once a month.□	□
6.□	Examination of the skin of partners and family members once a month.□	□
7.□	Completely avoid using tanning beds.□	□
8.□	Visit a dermatologist annually if you have a medium or high risk of skin cancer.□	□
9.□	People advised to strictly avoid sun exposure should supplement vitamin D through diet and supplements.□	□

Source: Ministry of Health of the Republic of Serbia, 2019.

Various risk factors contribute to the development of all types of skin cancer, although their interactions are not fully understood. Key endogenous factors include phototype, skin and eye color, the presence of melanocytic nevi (moles), dysplastic nevi, and personal or family history of skin cancer. Exogenous factors relevant to skin cancer development include the type and extent of cumulative sun exposure, history of sunburns, and adherence to protective measures. While malignant melanoma constitutes only 4% of skin cancer cases, it is responsible for 65% of all skin cancer-related deaths. (Gordon, 2013)

3. NEW MODELS IN DIAGNOSIS AND TREATMENT

The pathological diagnosis of cutaneous melanoma, recognized as one of the most metastatic cancers in humans, has traditionally relied on pathohistological characteristics and a straightforward set of immunohistochemical markers over the past few decades. However, Tímár and Ladányi (2022) note a shift in approach, with widespread dermatological melanoma screening programs now detecting premalignant lesions more frequently. This necessitates highly sensitive molecular tests to confirm malignancy.

For patients with advanced melanoma, Grozdić Milojević et al. (2023) stress the importance of utilizing multi-detector computed tomography or magnetic resonance imaging. They further highlight that numerous international studies and guidelines advocate for the utility of positron emission tomography combined with computed tomography using fluorodeoxyglucose in these cases. (18F-FDG PET/CT).

Numerous studies examining somatic mutations in melanoma at the single-gene level have provided valuable insights into critical pathways controlling the initiation and progression of the disease. Advances in next-generation sequencing have further enhanced mutational screening across multi-gene panels, exomes, and genomes. Zhang et al. (2016) argue for a reassessment of the melanoma mutational landscape to identify key genes and cellular pathways driving this cancer.

In their research on skin melanoma, Hosny et al. (2020) propose an automated classification method for color skin images. This method employs deep convolutional neural networks (DCNNs) and involves three primary steps: preprocessing of input color skin images by segmenting the region of interest (ROI), followed by image augmentation through rotation transformations and translations of the segmented image. The final step utilizes a DCNN architecture, particularly a modified GoogleNet, achieving a classification accuracy of 99.29%. The researchers highlight significant improvements in the classification process with their approach.

Melanoma primarily affects adults, with over half of cases originating in seemingly normal skin areas. While melanoma can develop anywhere, it typically occurs on the trunk or head and neck in men,

and on the extremities in women. Early signs of malignant transformation in a nevus include darker or variable discoloration, itching, size increase, development of satellites, and ulceration or bleeding (late signs).

Figure 2. Melanomas with characteristic asymmetry, border irregularity, color variation, and large diameter



Source: National Cancer Institute, 2024.

To comprehensively understand the impact of diseases on populations, it is essential to utilize metric data beyond just incidence and mortality rates. One such approach involves assessing Disability-Adjusted Life Years (DALYs), where each DALY represents one year of healthy life lost. Previous studies have employed DALYs to examine the burden of melanoma globally and within specific countries, alongside traditional metrics like incidence, mortality, and prevention efforts.

DALYs are integral to initiatives such as the Global Burden of Disease (GBD) study, which evaluates multiple diseases including melanoma. The GBD study utilizes a systems science approach to quantifying the comparative health loss due to diseases, injuries, and risk factors across different age groups, genders, and geographic regions over time. (Karimkhani et al., 2017)

Several treatment options exist for skin melanoma, including surgical excision, chemotherapy, immunotherapy, and radiotherapy. Surgical excision is widely accepted as the primary treatment for cutaneous melanoma, despite drawbacks such as tissue defects, scarring, prolonged healing, and infection risks. Chemotherapy, though commonly used, is associated with severe side effects and the development of drug resistance over prolonged use, often employed in palliative care. Immunotherapy, a newer therapeutic approach, has shown effectiveness but is limited by high costs, treatment complexity, and the long-term survival of reprogrammed cells.

Radiotherapy's clinical utility is restricted by internal and environmental resistance, typically reserved for specific indications like bone or central nervous system metastases. Phototherapy, a form of radiotherapy that converts light into heat, plays an important role by raising local temperatures to remove tumor cells. (Song et al., 2021; Grozdić Milojević et al., 2023)

Đokanović et al. (2023) conducted a retrospective observational study at the Oncology Clinic of the University Clinical Center of the Republic of Srpska, Bosnia and Herzegovina, spanning from January 2015 to December 2020. The study aimed to assess the efficacy of various treatment approaches for metastatic melanoma, given limited access to newer medications. The primary outcomes evaluated were overall survival and progression-free survival among patients receiving first- or second-line systemic therapy for radiologically or pathohistologically confirmed metastatic melanoma. The study found a statistically significant difference in survival outcomes between the first and second lines in the pembrolizumab group. Specifically, the results indicated lower median overall survival and progression-free survival rates compared to those reported in clinical trials.

In a study examining melanoma mortality trends by gender and age in the Republic of Serbia from 2000 to 2021, Babić et al. (2024) observed a rising mortality trend from skin cancer melanoma, with rates of 2.24 per 100,000 inhabitants for men and 1.34 per 100,000 for women over the period. Mortality rates increased with age in both sexes, with the highest number of deaths occurring in individuals over 80 years old.

The potential applications of artificial intelligence in melanoma recognition, diagnosis, and treatment

are still under-researched but hold significant promise. AI offers advantages such as unbiased decision-making, devoid of fatigue and subjectivity, with vast capabilities for data comparison, memory retention, and reasoning. However, the reliability of AI-driven conclusions depends heavily on the quality and validity of the input data used to develop relevant algorithms. (Kostić et al., 2019)

4. CONCLUSION

Melanoma is becoming an increasing public health issue due to rising incidence and mortality rates, as well as the inadequate response from public health policymakers to these challenges. Particularly concerning is the fact that a small number of melanomas are detected in their early stages, when the disease is most treatable. The paper highlights global regions with the highest incidence and mortality rates of melanoma, indicating significant regional differences in disease burden. Melanoma is among the top 10 most common malignancies in most European countries.

Despite notable progress in prevention, diagnosis, and treatment, broader and more intensive preventive dermatological screening activities are recommended. Focused efforts in public education and raising awareness about the importance of reducing UV exposure, early detection and diagnosis, as well as genetic testing, can contribute to lowering incidence and mortality rates. The use of artificial intelligence in melanoma diagnosis will certainly play a role in the near future, helping to minimize potential errors in measuring clinical parameters.

The focus of researchers and practitioners must be on developing new therapeutic approaches where synergistic effects meet expectations for low doses and minimal side effects.

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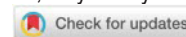
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INFLUENCE OF STRESS COPING BEHAVIOR ON THE EMOTIONAL LOAD OF TEACHERS

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Abstract: In connection with the intensification of professional activity and the acceleration of the pace of life of a modern person, the problem of the relationship between behavior to overcome stress and emotional load and the development of individual coping resources is becoming more and more relevant. There is a rather limited number of scientific works dedicated to the study of the problem of overcoming the emotional burden of teachers working with children, as well as the maintenance and development of individual coping resources. Teachers from the regional state educational institution (30 people) took part in the study. Observation, interview, and standardized testing techniques were used to diagnose teacher workload and behavioral strategies for coping with stress. Mathematical and statistical analysis methods were used to process the results.

Teachers who prefer non-constructive overcoming of professional difficulties, inadequately limit the scope and intensity of inclusion of emotions in professional communication (called „Inadequate emotional selective reaction“, which has an average value of $\bar{X}_{av}=18.6$). They seek to ease or reduce professional responsibilities requiring emotional costs. To a greater extent, those teachers who use constructive coping are aware of the psychotraumatic factors of professional activity and experience emotional emptiness and fatigue. Positive correlations were found between non-constructive coping („aggressive actions“) and all phases of emotional burnout („tension“; „resistance“; „exhaustion“). Aggression directed at others as a counterproductive coping strategy has been empirically shown to contribute to job frustration and job dissatisfaction and loss of professional interest. In other words, the professional stress experienced by teachers exceeds their coping resources, and the defensive-adaptive mechanism of behavior to overcome stress takes place at the level of psychological protection.

Keywords: state of stress; emotional overload of teachers working with children; strategies for coping with stress;

Field: Medical sciences

1. INTRODUCTION

In connection with the intensification of professional activity and the acceleration of the pace of life of a modern person, the problem of learning strategies to overcome various professional stresses, including emotional burnout, is becoming more and more relevant. To date, there is no generally accepted definition for it in the literature. In the psychological literature, emotional burnout is considered as a state of physical, emotional and mental exhaustion of a person caused by the relationship between a professional and his client (S. Hobfoll, 1994), and as a result of unconstructive overcoming of professional stress (Kokun O., Shamykh O., 2016). Also as a process of gradual loss of emotional, cognitive and physical resources as a result of the realization of all three stages of stress: tension, resistance and exhaustion (Boyko V.V., 1999). Professional burnout manifests itself mainly in the form of emotional fatigue and exhaustion of cognitive and physical resources, such as low self-esteem of professional competence in some professions (Bettini E.A., Cheyney K., Wang J., Leko C. Job Design, 2015) and is explained by their specific conditions and content (intensity, duration and complexity of interpersonal communication, various age groups of clients, severity of their problems, etc.). According to the resource „conservation“ model, S.E. Hobfoll and J. Freedy (1993) arises as a result of a process of constant loss of resources with the impossibility of their timely recovery (Bettini E.A., Cheyney K., Wang J., Leko C. Job Design, 2015). Some researchers believe that the stages of its development are determined by the destruction of the „resource base of resistance“, consisting of psychological resources for professional and personal development, stability and overcoming professional difficulties.

Recently, foreign studies have noted an increased interest in the emotional burnout of teachers working with children (Hobfoll S. E., Lerman M., 1989). Among the factors for its emergence N.C. Brunsting, M.A. Sreckovic, K.L. Lane, (2014) include teaching experience, student disability, role conflict, role ambiguity, lack of administrative support (Hobfoll S. E., Lerman M., 1989). The pathology of teachers with professional burnout often manifests itself as physical and verbal aggression, irritation, or they are more susceptible to them (Bettini E.A., Cheyney K., Wang J., Leko C. Job Design, 2015). They are characterized by rigidity of thinking and behavior, fewer contacts and at the same time greater dependence

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on others, difficulties in maintaining partnerships and insufficient clarity of life and professional directions (Maslach C., 1982). All this raises the issue of maintaining and developing personal coping resources and stress-resolving behaviors of burnout-prone teachers working with children.

Stress coping behavior is considered in various models (Vodopyanova N. E., 2009). In the opinion of H.E. Vodopyanova, E.S. Starchenkova (2001) presents the overcoming of stress as constructive, through the use of such productive coping strategies as: assertive actions, entering into social contact, as well as seeking social support. They define "non-constructive coping", which includes the implementation of such coping strategies as: caution, impulsivity, manipulateness (indirect methods), asociality, aggressive actions and avoidance (S. Hobfall, 1994). The "protective-adaptive" mechanism that underlies behavior to overcome stress is a model proposed by M.V. Bogdanova (2013). It is carried out in stages on four levels. At the first level, personal resources provide a basis for adaptation and resilience to minor life difficulties. At the same time, this level is already characterized by psychosomatic disorders and disorders in the form of emotional burnout. The second level - psychological protection is an increase in constructiveness, primary and secondary protection. The third level - coping, is provided by non-constructive, mixed and constructive coping. The fourth level - self-change is provided by resources of resilience, self-regulation and personal growth (Bogdanova M.V., 2013).

In the current research, we define as an object of research - the emotional burnout of teachers working with children, and a subject of research - the influence of behavior to overcome stress on its occurrence.

2. MATERIALS AND METHODS

The study was conducted regionally on the basis of state educational institutions with teachers working with children in kindergartens and primary schools. In each group or class in the Bulgarian institutions, there are from one to three children with special educational needs. This complicates the work of the teacher in fulfilling his professional duties. 30 female teachers with an average age of 35.5 years, with professional experience from 5 to 15 years, took part in the study. The package of psychodiagnostic methods included the following questionnaires: "Emotional burnout" (Boyko V.V., 1999), "Strategic approach to coping scale (SACS)" by S. Hobfoll (1994)", both adapted to Bulgarian. Mathematical and statistical methods were used: descriptive statistics, comparative (U-Mann-Whitney test), correlation (r-Spearman) and regression analysis. All teachers were informed about the objectives of the study, confidentiality rules and gave voluntary consent to participate.

3. RESULTS AND ANALYSIS

The study of emotional burnout of teachers working with children was carried out using the questionnaire "Emotional burnout (BURN-OUT)" by V. V. Boyko, adapted in Bulgarian and shows the following results (table 1). The methodology allows separating the next 3 phases in the development of stress: "tension", "resistance", "exhaustion". The comparison of the points obtained for the individual phases is not valid. It does not testify to their relative role or contribution to the syndrome, since the phenomena measured in them are significantly different: reaction to internal and external factors, methods of psychological protection, state of the nervous system. Quantitative indicators can only judge how much each phase has formed, which phase has formed to a greater or lesser extent.

The obtained results show the emerging symptoms of emotional burnout of teachers, as well as its degree of formation: indicator on the scale "Final indicator of burnout": Hsv.=180.9 phases as "Tension": Xsv.=42.5; "Resistance" Xmean=72.3 and "Exhaustion": Xmean=66.1 (Table 1).

From the conversations with the respondents, it was found that they are characterized by a growing awareness of the influence of psychotraumatic factors in professional activity and an emotional lack of participation in communication with family and friends. An increase in the desire to relieve or reduce the volume of official duties associated with emotional costs, the inability to provide emotional support to children, as well as psychosomatic and psychovegetative problems.

Table 1 Mean values of the indicators of the phases of emotional burnout of teachers

Name of index	Average value obtained x	Formative stage		
		I. The phase is not formed	II. The phase is in the formative stage	III. The phase is formed
1. Voltage	42,5	to 36 points and less	from 37 to 60 points	61 points and above
2. Resistance	72,3	to 36 points and less	from 37 to 60 points	61 points and above
3. Exhaustion	66,1	to 36 points and less	from 37 to 60 points	61 points and above
Σ Final burnout index	180,9			

Source: Author

Table 2. Average values of indicators of phases of emotional burnout of teachers and number of respondents distributed by phases of BURN-OUT formation

№	Indicator	Xcp.	Number of respondents		
			I phase	II phase	III phase
1.	Tension	42,5			
1.1.	<i>Experiencing psycho-traumatic circumstances</i>	11,4	-	15	-
1.2.	<i>Dissatisfaction with yourself</i>	7,5	18	-	-
1.3.	<i>Depression</i>	7,8	22	-	-
1.4.	<i>Anxiety and depression</i>	15,8	-	21	-
2.	Resistance	72,3			
2.1.	<i>Anxiety and depression</i>	22,9	-	13	-
2.2.	<i>Emotional and moral disorientation</i>	21,5	-	-	22
2.3.	<i>Expanding the realm of economizing emotions</i>	12,3	-	10	-
2.4.	<i>Reduction of professional duties</i>	15,6	-	24	-
3.	Exhaustion	66,1			
3.1.	<i>Emotional deficit</i>	9,8	-	23	-
3.2.	<i>Emotional detachment</i>	16,5	-	9	-
3.3.	<i>Personal alienation (depersonalization)</i>	24,1	-	-	25
3.4.	<i>Psychosomatic and <u>psychovegetative</u> disorders</i>	15,7	-	10	-

Source: Author

Table 2 shows that 80% of the respondents are in the beginning phase of the development of BURN-OUT syndrome, of which 73% have "Emotional and moral disorientation", and 83% have "Emotional deficit" - "Personal alienation".

A diagnosis of teachers' stress coping behavior was carried out using the questionnaire "Strategies for overcoming stressful situations" ("Strategic Approach to Coping Scale (SACS)" S. Hobfoll (1994) consisting of 54, (adapted to Bulgarian 2019).It determines the values of the following scales: "Assertive actions", "Introduction to social contact", "Seeking social support", "Attention", "Impulsive actions", "Avoidance", "Unacceptable actions", "Antisocial Manifestations' and 'Aggressive Actions' Maximum number of points for each scale is 30.

Table 3. Average values of indicators of diagnostic indicators stress coping behaviors of teachers working with children up to 10 years of age

№	Indicator	Average values, number of points Hsv.
1.	Assertive actions	21,5
2.	Entering into social contact	23,4
3.	Seeking social support	23,9
4.	Caution	22,8
5.	Impulsive actions	18,6
6.	Avoidance	17,9
7.	Unacceptable actions	17,3
8.	Antisocial events	18,2
9.	Aggressive actions	19,7

Source: Author

From Table 3, it can be seen that the average number of points on all indicators is elevated, especially "entering into social contact", "seeking social support" and "attention". All respondents are active and consistent in protecting their interests, respect the interests of the surrounding people and are ready to receive support from them. They are prone to impulsive actions, to unacceptable actions, they are aggressive and prone to antisocial behavior. They still have a desire to avoid risky and conflict situations. Thus, teachers inadequately limit the scope and intensity of including emotions in professional communication, seek to facilitate or reduce professional emotional responsibilities.

The value of "Impulsive actions" is high - an average value of 18.6 points. This indicator is also called "Inadequate emotional electoral response" in the literature.

Among the emerging symptoms among teachers is "Reduction of professional duties" phases "Tension", "Anxiety and depression" "Emotional deficit". From the phase "Resistance" is developed "Assertive behavior". Thus, teachers demonstrate resistance to the impact of psychologically traumatic circumstances of professional activity: they tend to fulfill the assumed responsibility, they are dependent on the mood and subjective preferences. There is a manifestation of inadequate emotional reactions in interpersonal relations in the form of "saving" with emotions and limiting emotional reciprocity.

The results obtained are consistent with the results of previously conducted studies. quality and foreign research (Brunsting, N.C., Sreckovic, M.A., Lane K.L., 2014). Thus, the present study demonstrated the relationship between teachers' emotional burnout and unproductive creative coping strategies in overcoming occupational stress. A.A. Kiseleva et al (2019) revealed the existence of positive correlations between relationships between "emotional exhaustion" and such unproductive coping strategies as "confrontation", "distancing" and "depersonalization", among experienced teachers with professional activity of up to five years (Bettini E.A., Cheyney K., Wang J., Leko C. Job Design, 2015). In such a case, their level of emotional burnout is diagnosed as remarkably low. However, in contrast to the results we obtained, teachers whose professional experience is more than five years demonstrate a high value of coping strategies - "Self-control" and "Planning when solving problems". A new study of the relationship between coping strategies and emotional burnout in French teachers working with children in different environmental settings (regular class in regular school, specialized class in regular school and specialized institution) testifies to repeated results (Brunsting, N.C., Sreckovic, M.A., Lane K.L., 2014).

Thus, teachers in a specialized institution have "emotional exhaustion" and "depersonalization". Here - unlike teachers of a specialized school, teachers of a profiled class of a regular school, positive correlations of emotional exhaustion were established. According to the author's research of E. Boujut, A. Dean, A. Grouselle, E. Cappe, obtained results show that teachers of specialized schools and classes have adaptive potential due to the presence of special training (Brunsting, N.C., Sreckovic, M.A., Lane K.L., 2014).

4. CONCLUSION

It has been empirically proven that teachers working with children have productive strategies, but at the same time demonstrate a high level of emotional burnout from an early age. The occurrence of a syndrome of BURN-OUT is based on unintended actions. Apparently, available coping resources do not allow them to overcome emotional burnout, which indicates the implementation of the second

level of defensive-adaptive behavior mechanism to overcome stress. It is characterized by an increase in constructiveness and psychological protection from professional difficulties and self-change. At the same time, confrontation and overcoming emotional burnout in a professional environment is possible. Dissatisfaction with professional self-esteem can contribute to expanding abilities to cope with stress behavior, updating resources for personal growth, i.e. moving to coping with self-change.

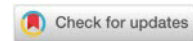
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FUNCTIONAL RECOVERY IN PATIENTS WITH ULNAR NERVE INJURY

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Abstract: Painful sensations that occur after peripheral nerve injury are a major problem for patients. They occur most often in the acute phase of muscle denervation (denervation pain) or in the early phase of the regeneration process (regenerative pain). The pathophysiology of these painful conditions is complex and results in difficult differentiation of different types of painful conditions that are of crucial importance for the selection of an appropriate therapeutic approach. The place, the degree of the injury, the age of the patient, as well as the delay in starting the treatment significantly affect the outcome of the rehabilitation of injuries of the ulnar nerve. Ulnar nerve rehabilitation in elderly patients, high-level injuries, and delayed cases may result in a poor prognosis. For high-level lesions and lesions that are close to the elbow, the nerve transposition treatment is used. Immobilization in wrist flexion and/or elbow extension with carpal tunnel and release of Guyon's canal are necessary for lesions closer to the wrist. Cubital tunnel syndrome is the second most common compression syndrome of the upper extremities, after carpal tunnel syndrome. The type and severity of nerve injury determines the extent of pathological changes, the capacity for regeneration and the prognosis for recovery. The aim of the study is to shorten the duration of the rehabilitation process and increase the functionality of the affected limb by timely recognizing the symptoms and starting the rehabilitation treatment of the patients, so that the patient would return completely to the activities of everyday life. Material and methods: The study included 10 subjects (5 male subjects and 5 female subjects) in whom the ulnar nerve was diagnosed during the examination. They are treated at the Public Health Institution University Clinic for physical medicine and rehabilitation in Skopje, for a period of 20 working days. The effect of the conducted physical and kinesiotherapy procedures is evaluated. The following were used during the treatment: paraffin therapy, electrical stimulation, Transcutaneous Electrical Nerve Stimulation, galvanic current, diadynamic currents, kinesiotherapeutic exercises (pastoral and actively assisted). Due to the number of studies, it is challenging to make a definitive recommendation before conducting research with a larger number of respondents.

Keywords: ulnar nerve paresis, cubital syndrome

Field: Public Health and Medicine

1. INTRODUCTION

There are several mechanisms of injury to the ulnar nerve: traumatic (fracture, cut) and mechanical, which occurs when n. ulnaris suffers prolonged pressure, usually in the back of the elbow area where it is placed most superficially under the skin. N. ulnaris emerges from the medial bundle of the plexus brachialis (C8 and Th1) and in the upper part of the upper arm lies medial to a. brachialis. Then it goes to the sulcus nervus ulnaris on the outside of the epicondyle of the humerus, and from there it goes to the forearm in the sulcus antebrachii medialis. On the forearm it goes together with the ulnar artery, and with final branches it divides on the medial part of the palm. N. ulnaris is a mixed nerve. Motor innervates m. flexor carpi ulnaris, hypothenar muscles, part of the thenar muscles not innervated by n. medianus, all interosseous muscles and the two medial lumbrical muscles. It sensory innervates the skin of the hypothenar and partially the skin of the fingers.

2. MATERIAL AND METHODS

The study included 10 subjects (5 male subjects and 5 female subjects) who were diagnosed with a rupture of the ulnar nerve during the examination. They are treated at the Public Health Institution University Clinic for physical medicine and rehabilitation in Skopje, for a period of 20 working days.

- Method of kinesiotherapy:

During the treatment, physical procedures (heat procedures and electrical procedures) and kinesiotherapeutic exercises were used in order to reduce pain, improve trophism and allow a faster return of the complete function of the affected limb. During the dosing of all the above-mentioned procedures, attention was paid to the patient's condition in terms of fatigue and load. The following methods were used during the treatment: paraffin therapy, electrical stimulation, TENS, galvanic current, diadynamic currents, kinesiotherapeutic exercises (pastoral and actively assisted).

- Examination methods:

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In the course of the research, functional diagnostic methods were applied, summarizing the results obtained at the beginning of the treatment, on the tenth day and on the twentieth day of the treatment. The results and condition of the muscles (m. flexor carpi ulnaris and m. opponens digiti minimi) are registered and evaluated with the MMT and the mobility of the wrist with a goniometer.

Tab.1. Tabular presentation of subjects with injury of n. ulnaris

Group of respondents	Age	Duration of the problem
10 patients (5 men and 5 women)	36,5 ± 9,4	From 2 months to 6 months

Source: Authors' own research Vasileva, D. and Andonovska, T.

- Statistical methods:

For the purposes of the research, a program for qualitative data processing was used. They are processed with variation (Student-Fisher t-test) and alternative analysis, which summarize the changes during the therapy.

3. RESULTS

After finishing the treatment and summarizing the obtained results, a comparison was made of the achieved changes after two ie. four weeks. The obtained data are shown in tab.2, tab.3, figure 1. and figure 2. through which a significant improvement in the condition of the majority of patients was observed.

Tab.2. Tabular data display of changes in m.flexor carpi ulnaris and m. opponens digiti minimi

Musculus	Day 1, X ±SD	Day 10, X ±SD	Day 20, X ±SD
m. flexor carpi ulnaris	1.4 ± 0.62 **	2.27 ± 0.77 **	3.84 ± 0.93 **
m. opponens digiti minimi	0.63 ± 0.54 **	1.83 ± 0.67 **	2.82 ± 0.73 **

** p<0,05 – significant changes in movements in relation to the beginning and end of the treatments

Source: Authors' own research Vasileva, D. and Andonovska, T.

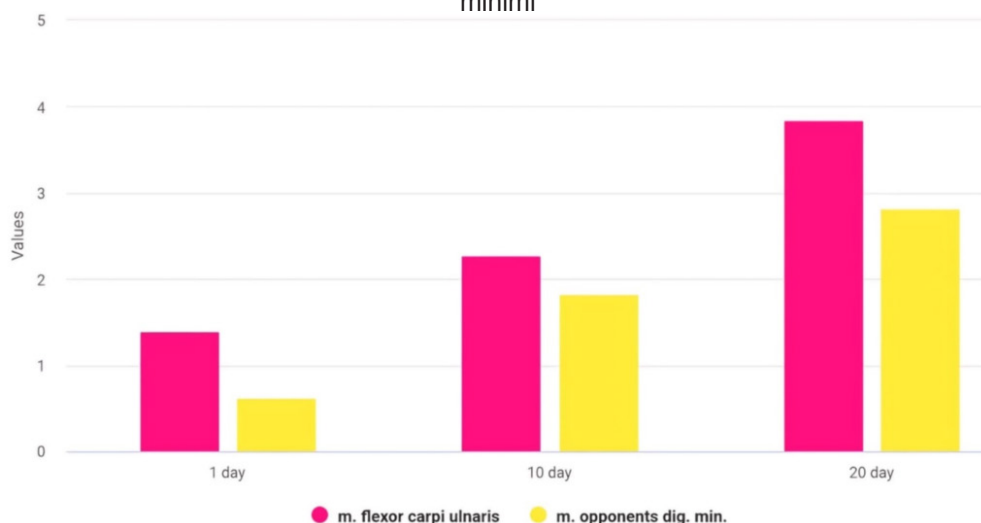
Tab.3. Tabular data display of changes in movements of the wrist

ROM	Day 1, X ±SD	Day 20, X ±SD
Dorsiflexion	42 ± 12.48 **	59 ± 10.44 **
Palmar flexion	48 ± 10.53 **	65.5 ± 12.93 **
Radial deviation	10 ± 3.87 **	17.5 ± 4.6 **
Ulnar deviation	1.5 ± 5.5 **	13.5 ± 6.72 **

** p<0,05 – significant changes in movements in relation to the beginning and end of the treatments

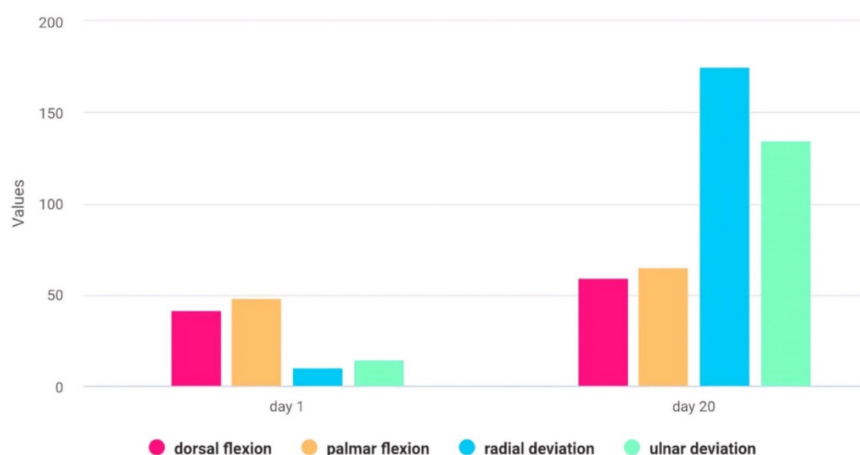
Source: Authors' own research Vasileva, D. and Andonovska, T.

Figure 1. Results obtained by manual muscle test of m. flexor carpi ulnaris and m.opponens digiti minimi



Source: Authors' own research Vasileva, D. and Andonovska, T.

Figure2. Changes obtained by measuring movements of the wrist



Source: Authors' own research Vasileva, D. and Andonovska, T.

4. DISCUSSION AND CONCLUSION

Ulnar nerve impingement is a common occurrence in forearm bone injuries. Patients face difficulties in performing daily life activities and are dysfunctional in society. With timely recognition of the symptoms and starting the rehabilitation treatment of the patients, the duration of the rehabilitation process is shortened and the functionality of the affected limb is increased.

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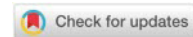
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MEASURED - REAL VALUES OF INTRAOCULAR TENSION, 24 H AFTER THE APPLICATION OF BROLUCIZUMAB INTRAVITREAL INJECTION IN PATIENTS WITH wAMD

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Abstract: Intraocular tension (OHT) refers to any situation in which the intraocular pressure (IOP) is greater than 21 mm Hg in one or both eyes, measured with a non-contact tonometer on 2 or more occasions. To present the real values of intraocular tension 24h after the application of Brolucizumab intravitreal injection of wAMD (wet Age-related macular degeneration) in the age over 50 years. Screening examination of patients for intraocular tension was done between 2023 and 2024 at the Italian Eye Hospital in Pristina 24h after the application of Brolucizumab wAMD intravitreal injection. Results: A total of 100 patients participated in the studies, 36 women and 64 men over 50 years old. After measuring intraocular pressure (IOP), only 10 patients had IOP values of 21mmHg or 10%, where most were male, 6% and 4% were female, and age. most of them were over 60 years old, only in one case the age was 56 years. Conclusions: Management of patients with intraocular pressure risk a global risk that plays a vital role despite all the unreliable data considering patients, status, life expectancy and personal preferences. Looking at our tension is presented in the intraocular in the number of patients passed after the application of wAMD is the last considering also the age of patients over 60 years 99% and only 1% 56 years. We can a clear relationship between intraocular tension and the establishment of the application of Brolucizumab intravitreal injection in patients with wAMD with a real reduction in the incidence of blindness from wAMD, which has a cost to the health care system. However, there is mixed evidence on the impact of anti-VEGF on other patient-related outcomes.

Keywords: Intraocular tension, wAMD, Brolucizumab intravitreal injection.

Field: Medical sciences and Health© 2024 by the authors.

1. INTRODUCTION

Ocular hypertension is a term used to describe intraocular pressure (IOP) greater than two standard deviations above the mean, above 21 mm Hg from population studies (mean = 16 mmHg, normal range 10-21 mm Hg), in the absence damage to the optic nerve or vision. However, 5% of all patients are found to have IOP above 21 mm Hg (10% of patients above 40). Traditionally, people have struggled with the decision to treat these patients, who are called suspected ocular hypertensives or suspected ocular hypertensives glaucoma. Criteria were lacking to distinguish those patients who are at a higher risk of progression to primary open-angle glaucoma (POAG) from those who will not progress to POAG without intervention (Kaushik et al, 2021)

Age-related macular degeneration (AMD) is a progressive disease of the retina that leads to damage to the cells responsible for vision. The condition can severely affect an individual's independence and quality of life. Sight loss often causes numerous problems with performing everyday activities such as reading, driving and recognizing faces, and this affects mobility with the risk of isolation. (Thomas et al, 2021; Brandl et al., 2019; 2019; Joachim et al. 2019).

Age-related macular degeneration (AMD) is a degenerative disease of the human retina that affects individuals over the age of 55. This heterogeneous condition arises from a complex interaction between age, genetics, and environmental factors, including smoking and diet. It is the leading cause of blindness in industrialized countries. Worldwide, the number of people with AMD is projected to increase from 196 million in 2020 to 288 million by 2040. (Keenan et al., 2021; Wong et al., 2019; Korb et al., 2019; Li et al. 2019; Colijn et al. 2019; Wild et al., 2019).

Those whose complications of wet macular degeneration have progressed to loss of central vision have a higher risk of depression and social isolation. With profound vision loss, people may experience visual hallucinations. This condition is known as Charles Bonnet syndrome.

It is important to have routine eye examinations to identify early signs of macular degeneration to prevent complications that result from this disease.

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2. AIM OF THE STUDY

When drugs alone do not help, the Italian Eye Hospital in Pristina offers a number of treatment options, including anti-VEGF injections (Brolucizumab), photodynamic therapy and laser surgery that destroys the problematic blood vessels under the retina. Brolucizumab is FDA-approved for the treatment of age-related neovascular (wet) macular degeneration and DME. (Peter Stein et al, 2019)

3. MATERIAL AND METHODS

Ophthalmologists at the Italian Eye Hospital in Pristina trained in retinal diseases have extensive experience with wet macular degeneration, treating more than 200 patients with this condition each year. Screening of patients for intraocular tension was done between 2023 and 2024 at the Italian Eye Hospital 24h after wAMD application. Participants provided both oral and written informed consent after a thorough explanation of the studies. We included patients with AMD according to the classification system introduced by the Beckman Macular Research Classification Committee.

4. RESULTS

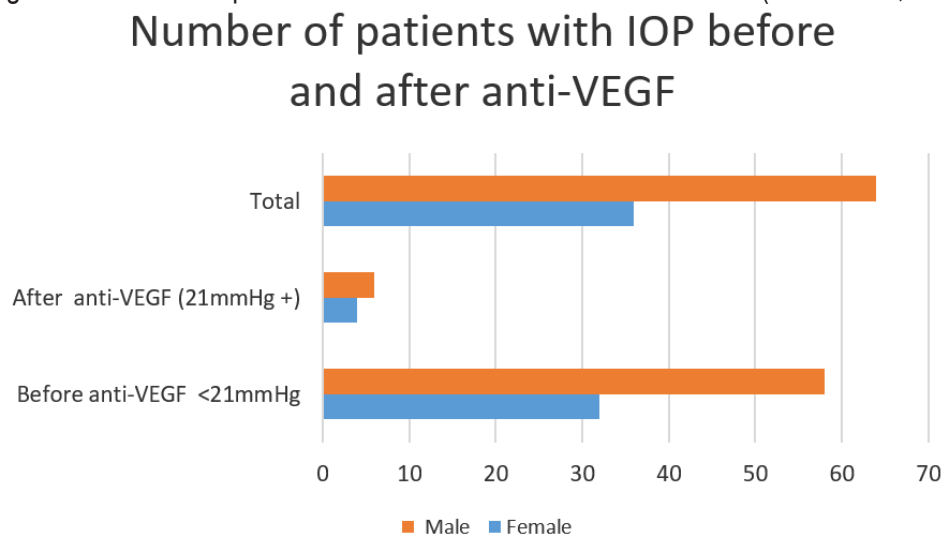
Out of 100 patients before receiving the anti-VEGF injection (Brolucizumab) with blood pressure below 21 mmHg, there were a total of 90 patients, while with IOP 21 mmHg + only 10 patients, of which 4 are women and 6 are men (Table 1. and Figure 1).

Table 1. Number of patients with IOP before and after anti-VEGF

Gender	Female	Male	Percentage
Before anti-VEGF < 21mmHg	32	58	90%
After anti-VEGF (21mmHg +)	4	6	10%
Total	36	64	100%

Source: Authors research

Figure 1. Number of patients with IOP before and after anti-VEGF (blue-Males, red-Female)



Source: Authors research

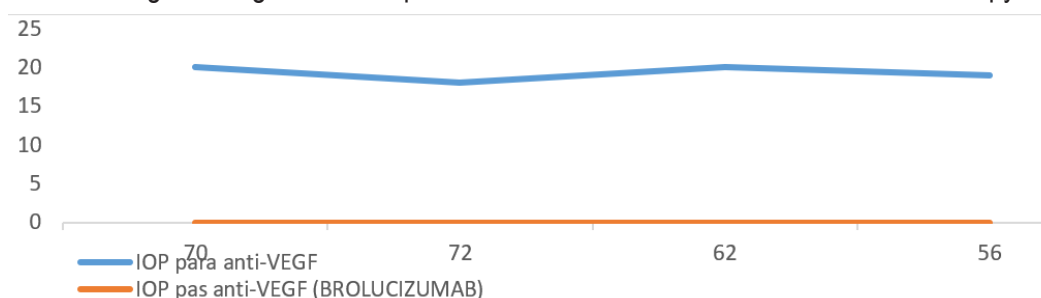
All of the female patients before receiving the anti-VEGF injection (Brolucizumab) have a IOP below 21 mmHg, after the treatment the IOP was 21 mmHg (Table 2. and Figure 2).

Table 2. Age of female patients and IOP before and after anti-VEGF therapy

Gender	Age	IOP before anti-VEGF	IOP after anti-VEGF (Brolucizumab)
Female	70	20	21 mmHg
Female	72	18	21mmHg
Female	62	20	21mmHg
Female	56	19	21mmHg

Source: Authors research

Figure 2. Age of female patients and IOP before and after anti-VEGF therapy



Source: Authors research

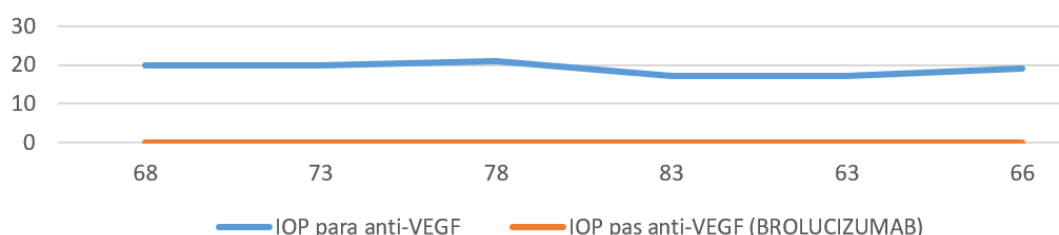
Five of the male patients (before receiving the anti-VEGF injection (Brolucizumab) have an IOP below 21 mmHg, after the treatment the IOP was 21 mmHg (Table 3. and Figure 3).

Table 3. Age of male patients and IOP before and after anti-VEGF therapy

Gender	Age	IOP before anti-VEGF	IOP after anti-VEGF (BROLUCIZUMAB)
Male	68	20	21mmHg
Male	73	20	21mmHg
Male	78	21	21mmHg
Male	83	17	21mmHg
Male	63	17	21mmHg
Male	66	19	21mmHg

Source: Authors research

Figure 3. Age of male patients and IOP before and after anti-VEG therapy
Age and IOP of male patients after anti-VEGF



Source: Authors research

5. CONCLUSIONS

AMD-related macular degeneration (AMD) is a chronic eye disease characterized by progressive degeneration in the central retina (the macula) is the main cause of severe visual impairment in all. Genetic, environmental and animal factors are strongly associated with AMD. Common symptoms are visual distortions such as metamorphopsia (straight lines appear wavy), blurred vision and scotoma (blind spots). These symptoms are seen in later stages of AMD. AMD is classified into two different forms: the

non-neovascular or atrophic (dry) form and the neovascular or exudative (wet) form. Brolucizumab was demonstrated as a safe and effective alternative in improving anatomical and functional parameters of eyes with wAMD in this analysis of 100 subjects respectively. Clinical studies included in this dossier support forms of BEOVU (Brolucizumab-dbl) for familial neovascular macular degeneration associated with me. Although it is not possible to be anti-VEGF for wAMD, following therapy shows progressive picture over time, due to macular atrophy and fibrosis. (Liisborg, 2022). Looking at our tension is presented in the intraocular in the number of patients passed after the application of wAMD is the last considering also the age of patients over 60 years 99% and only 1% 56 years. We can a clear relationship between intraocular tension and the establishment of the application of Brolucizumab intravitreal injection in patients with wAMD with a real reduction in the incidence of blindness from wAMD, which has a cost to the health care system. However, there is mixed evidence on the impact of anti-VEGF on other patient-related outcomes.

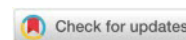
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CHILD TOXOPLASMOSIS AND LIMPHADENOPATHY - CASE REPORT

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Abstract: The purpose of this paper is to increase awareness of medical doctors to consider toxoplasmosis as one of the possible causes of lymphadenopathy in older children. Toxoplasmosis is one of the most common and widespread parasitic diseases in the world, even 22.5% of children over 12 years old are infected with Toxoplasmosis. The disease is caused by the parasite *Toxoplasma gondii*. The disease is transmitted through the feces of infected cats that are carriers of the parasite. We report the case of a 13-year-old child who appears to be a healthy and immunocompetent child and who clinically presents with enlargement of 2 lymph nodes in the left neck region that are unpalpable on palpation, one of which measures 4/5 cm and the other with dimensions of 1/2 cm. The child is in good general condition without significant health disorders. The epidemiological survey is positive for frequent contact with a domestic cat. The performed serological tests show strongly positive values for the presence of IgM and especially for IgG antibodies for Toxoplasmosis. Surgical extirpation of the one bigger lymph node because of diagnostic dilemmas was carried out. Pathohistological analysis confirms diagnosis of Toxoplasmosis and malignancy was excluded. From the results obtained from the Enzyme Immune Test for the age of IgG antibodies (avidity), a low avidity of IgG antibodies was determined. Additional research is needed whether excessive exposure to the parasite *Toxoplasma gondii* can be associated with a more severe clinical picture of the disease.

Keywords: Toxoplasmosis, Children, Lymphadenopathy

Field: Medical sciences and Health

1. INTRODUCTION

Toxoplasmosis is one of the most widespread parasitic diseases in the world, caused by the parasite *Toxoplasma gondii*. The definitive hosts of the parasite are cats (Felidae), while birds and many mammals act as intermediate hosts (Dubey, 1996). Infection occurs through the ingestion of food or water contaminated with oocysts or live microorganisms. The infection can also be transmitted to humans through contaminated hands or by ingesting food and water contaminated with cat feces (Arranz-Solís & Saeij, 2022). Pregnant women can transmit the infection trans placentally to the fetus, which may result in congenital malformations (Sharifi et al., 2019). Infestation most commonly occurs through the consumption of undercooked meat, unwashed vegetables and fruits, or by working in contaminated soil (Ayoade & Chandranesan, 2022).

When *Toxoplasma gondii* enters the body, it invades through the intestinal epithelium and spreads to the tissues where it reproduces (Dubey, 1996). In cats, the parasite reproduces sexually in the intestinal epithelium, producing oocysts that are excreted with the host's feces (Arranz-Solís & Saeij, 2022). Immunocompetent hosts generally mount a strong immune response that controls the infection within weeks or months, leading to immunity that prevents reinfection (Ayoade & Chandranesan, 2022). In these hosts, the tissue cysts remain inactive and may persist without causing symptoms throughout their lives (Dunay et al., 2018).

However, in immunocompromised individuals, the disease may manifest with various clinical symptoms, including myocarditis, pneumonitis, and central nervous system (CNS) involvement (Dunay et al., 2018). Transplacental transmission may result in congenital toxoplasmosis, which can affect vision or cause other malformations (Sharifi et al., 2019). In immunocompetent individuals, toxoplasmosis is often asymptomatic, though 10-20% may develop lymphadenopathy or flu-like symptoms (Khawar Tariq & Shahid, 2022). Severe cases involving the CNS are rare but possible in otherwise healthy individuals (Khawar Tariq & Shahid, 2022).

A certain number of immunocompetent patients with acute infection may experience fever, myalgia, rash, splenomegaly, headache, pharyngitis, and painless lymphadenopathy, which may last for weeks (Kaparos et al., 2014). Diagnosis of toxoplasmosis is primarily based on serological testing, identifying *Toxoplasma gondii* IgM and IgG antibodies (Sharifi et al., 2019). Molecular methods like PCR can also detect the parasite's DNA in blood or other fluids (Madireddy et al., 2024). For tissue cyst identification, biopsies may provide a definitive diagnosis (Mercadante & Tadi, 2024).

Once diagnosed, treatment typically involves a combination of pyrimethamine and sulfadiazine for

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6 weeks, particularly for immunocompromised patients, alongside folic acid supplementation (Dunay et al., 2018). Prophylaxis may also be necessary for these patients to prevent reactivation of latent infection (Khawar Tariq & Shahid, 2022). Differential diagnosis in children can include cytomegalovirus (CMV), bacterial or viral infections, and malignancies of other etiologies (Madireddy et al., 2024). Some studies suggest that both toxoplasmosis and CMV may play a role in the etiology of autism (Hassan et al., 2023). While toxoplasmosis is generally self-limiting in immunocompetent patients with a favorable prognosis, the risk of reactivation remains due to latent infection (Khawar Tariq & Shahid, 2022). Preventative measures include thoroughly cooking food, washing hands, fruits, and vegetables, avoiding unpasteurized milk, and limiting contact between children and cats (Mirza Alizadeh et al., 2018).

2. MATERIALS AND METHODS

A 13-year-old male child comes to the examination. He is conscious, oriented in time and space, afebrile, with the presence of enlarged painless lymph nodes in the left anterior neck region that have increased without the presence of other symptoms in the last 4 weeks ago. The parents did not consider it seriously. After 2 weeks, one lymph node becomes enlarged, which is why the child's father visits the doctor for an examination. The child lives in the village and has a positive history of contact with a domestic cat. During the physical examination, there are no significant deviations, except during palpation of the lymph nodes in the front left neck region, two painless lymph nodes are palpated, one of which is 4/5 cm, and the other is 1/2 cm. Due to the enlargement of one lymph node, the child was referred for further investigation. A serological analysis was performed to determine infection with *Toxoplasma* by identifying IgM and IgG antibodies and an enzyme immunological test was performed for the age of the IgG antibodies (avidity). Other serological analysis was done to exclude CMV, EBV, and HIV infections. Biochemical analysis was also done to rule out hepatic involvement and other diseases. To rule out malignancy, surgical extirpation of the enlarged lymph gland was performed and submitted for histopathological analysis. The results obtained from the analysis show Toxoplasmosis infection and chronic inflammation of the lymph node, and the existence of a malignant process is excluded. Informed Consent: Written informed consent was obtained from the patient's guardian.

3. RESULTS

Table 1 – Serological analysis

	Referent value/ml U/ml	Results- First	Results/Second
CMV IgG	>6 positive	+226.5	
CMV IgM	>1.0 positive	0 (negative)	
EBV IgG	>1.0 positive	0	
EBV IgM	>1.0 positive	0	
The Architect <u>Toxo</u> IgG immunoassay	>3.0 positive	139.0	146
The Architect <u>Toxo</u> IgM immunoassay	>1. positive	7.44	8.68
ELISA HIV		negative	

Source: Institute for Public Health of the Republic of North Macedonia-Skopje; 50th Division Skopje Diagnostic laboratory-Laboratory for Cytology and Histology; Street. 1738 no. 20/1 1000 Skopje Republic of North Macedonia

An enzyme immunological test for the age of the IgG antibodies (avidity) for *Toxoplasma* was also performed. Avidity of IgG antibodies for *Toxoplasma*: 0.082 and indicated a low avidity and an infection that occurred in an interval of less than 3 months, which excludes the existence of congenital toxoplasmosis.

Analysis of blood count was in normal range, CRP-1 (normal), ASO=939 (0-200 normal), Analyses of liver function: ALT =11, AST= 19 (normal range), glucose 5.8 mmol/2-normal range.

Microscopic Examination of the sections from the extirpated lymph node showed Preserved Architectonics with Hyperplastic Lymphoid Follicles: The overall structure of the lymph node was maintained. There were many mature lymphocytes in the cortex with hyperplastic (enlarged) lymphoid follicles and prominent germinal centers. Presence of Macrophages with Tangible Bodies: Numerous macrophages containing phagocytized debris, indicative of active immune response, were seen in the germinal centers. Dilated Sinuses in the Medulla with Hyperplastic Sinus Macrophages: The medullary sinuses were expanded and filled with numerous macrophages, suggesting increased immune activity.

Preserved Capsule and Peripheral Collagen Tissue: The capsule of the lymph node and surrounding collagen tissue were intact, indicating no invasion or destruction typical of cancer.

Immunohistochemical Analysis: CD-20 and CD-79 Positive (+++): These are markers for B-cells, indicated a significant presence of B-cells, which are part of the immune response. CD-3 Positive (++): This is a marker for T-cells, showed that T-cells were also present and active. Bcl-2 Negative in Germinal Centers: Bcl-2 was a marker that inhibited apoptosis (cell death). Its absence in germinal centers suggested normal cell turnover and not a neoplastic process. Ki-67 was weakly positive only in germinal centers (+): Ki-67 is a marker for cell proliferation. Weak positivity indicated some cell proliferation, which is normal in an immune response. CD 15 was negative and CD 30 positive in activated hyperplastic lymphocytes: CD 15 negativity and CD 30 positivity in immunoblasts (activated lymphocytes) further supported a reactive process rather than a neoplastic one.

Correlation with Toxoplasmosis: Therefore, the immunohistochemical analysis confirms that the lymphadenopathy observed in this case is due to a reactive immune response to *Toxoplasma gondii* infection, rather than a neoplastic process. This supports the clinical findings and serological tests, further validating toxoplasmosis as the cause of lymphadenopathy in this patient.

4. DISCUSSION

Toxoplasmosis is a parasitic infection caused by *Toxoplasma gondii*, which can manifest in various clinical forms, ranging from asymptomatic to severe, especially in immunocompromised individuals. Serological analysis, histopathological examination, and immunohistochemical testing of excised lymph nodes can provide valuable insights into the lymphadenopathy observed in infected patients (Sharifi et al., 2019). In this case, the lymph node analysis revealed several features consistent with a reactive process due to toxoplasmosis. The lymph node maintained its structural integrity, which is typical of reactive conditions, as opposed to malignant processes that often disrupt normal architecture (Obiorah & Okoro, 2014). Additionally, the intact capsule and peripheral collagen tissue suggest a non-neoplastic process, unlike cancerous conditions that tend to show invasive characteristics (Obiorah & Okoro, 2014).

Immunohistochemical analysis further complemented the histopathological findings by identifying specific cell markers, indicating that the immune response involves a strong humoral component (Mercadante & Tadi, 2024). T-cell marker expression demonstrated that T-cells actively participated in the immune response. The absence of Bcl-2 in the germinal centers, indicating normal apoptotic processes, contrasted with neoplastic conditions, where Bcl-2 is frequently overexpressed to inhibit apoptosis (Qian et al., 2022). The weak positivity for Ki-67, a proliferation marker, suggested moderate cell proliferation, which is characteristic of reactive lymph nodes responding to infection. Furthermore, the immunohistochemical negativity for CD15 and positivity for CD30 in activated hyperplastic lymphocytes supported a reactive rather than neoplastic process (Obiorah & Okoro, 2014).

In some cases, such as this one, surgical extirpation of the lymph node may be necessary to exclude malignancy, especially when there are concerns from parents regarding the potential future risk of cancer (Obiorah & Okoro, 2014).

5. CONCLUSION

In conclusion, this paper underscores the importance for medical professionals to consider toxoplasmosis as a potential cause of lymphadenopathy in older children. The presented case of a 13-year-old child with painless lymph node enlargement and positive serological tests for toxoplasmosis highlights the clinical relevance of this parasitic infection. Pathohistological analysis confirmed the diagnosis, excluding malignancy, and identified a recent infection based on low IgG antibody avidity. The findings emphasize the need for heightened awareness and consideration of toxoplasmosis in differential diagnoses, especially in children with frequent exposure to domestic cats. Further research is warranted to explore the implications of prolonged exposure to *Toxoplasma gondii* on the severity of the disease.

ACKNOWLEDGEMENTS

We would like to express our sincere gratitude to all those who contributed to this study. Our heartfelt thanks go to the medical team of PZU Vitalino Veles, and for their invaluable assistance and collaboration in conducting this research. Special thanks to the patient's family for their cooperation and consent, allowing us to share this case. We extend our appreciation to the staff at the laboratory for their meticulous work in conducting the serological tests and pathohistological analysis, which were crucial to

the success of this study.

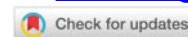
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UTERINE ARTERIOVENOUS MALFORMATIONS – DIAGNOSIS AND TREATMENT IN SERIES OF CASES

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Abstract: Uterine arteriovenous malformation (UAVM) is a rare but potentially life-threatening diagnosis. Misdiagnosed and inappropriately treated Uterine arteriovenous malformation can lead to excessive hemorrhage because of specific conditions: abnormal direct multiple fistulous communication between an artery and vein without an intervening capillary bed. This makes a high-pressure gradient into venous system, enlargement of some venous vessels and multidirectional high velocity blood flow. There are different treatment options, one of which is embolization of uterine arteries.

The aim of this study is to present the etiology, clinical presentation, diagnostic options and therapeutic approaches to patients with Uterine arteriovenous malformation.

This study is a prospective follow-up of series of cases with Uterine arteriovenous malformation, which have different etiology and different uterine localization - cervical and corporal.

Our diagnostic method is ultrasonography – transvaginal, using both 2D grayscale, Color Doppler and Pulsed Wave Doppler. The machines used in this study are Samsung Hera and Medison.

We present four cases of arteriovenous malformation (one of them congenital and three others: after normal delivery, after caesarean section; dilatation and curettage were executed for all of them). All the cases resulted in hemorrhagic shock and were successfully treated later with uterine artery embolization.

Our study presents to the auditory unique cases initially misdiagnosed and mistreated with uterine curettage. They were correctly diagnosed later by ultrasonography and treated successfully through selective embolization of the feeding vessels. The research represents our personal experience in diagnosis and treatment of that life threatening condition and all cases were well illustrated with sonographic images, Color Doppler technic and embolization technics.

A good therapeutic outcome is a result of obtained collaboration between a gynecologist, an expert sonographer and an invasive cardiologist.

Uterine arteriovenous malformation can be safely and effectively treated with uterine artery embolization with even high chances of preserving women's childbearing function.

Keywords: Uterine arteriovenous malformations, embolization of uterine arteries, hemorrhagic shock, endovascular treatment.

Field: Medical sciences and Health

1. INTRODUCTION

Uterine arteriovenous malformation (UAVM) is defined as a communication between an artery and vein without an intervening capillary bed (Ruiz Labarta, Pintado Recarte, González Leyte, Arribas, Álvarez Luque, Cuñarro López, García-Montero, Fraile-Martinez, Ortega and De León-Luis, 2022). UAVM are divided into two groups – congenital and acquired or traumatic. Congenital UAVMs are the result of abnormal embryologic development of primitive vascular structures, which have multiple feeding arteries, a central nidus and numerous large draining veins (Hoang, Van, Trinh, et al. 2021). Acquired UAVM are complications of dilatation and curettage (D&C), cesarean section, gestational trophoblastic disease (GTD), endometrial cancer, infection (Nakashololo, Khan, Dunn, Snyman and Mh Ismail, 2021 May), (Lamrissi, Mabengui, Mourabbih, Jalal, Fichtali and Bouhya, 2022 May), (Hammad, Nausheen and Malik, 2022 July). They are described as arteriovenous fistulas between intramural arterial branches and the myometrial venous plexus infection (Nakashololo, Khan, Dunn, Snyman and Mh Ismail, 2021 May). UAVM is an uncommon but eventually life-threatening diagnosis (Hammad, Nausheen and Malik, 2022 July). Its clinical presentation is vaginal bleeding, which has potential to become excessive leading to hemorrhagic shock (Farias, Santi, Lima, Teixeira and De Biase, 2014 March). Therefore, UAVM should be suspected in every patient with severe metrorrhagia.

The aim of this study is to present the etiology, clinical presentation, diagnostic options and therapeutic approaches to patients with UAVM.

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2. MATERIALS AND METHODS

This study is a prospective follow-up of series of cases with UAVM, which have different etiology and localization.

Our method of diagnosis is ultrasonography – transvaginal, using both 2D grayscale, Color Doppler and Pulsed Wave Doppler or Samsung machines.

Digital subtraction angiography is a unique invasive method for both diagnostic and therapeutic purposes. Uterine artery embolization is the gold standard for UAVM treatment.

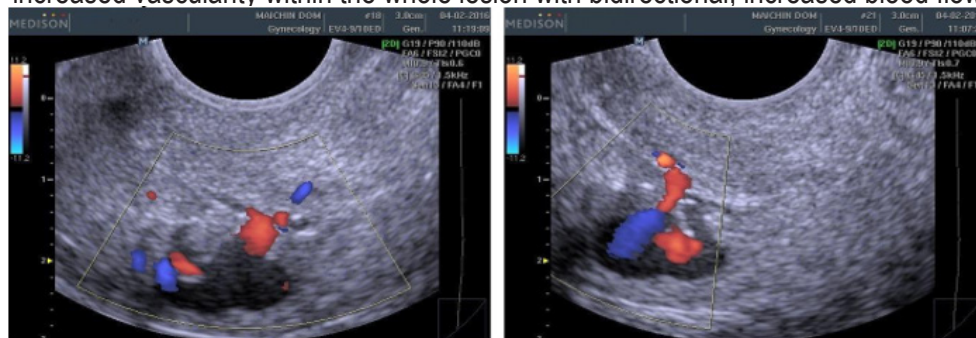
3. RESULTS

Our study presents unique cases of UAVM with different localization and successful embolization of the feeding vessels.

3.1. Case 1

A 20-year-old female, G0P0A0, presented to the emergency room with severe vaginal bleeding which has begun after intensive physical exercise. She denied any previous operative procedures incl. curettages and admission of antithrombotic medications. After admission to the hospital the patient underwent dilatation and curettage (D&C). She stayed in the reanimation unit for 5 days because of an excessive hemorrhage that led to a hemorrhagic shock and a hemotransfusion. An attempt to vaginal ligation of the uterine arteries was made without success. On the fifth day the patient was diagnosed with cervical AVM, and urgent endovascular embolization of the uterine arteries was performed.

Figure 1. TVUS Color Doppler of hypoechoic mass, localized in the uterine cervix, presenting increased vascularity within the whole lesion with bidirectional, increased blood flow



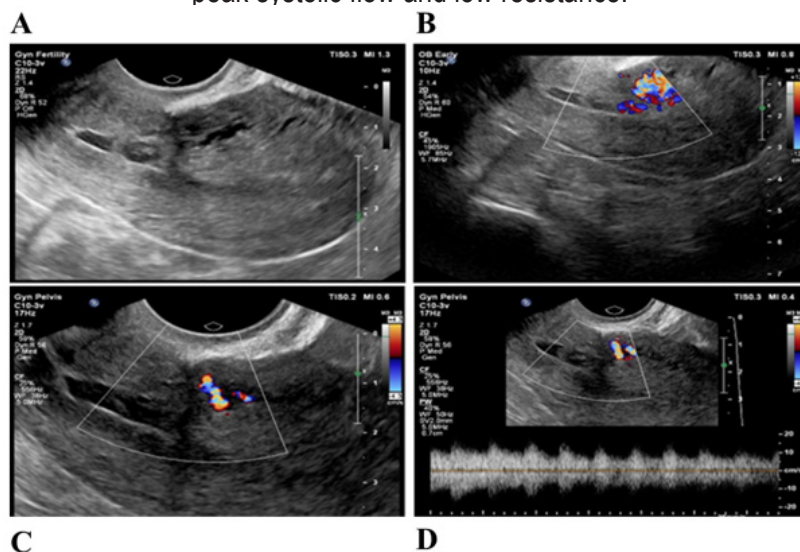
Source: Tsankova M., University hospital of obstetrics and gynecology „Maichin Dom“ Department, Medical University, Bulgaria

In Cases 2, 3 and 4 we are presenting uterine AVM in corporal part of the uterus

3.2. Case 2

A 39-year-old female, G2P1(PN)A1 was admitted to the gynecology department due to severe intermenstrual metrorrhagia. The patient reported one D&C due to spontaneous abortion in 12-th g. w. 13 years ago. There was no history of admission of any antithrombotic medications. The initial treatment was dilatation and curettage (D&C). In the postoperative period another episode of vaginal bleeding led to a second D&C which resulted in hemorrhagic shock and reanimation procedures. A month later the uterine AVM was diagnosed, and embolization of the uterine arteries was performed.

Figure 2. A. 2D – Gray scale TVUS revealing ill-defined hypoechoic mass in the myometrium of anterior uterine wall. B. and C. – Color Doppler sonography of the presented mass showing increased vascularization with aliasing, turbulent high-velocity flow. D. PW Doppler applied to the mass – revealing peak systolic flow and low resistance.

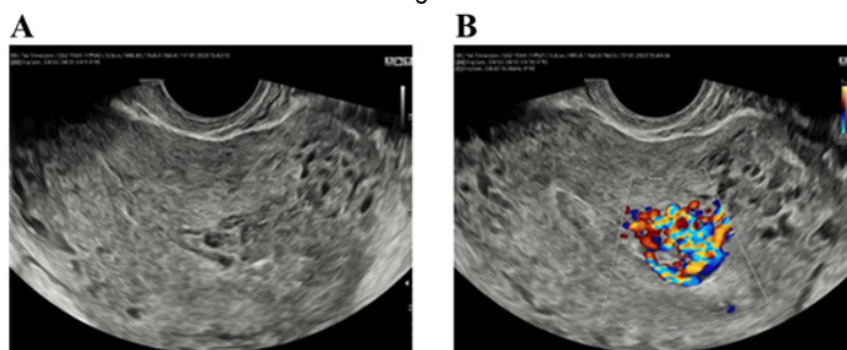


Source: Tsankova M., University hospital of obstetrics and gynecology „Maichin Dom“ Department, Medical University, Bulgaria

3.3. Case 3

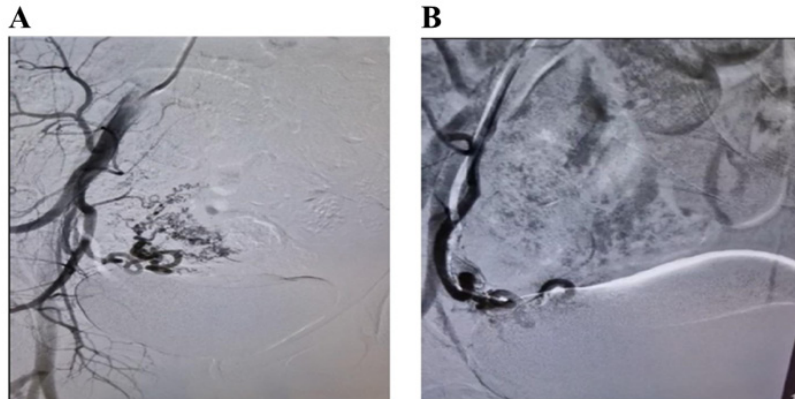
A 32-year-old female, G3P2(SC)A1 presented to the emergency with profound and continuous intermenstrual vaginal bleeding. The patient had a history of two cesarean sections and one D&C due to spontaneous abortion. The patient complained of often episodes of heavy menstruations, which have been treated with hormones (both oral contraceptives and gestagens), hemostatic medications without a result. They led to secondary anemia and impaired quality of life, including disorders of psychiatric spectrum (depression). The patient was sent to the hospital for a therapeutic uterine curettage. A transvaginal ultrasound (TVUS) was performed. On a 2D-Doppler image an enlarged uterus with no signs of intra- or extrauterine gestation was shown. An anechoic mass in the anterior wall was visualized, which after application of Color Doppler US showed increased vascularity and color aliasing phenomenon. Pulsed Wave Doppler revealed high velocity flow with low resistance. This led to diagnosing UAVM. The patient was referred to a cardiology department, where uterine artery embolization was performed. Digital subtraction angiography was performed and revealed increased vascularization in the arterial phase. After the embolization, the arterial phases show reduction in the vascularization of the UAVM.

Figure 3. A. 2D Gray scale TVUS of lesion within the myometrial layer with heterogeneous echogenicity (compared to the previous cases). B. Application of Color Doppler reveals high number of vascular structures with aliasing and multi-directional blood flow.



Source: Tsankova M., University hospital of obstetrics and gynecology „Maichin Dom“ Department, Medical University, Bulgaria

Figure 4. Fluoroscopy images obtained during digital subtraction angiogram of the right uterine artery. A. Before treatment – during the arterial phase a tortuous and dilated uterine artery is presented, suspicious for UAVM. B. Presents the obstructed blood flow of the described vessel after the embolization has been performed.



Source: Petrov, I., Cardiology, Angiology and Electrophysiology Department, Acibadem City Clinic Cardiovascular Center, Bulgaria

In our cases -2-coin catheters 3/4 and 4/8 mm and 2 flacons particles PVA 100 micr. both sides.

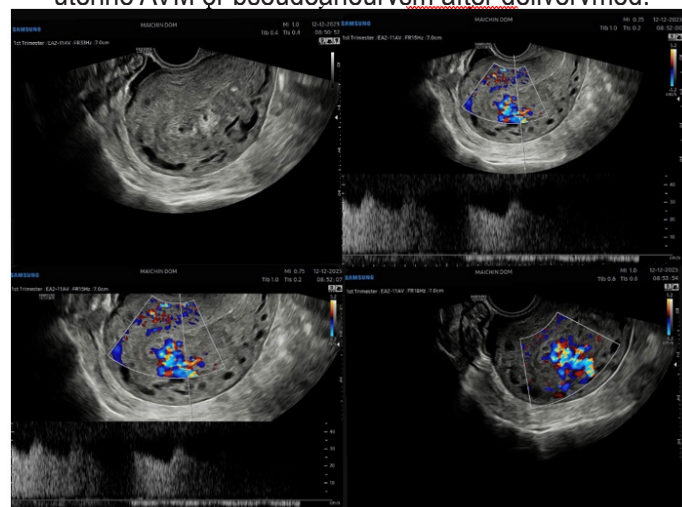
The coil embolization procedure is a catheter - based precise closure of abnormal blood in aneurysmal malformations. Once in a place, the catheter inserts different embolic agents, particles made of gelatin or plastic, that will block high velocity blood flow of uterine arteriovenous malformations and reaches directly abnormal communication between intramural arterial branches and myometrial venous plexus.

The presented cases are fully documented and therefore can be presented to the audience. Our first case was reported in 2016 and the next cases coming in 2022-2023.

3.4. Case 4

The last case of 2023 year. A patient, G1P1(PN)A0, 25 days after normal delivery. The placental period of delivery was normal. She has three episodes of heavy bleeding and uterine curettage in the postpartum period. The patient attends to the emergency department due to heavy bleeding. On Color Doppler has been diagnosed atypical low velocity blood flow of vessels in the uterus, AVM or pseudoaneurysms. An urgent embolization was performed.

Figure 5. Group of images – Gray scale sagittal scan of uterus with clearly visible uterine cavity with hypoechoic “lakes” surrounded by hyperechogenic irregular lines and color Doppler with multidirectional blood flow, aliasing effect and low resistance index of uterine branches inside. Specific characteristics of uterine AVM or pseudoaneurysm after delivery med.



Source: Tsankova M., University hospital of obstetrics and gynecology „Maichin Dom“ Department, Medical University, Bulgaria

4. DISCUSSIONS

Uterine arteriovenous malformations were described by G.Dubreil and E.Loubat in 1926 (Dubreil and Loubat, nd). Although the incidence of this condition is considered relatively rare, a prospective study of 959 women found UAVM in 5.2% of women after D&C and in 0.22% of women after delivery. Only one of all UAVM was classified as clinically significant (Yazawa, Soeda Hiraiwa, et al. 2013). This may be since most of the studies include only symptomatic UAVM or have a retrospective model.

UAVM can be diagnosed using various imaging studies – ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), digital subtraction angiography (DSA). The initial investigation is usually ultrasound, trans-abdominal or transvaginal. On 2D Gray scale ultrasound UAVM appear as heterogeneous, ill-defined mass with multiple hypoechoic structures of different size, eventually with endometrial and/or myometrial thickening. Nakasholo, Khan, et al. 2021 May), (Timmerman, Wauters, Van Calenbergh, Van Schoubroeck, Maleux, Van Den Bosch and Spitz, 2023 June), (Timor-Tritsch, Haynes, Monteagudo, Khatib and Kovács, 2016 June), (Vijayakumar, Srinivas, Chandrashekar and Vijayakumar, 2013). Typical findings on Color Doppler ultrasound are multidirectional blood flow with aliasing phenomenon, localized in different zones (in myometrium or rarely uterine cervix) with high velocity blood flow rate and low velocity indexes (Timmerman, Wauters, Van Calenbergh, Van Schoubroeck, Maleux, Van Den Bosch and Spitz, 2023 June), (Timor-Tritsch, Haynes, Monteagudo, Khatib and Kovács, 2016 June), (Vijayakumar, Srinivas, Chandrashekar and Vijayakumar, 2013). Peak systolic velocity flow can be used as a sign for UAVM prognosis (Timmerman, Wauters, Van Calenbergh, Van Schoubroeck, Maleux, Van Den Bosch and Spitz, 2023 June), (Timor-Tritsch, Haynes, Monteagudo, Khatib and Kovács, 2016 June), (Vijayakumar, Srinivas, Chandrashekar and Vijayakumar, 2013). Results of a study of 30 patients with UAVM showed that UAVM with peak systolic velocity flow (PSVF) $<0.39\text{m/sec}$ have a good possibility of spontaneous resolution, whereas UAVM with PSVF $>0.83\text{m/sec}$ usually require conservative or surgical treatment (Timmerman, Wauters, Van Calenbergh, Van Schoubroeck, Maleux, Van Den Bosch and Spitz, 2023 June). Other imaging tools can also be used, if necessary, for example CT angiography and MRI with angiography (Masood, Rana, Khan, et al. 2022). Hysteroscopic identification of UAVM is a feasible option for diagnosis and treatment (Calzolari, Cozzolino, Castellacci, Dubini, Farruggia and Sisti, 2017 April-June). Digital subtraction angiography (DSA) is the gold standard for diagnosing UAVM. It provides detailed images and information regarding the arterial supply of the lesion, its size and venous drainage. Because of the invasiveness of the procedure, its use is limited only to cases required to be treated with endovascular embolization, transforming the procedure from diagnostic to therapeutic (Masood, Rana, Khan, et al. 2022). Histopathologically, UAVM is described as a very thick venous structure, in which the arteries have incomplete or complete absence of elastic membranes and a completely absent tunica muscularis media (Calzolari, Cozzolino, Castellacci, Dubini, Farruggia and Sisti, 2017 April-June). Treatment of UAVM depends on the clinical presentation. As earlier discussed, most of the UAVM are diagnosed only after becoming symptomatic, so a treatment plan is intended. It depends on the regularity and intensity of bleeding. Hemodynamically stable patients with mild to moderate bleeding, which has resolved spontaneously, can be treated conservatively for up to 6 months, using medicaments such as GnRH antagonists and danazol. This approach is associated with a low chance of success (Nonaka, Yahata, Kashima and Tanaka, 2011 February). All other patients, inappropriate for conservative approach, especially those presenting with recurrent and/or profuse, life-threatening bleeding, possibly leading to hemorrhagic shock (as the presented cases) should be treated interventional and/or surgically. Transcatheter uterine artery embolization and ligation of uterine/internal iliac artery are minimally invasive and fertility-preserving methods with high success rates (Kim, Shin, Kim, Yoon, Ko, Gwon, Yang and Sung, 2014 March). A systematic review of uterine artery embolization of UAVM, which includes 371 patients in 95 studies, showed global success rate of 88.4% with a low risk 1.8% of adverse outcomes (one case of disseminated intravascular coagulopathy, one uterine artery rupture, one non-flow limiting dissection of the internal iliac artery and three cases of pulmonary embolism) even in patients with later pregnancies. 15.6% of all patients experienced mild complications defined as post-embolization syndrome – pelvic/abdominal pain with or without fever, transient or permanent amenorrhea (Ruiz Labarta, et al. 2022). Hysteroscopy is another possible option, also preserving fertility (Calzolari, et al. 2017 April-June). Hysterectomy is definitive surgical treatment option in case of failure of minimally invasive methods or lack of desire for future childbearing (Ore, Lynch and Rumsey, 2015 January). There are a lot of examples of successful pregnancy after UAE or UAVM described in the literature. (Ruiz Labarta, et al. 2022), (Delplanque, Le Lous, Proisy, Joueidi, Bauville, Rozel, Beraud, Bruneau, Levêque, Lavoué and Nyangoh Timoh, 2019 January). Some of the reported obstetric complications in this specific group are spontaneous abortions, placenta previa or accreta, postpartum hemorrhage and higher rate of cesarean

section in comparison to the normal population. (Ruiz Labarta, et al. 2022), (Soeda, Kyozyuka, Suzuki, Yasuda, Nomura and Fujimori, 2014).

A differential diagnosis of UAVM includes retained products of conception, gestational trophoblastic disease (GTD), uterine postpartum pseudo aneurysmal retained parties of placenta and abnormally invasive placenta (Nakashololo, Khan, Dunn, Snyman and Mh Ismail, 2021 May). Serum levels of b-Hcg are elevated in cases of GTD and uterine pseudoaneurysm.

5. CONCLUSIONS

The presented cases clearly demonstrated typical ultrasound images of uterine AVM because of excessive uterine bleeding and related complications. Uterine artery embolization proved to be an effective in our cases life-saving procedure. The study shows different clinical situations for iteral AVM: congenital, after normal delivery, after C section and after uterine curettage.

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