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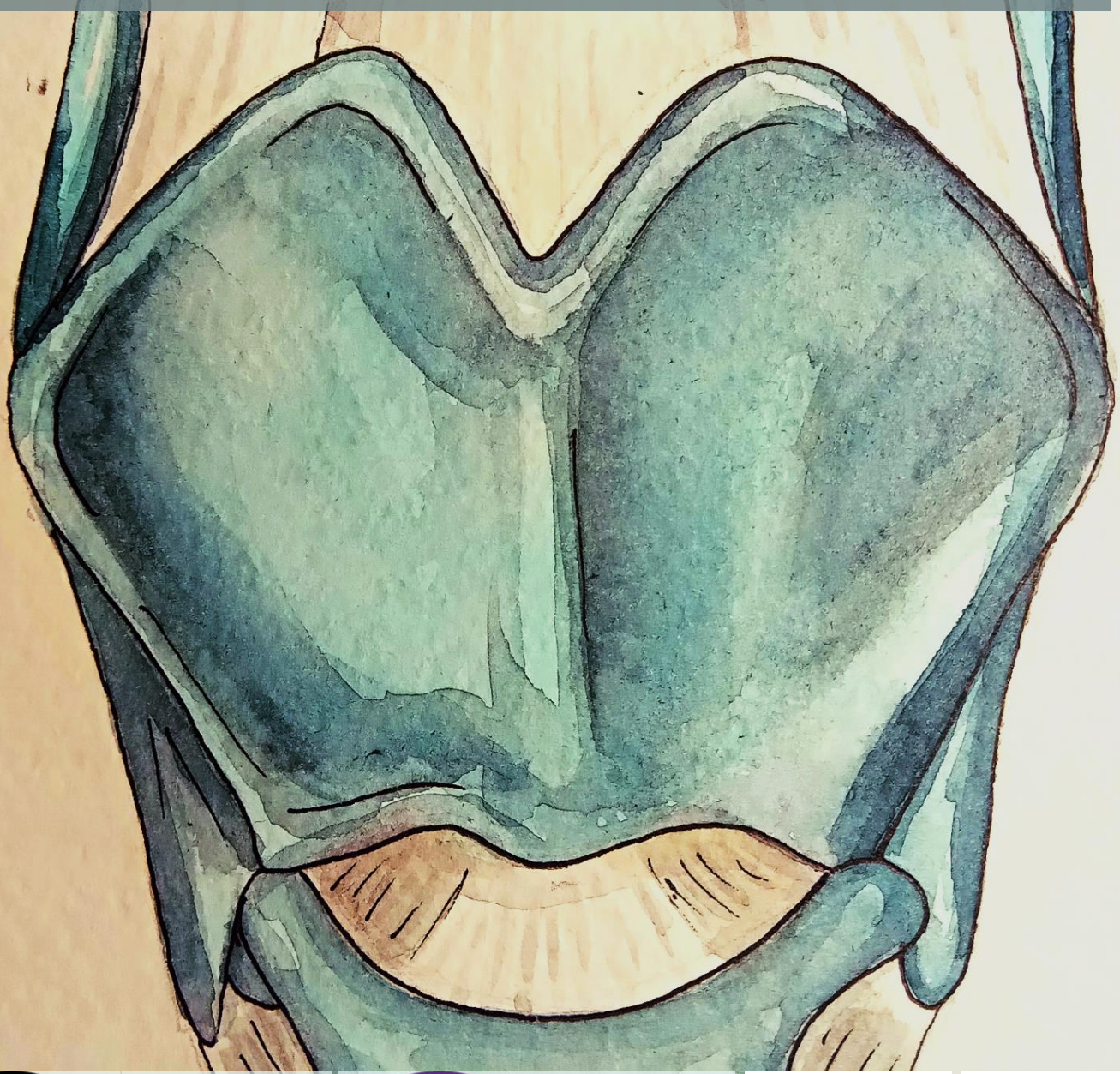

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Contents

Original article

Population Based Study and Global Estimates of Hearing Impairment in Schoolchildren

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Abstract: Hearing impairments in schoolchildren affects learning and communication. Reliable data on hearing loss prevalence in this group are necessary for planning the audiological care.

Aim. To compare data from a population based study of the hearing loss prevalence in schoolchildren and estimates from the Global Burden of Disease (GBD) study in the Republic of Yemen.

Materials and methods. Data extraction was performed from the GBD database on the prevalence of bilateral hearing loss >20 dB among children aged 5–9 years in the Republic of Yemen. A two stage study of hearing loss prevalence among primary school students aged 6–9 years in Sana'a, Republic of Yemen, in a sample of 2200 children using screening audiometry at 20 dB at 0.5, 1, 2, and 4 kHz is school settings, followed by tonal threshold audiometry and tympanometry in a specialized clinic. Hearing loss was assessed as unilateral or bilateral when hearing thresholds were higher than 25 dB.

Results. According to GBD estimates, bilateral hearing impairment in this population is 2.2%, including 1.4% of mild degree. According to the results of a Yemenian population study, mild and moderate hearing impairment was detected in 10.6%, of which 6.8% – unilateral, 3.8% – bilateral hearing loss. There were no cases of severe or profound hearing loss. The prevalence of otitis media with effusion was 6%, chronic suppurative otitis media – 1.8%, sensorineural hearing loss – 1.6%.

Conclusion. Bilateral hearing impairments occur in 2.2–3.8% of primary school students, with unilateral impairments the prevalence is up to 10.6%. Of these, at least 65% have conductive hearing loss due to pathology of the middle ear. The data obtained will improve the efficiency of ear and hearing care for schoolchildren.

Keywords: hearing impairment, hearing loss, prevalence, schoolchildren, epidemiology, global burden of disease.

1. Introduction

The problem of timely detection of hearing disorders in children has not only medical, but also social significance. Hearing loss hinders speech development, has a significant impact on the psychosocial adaptation of the child, significantly limiting the possibility of education, communication, which is important for full development [1-3].

To plan care for ear diseases and hearing disorders, it is necessary to know their prevalence among the entire population or in certain groups. There are various methods for studying the prevalence of diseases, while each has its own advantages and limitations. The registration of cases of the disease by appeal identifies persons with active complaints, which may not be effective enough in detecting mild and moderate hearing disorders, as well as non-purulent ear diseases, not accompanied by painful or uncomfortable sensations [4, 5]. In this regard, medical examinations or medical examinations, as well as screening for hearing disorders, are more appropriate. More accurate data on the prevalence of diseases can be obtained on the basis of population studies of sufficiently large representative samples of the population. In different countries, depending on the threshold of audibility, taken as clinically significant, and taking into account cases of unilateral or bilateral hearing loss, the prevalence of hearing loss among school-age children is 1.6-22.6% [6-11]. In Russia, hearing disorders and ear diseases among schoolchildren were detected in 15-19% in different

regions [12, 13]. According to estimates of meta-analysis, 88 population studies, the prevalence of hearing loss in children is 13.1% with an average hearing threshold at frequencies of 0.5, 1, 2 and 4 kHz on a better hearing ear of more than 15 dB, 2.2% – more than 25 dB, 0.9% – more than 40 dB [14]. The World Health Organization, within the framework of the program for the prevention of deafness and hearing loss, has developed a methodology for a population-based epidemiological study of the prevalence of ear diseases and hearing disorders Ear and Hearing Survey5. The algorithm includes, at the first stage, registration of otoacoustic emissions for children aged 0-4 years or automatic audiometry for children over 5 years and adults, otoscopy (when detecting sulfur plugs, foreign bodies, their removal), tympanometry. At the second stage, the audibility thresholds are evaluated by the tonal threshold audiometry method. The application of the proposed algorithm in different countries will allow comparing the prevalence of hearing loss in individual populations based on uniform criteria [15]. In case of insufficient epidemiological data, it is possible to determine the prevalence of various diseases and conditions by calculating estimates based on the use of Bayesian statistics methods. To this end , with They are publicly available on the Internet and are regularly updated, the last revision was made in 20196. As part of the GBD study, an international expert group calculates estimates of the prevalence of hearing disorders globally and by individual regions, subregions, gender, age and severity. To calculate, data from population studies and articles included in systematic reviews are analyzed, and detailed data is requested from researchers if necessary [16-18].

Despite the fact that the GBD study is based on the results of previously conducted population studies, comparison with more up-to-date data will help improve the methodology of subsequent assessments. The aim of the study is to compare the data of a population epidemiological study of the prevalence of hearing disorders in schoolchildren and the estimates of the Global Burden of Disease study on the example of the Republic of Yemen.

2. Patients and Methods

The data was extracted from the GBD open database on the prevalence of hearing disorders among children aged 5-9 years in the Republic of Yemen in 2009. The data obtained were compared with the results of a population study of the prevalence of hearing disorders among primary school students aged 6-9 years in the city of Sanaa of the Republic of Yemen in a sample of 2,200 children conducted in 2009-2010. At the first stage, a hearing test was performed using an AD 229b audiometer in a screening mode in school conditions. Each ear was presented with a tone intensity of 20 dB with a frequency of 500, 1000, 2000, 4000 Hz. The absence of a reaction at least at one frequency on one or both sides was assessed as a "failed" result. At the second stage, these children underwent a complete audiological diagnosis (tonal threshold audiometry for air and bone conduction at frequencies 125-8000 Hz, tympanometry, otoscopy) in a specialized center. The criteria for determining hearing loss in both studies are given in Tabl 1.

3. Results

According to the GBD study, the prevalence of bilateral hearing impairment among children aged 5-9 years in the Republic of Yemen in 2009 It was estimated at 2.2%, or 2,228 cases per 100,000 of the corresponding population (95% uncertainty interval (IN) 1,828-2,626) with a predominance of mild hearing loss – 1.4%, or 1,415 cases per 100,000 of the corresponding population (95% IN 1,167-1699) (Table 2). According to According to a population study, the prevalence of all hearing disorders with an audibility threshold of more than 25 dB among children aged 6-9 years in the Republic of Yemen was 10.6%, of which 6.8% were unilateral, 3.8% were bilateral (Table 3). In the study sample, all identified cases of hearing loss corresponded to mild and moderate degrees. Among the identified hearing disorders, unilateral conductive hearing loss accounted for 54% (126 cases), unilateral sensorineural hearing loss – 10% (24 cases), bilateral conductive hearing loss – 31% (72 cases), bilateral sensorineural hearing loss – 2% (5 cases). Bilateral conductive hearing loss on the one hand and sensorineural hearing loss on the other was detected in 7 children (3% of cases). In accordance with the GBD hierarchy, otitis media, age-related and other hearing disorders (including sensorineural hearing loss), congenital ear abnormalities and meningitis are distinguished among the causes of hearing disorders. Thus, according to GBD estimates, among children aged 5-9 years in the Republic of Yemen, the prevalence of hearing impairment due to otitis media is 1.4% (1,416 per 100,000 children), sensorineural hearing loss is 0.7% (720 per 100,000). Congenital anomalies of the ear are the cause of hearing loss in 54 children per 100,000 in this age group. The prevalence of hearing loss due to meningitis is estimated at 8 per 100,000. In the structure of the causes, 2/3 are hearing disorders due to otitis media, 1/3 are sensorineural hearing loss (Table 4). Table 1 Criteria for determining hearing loss and classification by severity in the GBD study and population study.

Table 1. Hearing loss identification criteria and severity classification in the GBD study and population based study.

Criteria	Global Burden of Disease	Population-based research
Two - sided /one - sided	two - sided	two - sided ,one - sided
Hearing impairment (average threshold at 0.5, 1, 2, 4 Hz)	>20 дБ	> 25 дБ
Severity		
mild	20-34 дБ	25-40 дБ
moderate	35-49 дБ	41-55 дБ
moderate-severe	50-64 дБ	56-70 дБ
severe	65-79 дБ	71-90 дБ
deep	80-94 дБ	
deafness	>=95 дБ	>90 дБ

Table 2. Distribution of abnormalities of hearing by severity among children aged 5 to 9 years in the Republic of Yemen,estimated by the Global Burden of Disease study.

Degree of hearing loss	Number of cases per 100 000 population	95% IN	Fraction,%
Mild	1415	1167-1699	63
Moderate	440	281-613	20
Moderate-severe	131	75-203	6
Severe	70	39-115	3
Deep	106	63-164	5
Deafness	64	36-101	3
All cases	2228	1828-2626	100

Table 3. Prevalence of hearing loss among children aged 6 to 9 years in the Republic of Yemen according to the population based study.

	Number of cases	Fraction,%	Share in the sample (n=2200), %
One - sided	150	64	6,8
Two - sided	84	36	3,8
All cases	234	100	10,6

Table 4. Cause of hearing loss profiles among children aged 5–9 years in the Republic of Yemen as estimated by the Global Burden of Disease study.

Reason	Number of cases per 100 000 population	95% IN	Fraction,%
Otitis media	1446	1194-1721	65
Sensorineural hearing loss	720	473-1039	32
Congenital anomalies of the ear	54	16-123	2,5
Meningitis	8	2-12	0,5

All cases	2228	1828-2626	100

Table 5. Cause of hearing loss profiles among children aged 5 to 9 years in the Republic of Yemen as estimated by the population based study.

Reason	Number of cases	Fraction (n=234)	Prevalence (n=2200)
Exudative otitis media	131	56%	6%
Perforation of the eardrum	40	17%	1,8%
Chronic otitis media with suppuration	39	17%	1,8%
Eustachian tube dysfunction	28	12%	1,3%
Sensorineural hearing loss	36	15%	1,6%

In a population study, the prevalence of middle ear pathology was revealed in the etiological structure of hearing disorders among schoolchildren with confirmed hearing impairment: in 56% of cases, exudative otitis media was diagnosed, in 17% – perforation of the eardrum, in 17% – chronic otitis media with suppuration. Auditory tube dysfunction was detected in 12% of cases, sensorineural hearing loss – in 15%. It is worth noting that one child could have different pathology of the hearing organ. Thus, the prevalence of exudative otitis media in the study population was 6%, perforated otitis media and chronic otitis media with suppuration -1.8%, auditory tube dysfunction – 1.3%. Unilateral and bilateral sensorineural hearing loss occurs in this population with frequency 1.6% (Table 5). In the study sample, 1% of children (21/2200) had sulfur plugs, after removal of which the auditory function was restored, so these cases were not included in the general analysis. Congenital anomalies of the ear and cases of hearing impairment due to meningitis were not detected in the population study, which is in accordance with the sample size.

4. Discussion

The problem of timely detection of hearing loss is due to its non-obviousness both for persons with hearing impairment themselves and for their environment, especially in the children's population. In the present paper, the prevalence of hearing impairment is compared based on a population study of schoolchildren in the Republic of Yemen and global estimates in a similar population. Similar comparative publications on this pathology were not found by the authors. According to the GBD study in the Republic of Yemen, bilateral hearing impairments among children aged 5-9 years occur with a frequency of 2.2%. According to the results of a study of a population of children similar in age and year of study, the prevalence of bilateral hearing loss is higher and is 3.8%. The data obtained are consistent with a number of other population studies in developing countries, according to the results of which the prevalence of bilateral hearing loss was detected with a frequency of 1.8–5.7% [19-23]. In Zimbabwe, C. Pedersen et al. Data were obtained on the prevalence of all unilateral and bilateral hearing disorders in children at the level of 10.6%, which fully corresponds to the presented results from Yemen [24]. Based on the data obtained in the GBD study, 2/3 of all cases of hearing impairment account for mild hearing loss. In a population study in the Republic of Yemen, only mild and moderate hearing impairments were detected. According to the GBD results, it was possible to expect the detection of 2,200 children up to 4 cases of severe hearing loss and deafness in the study sample. Their absence can be explain the design of the study, which was conducted in mass schools where children with profound hearing loss do not study. The generally recognized problem of comparing different studies of the prevalence of hearing disorders is recognized by different criteria of hearing loss. The most relevant works evaluate the frequency of hearing loss in the study sample based on several criteria. Thus, C. Pedersen et al. In 2022, data on the prevalence of hearing disorders in children were published at the level of 4.2% with hearing thresholds of more than 25 dB and at the level of 0.4% with hearing thresholds of more than 30 dB in a better hearing ear [24]. A meta–analysis of population studies from countries with different socio-economic levels showed the prevalence of childhood hearing loss of 2.2% with hearing thresholds in the better-hearing ear of more than 25 dB, 0.9% - more than 40 dB [14]. According to the results of a similar meta–analysis of 21 studies in central and South Africa, data were obtained on the frequency of childhood hearing loss of 17% with hearing thresholds of 20 dB, 2% - more30 dB [25]. Among school-age children, especially in elementary grades, the leading cause of hearing disorders is the pathology of the middle ear. Both according to the results of population studies and GBD estimates, purulent and non–purulent otitis media cause at least 2/3 of all hearing disorders in early school age, accounting for up to 85-95% in the etiological structure of hearing loss [19-22]. At the same time, the prevalence of exudative otitis media in the population of schoolchildren according to the presented study is 6% in Yemen, according to F. Mahomed Asmail et al. in South Africa – 7.5% [20]. Sensorineural disorders in the population of children of early school

age are less common, their prevalence in the Republic of Yemen is estimated at 0.7% according to GBD data, 1,6% – according to the results of a population study. A possible limitation of the presented population study is the insufficient representativeness of the sample represented by primary school students of the capital of the Republic of Yemen, the city of Sanaa. As a rule, residents of metropolitan regions are in more favorable socio-economic conditions, which contributes to a lower incidence, including ear diseases.

5. Conclusions

The comparison of the GBD study data and the population study of the prevalence of hearing disorders among schoolchildren of the Republic of Yemen showed the comparability of the results of both studies. Bilateral hearing disorders occur in 2.2–3.8% of primary school students, taking into account unilateral disorders, the prevalence increases to 10.6%. Of these, at least 65% have conductive hearing loss due to the pathology of the middle ear. The data obtained will improve the effectiveness of providing assistance to children with ear diseases and hearing disorders.

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The use of artificial intelligence: the article is written without the use of artificial intelligence technologies.

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Clinical case

Psychological Factors of Effectiveness in Speech Rehabilitation After Laryngectomy: a Case Study

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Abstract:

Relevance. The purpose of the study was to reveal and describe psychological factors of effectiveness in voice rehabilitation after laryngectomy. Authors submit the results of speech rehabilitation work of speech pathologist with patient M., who achieved alaryngeal communication without any limitations under conditions of extremely problematic state of health.

Description of the clinical observation. Rehabilitation of voice function was conducted according to an esophageal speech training method. To study in detail the motivation of patient M., a narrative psychological interview and standardized tests were conducted. Despite the poor health, a lot of complex diagnoses and poor preconditions for speech rehabilitation, patient M. showed great success in alaryngeal communication, which is not always typical for patients with less severe conditions for rehabilitation. **Conclusion.** The study shows that the effectiveness of the alaryngeal speech rehabilitation course after laryngectomy can be ensured by meaning work of personality, designing creative motivation, focusing on asserting and affirming life, and creating new meanings.

Keywords: psycho-oncology, speech alaryngeal, laryngectomy, interview psychological, speech-language pathology.

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1. Introduction

The problem of laryngeal cancer is currently unique in oncology. It is related to providing medical care for patients and developing and carrying out rehabilitation activities [1 – 6]. The treatment results, especially in patients without regional metastasis, are entirely satisfactory (about 80%). However, many researchers denote refusal of surgical treatment as one of the causes of mortality in laryngeal cancer. More often, the main motive of such a decision is a profound disability resulting from surgery. The most severe consequence of laryngectomy is the loss of sonorous speech ability and impaired respiratory function. Patients' appearance changes and they lose the ability to communicate verbally. Aphonia and breathing changes ensue – all of it leads to loss of communicative function of speech and the emergence of negative psychological personality straits. As a result, the patient faces many difficulties returning to work and active social life [7, 8].

Therefore, one of the most critical postoperative tasks and rehabilitation directions for patients, who have undergone a laryngectomy, is the voice function recovery, which gives patients the opportunity to return to social life and work. Most researchers believe that voice function recovery after such surgeries is a priority direction of rehabilitation: voice function should be recovered after each laryngectomy [9 – 11].

Since the first laryngectomy (1873, T. Billroth), the search for the most effective ways of voice function recovery after such surgeries continues. There are several main directions of voice function rehabilitation. Among the most popular forms of voice rehabilitation, there are esophageal speech and tracheoesophageal speech.

Esophageal speech (ES) is a method of speech production that involves oscillation of the esophagus when air is injected into the upper esophagus and then released in a controlled manner to create a sound for producing sonorous speech. It is a learned skill that requires specific work of the patient with a speech pathologist.

In a tracheoesophageal speech (TES), a surgical fistula (TE puncture) is created in the wall separating the trachea and esophagus, allowing the placement of a phonatory prosthesis for producing sonorous speech.

Using an artificial larynx (AL) – a handheld device that is pressed against the neck and creates vibrations that produce a sound while the patient moves his or her mouth to create speech.

An issue status of voice function rehabilitation and a variety of speech rehabilitation methods after laryngectomy make it necessary to choose the preferred speech rehabilitation method not only after discussion within a multidisciplinary team but with patient informing about all available variety of speech rehabilitation methods after laryngectomy. If medical indications allow several speech rehabilitation methods – it is the patient's prerogative to choose the one to be used.

Voice prosthetics and tracheoesophageal bypass after laryngectomy are common in the world [12 – 17]. Nevertheless, esophageal speech is associated with a significantly higher physical functional capacity [18]. In Russia, for example, patients often refuse to use voice prosthetics and tracheoesophageal bypass – due to short periods of using them and the recurrent need to replace the prosthesis. They prefer to seek help from speech pathologists as a traditional method of voice function recovery by learning to use esophageal speech [19]. This method is characterized by non-invasiveness (there is no need for a new surgery to recover speech). As a result of speech therapy sessions, the persistent skill of using the mechanism of outlaryngeal phonation replacement is developed.

Modern scientific research shows that using methods of voice function recovery in patients who have undergone a laryngectomy can increase the effectiveness of voice rehabilitation up to 92%. It can also reduce the number of patients recognized as disabled by disease by 20%; it can return the working-age patients to the workplace and significantly improve their social adaptation and quality of life [20, 21]. According to our data, the vast majority of patients (94%) who completed a full speech rehabilitation course – were discharged with full recovery or significant improvement of speech function.

Cancer diagnosis certainly is a traumatic factor. However, a person is not only exposed to stressors – but has the ability to show resilience and cope with psychological trauma [22 – 25]. Modern psychological researches show more and more proof that there are three main types of trauma effects: disorder – resilience – growth [26, 27]. Patients after laryngectomy suddenly find themselves in an unaccustomed life, but our narrative psychological interviews, conducted with such patients, show that most of them (77%) are future-oriented and have clear ideas of what they will do after leaving the hospital.

We consider the cooperative work of a psychologist and a speech pathologist to play an essential role in the process of alaryngeal speech rehabilitation within the multidisciplinary approach, which provides for the optimized method of speech rehabilitation. However, it cannot be denied that speech rehabilitation results depend a lot on the patient's desire and motivation to recover the lost speech.

2. Patients and Methods

In this sense, indicative, in our opinion, is the particular case of alaryngeal speech rehabilitation in the patient M., 59 years old, admitted to the Oncology Department №2 (head and neck tumors) of Central Clinical Hospital "RZD-Medicine" with a diagnosis of laryngeal squamous cell carcinoma. 10.08.16 – lower tracheostomy was performed in case of larynx tumor stenosis. Total laryngectomy and resection of the thyroid gland were performed on 23.11.16.

On the 7th day after the operation, there was an episode of gastric bleeding, the source of which was acute ulcers of the stomach and duodenum. On 02.12.16, there was a relapse of stomach bleeding. According to the ulcer's size, amount of blood loss, ineffective attempts of endoscopic hemostasis – emergency gastrectomy was performed 02.12.16. Postoperative period without complications.

The patient entered the course of speech rehabilitation with complaints of expressed difficulties in verbal contact. Before this, discussing the opportunities of speech rehabilitation, the multidisciplinary team decided to reject tracheoesophageal speech due to its invasiveness. Patient M. was offered to choose from the two methods – electrical larynx or esophageal speech. We will note that the success of voice recovery with esophageal speech was also uncertain for the multidisciplinary team due to the burdened surgical history. However, patient M. chose esophageal speech.

09.08.2017 Local Ethical Committee approved the application of the selected speech rehabilitation method for patient M. Patient M. has given his written informed consent. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

During the first consultation on 14.08.2017 communication was carried out partly in writing, actively using non-verbal communication such as gestures and facial expressions. The initial conversation was marked by spontaneous, uncontrollable outbursts of sounds/esophageal speech. Af-

ter the conversation, which reflected the essence of the disorder and the possible ways of its correction, the patient confirmed his intention to recover the lost sonorous speech with the help of pedagogical methods of rehabilitation of verbal communication (esophageal speech).

The pedagogical method of speech rehabilitation after laryngectomy is based on the development of the mechanism of laryngeal phonation replacement, where the sound generator is the folds of the mucous membrane of the mouth of the esophagus. Timbral coloration and the possibility of phonemes formation are carried out by the preserved anatomical structures of the upper resonator. The main difficulty in using this speech method is to provide the energy base of the phonation, delivery of an air jet. The esophagus takes the air tank's function, but, of course, it cannot provide the required volume of exhalation, like that of a normal speech. In this regard, the success of recovery in the case of patient M. was highly doubtful due to the presence of several factors: a history of strokes in the basin of the anterior cerebral artery from 2000; myocardial infarction from 05.12.16; operations on the organs of the gastrointestinal tract; general somatic weakness. All of these could have a negative impact on the formation of a new sound generator and the energy base of the phonation.

Alaryngeal speech rehabilitation was conducted according to an esophageal speech training method.

Logopaedic work was carried out in four stages:

preparatory stage – conversations, explaining to the patient his health status and possibilities to rehabilitation, work on breathing;

formation of mechanisms of laryngeal speech replacement (we used various techniques that allow the patient to receive the first short sound of voice both on the traditional material of consonants P, T, K and on the material of vowels);

mastering skills of using alaryngeal speech on the easy speech material within elementary everyday situations;

working on automating capabilities of using alaryngeal speech and introducing it to everyday speech (extending sound range, improving modulations, training voice endurance, etc.).

Despite the poor health, many complex diagnoses and poor preconditions for speech rehabilitation, patient M. worked hard to form alaryngeal speech. The therapy was conducted by a speech pathologist with the support of a psychologist.

Patient M. underwent two courses of speech therapy for 10 days each. During each course, he was trained in 3 sessions lasting 5-7 minutes daily, taking into account his somatic weakening. To consolidate developed skills, independent work tasks were proposed and were recommended to be performed for 5 minutes 8-10 times daily. During the one-month interval between the courses, an independent work program was also proposed to consolidate using alaryngeal speech. In addition, patient M. had an opportunity to contact the speech pathologist online in case of any questions while completing tasks.

Patient M. did not miss classes, performed all tasks assigned by the speech pathologist, and showed great success in speech rehabilitation, which is not always typical for patients with less severe conditions for rehabilitation. At the end of the course, patient M. used verbal communication successfully. An acquired skill allowed him to use alaryngeal communication without difficulties, including telephone communication. The sound had sufficient strength and volume, the duration of the sounding phrase was 4-5 words. The maximum phonation time of vowel sounds was 1.06 seconds. So, logopaedic work with patient **M**. was completed with high efficiency in the esophageal speech development in a relatively short time despite the poor health and poor preconditions for speech rehabilitation.

During the speech rehabilitation process, we suggested an essential role of the psychological features of patient M. in the excellent results of his rehabilitation. To reveal and describe them, at first, we conducted a narrative psychological interview. We asked patient M. to make narratives, talk about his life, including a number of significant aspects of life situation: about his diagnosis history; about his family, about his work, about his friends and acquaintances; about his relationship with others after diagnosis and surgery; about his plans after hospital discharge. Based on the results of the narrative psychological interview, we decided to use (additionally) the Achievement motivation test and the Affiliation motivation test, developed by A.Mehrabian and modified in Russia by M.Sh.Magomed-Eminov [28, 29] to further investigate his motivation.

3. Results

According to the analysis of narrative psychological interview with patient M., it revealed, that most of his statements, despite the extremely problematic state of health, are directed to the life, to the future, to creation: "I want to live," "I have a desire to work", "I love my grandson", "I love my family," "I will restore order in the house" and others. Patient M. did not speak negatively or accusingly about anyone or anything (the most "negative" of his statements about the people around him: "there are those who shun"; but at the same time, basically: "the relationship has not changed, I was respected before, and now"). While it is objectively difficult, he is set on creating

something new, contributing to his grandson's upbringing and the life of his family as a whole. Then we resorted to the Affiliation motivation test, which showed us an unexpected result: a low affiliative tendency in combination with a high sensitivity to rejection. According to the standard interpretation, patient M. actively avoids contact, seeks solitude, and is a difficult patient for a speech pathologist. But let us return to the analysis of the narrative psychological interview and, specifically, pay attention to the results of the Achievement motivation test that showed striving for success as his result tendency. Contrary to illness, patient M. is oriented to success in anything he does, he attaches great value to his family and tries to participate in its everyday life, he constructs his life world in new conditions for himself, aimed at the continuation of life, creation, creativity, and rehabilitation. We observe a comprehensive motivational combination: striving for success and high sensitivity to rejection in conjunction with his desire to live and work, participate actively in his family's life – and we suggest that such combination became an important factor of success in alaryngeal speech rehabilitation results of patient M.

4. Discussion

Not long ago, the very fact of turning to an oncologist tore the person from an existing worldview and transformed him/her into a stereotype of an "oncological patient", inseparably linked to the notion of inevitable death and the formation of the motive for preparing for death, pushing aside all other leading motives. Modern possibilities of medicine allow us to talk about shifting the emphasis in the lifeworld of a cancer patient from waiting for the end to continue living and building his/her life, relationships with self, other people, and the world around – the world with the illness, operation and the resulting disorder. The illness has changed the world in which the person lived before, into the world in which he needs to make peace with his condition and build life anew [22 – 25].

5. Conclusions

Our studies, as well as a particular case of a patient M., show that the success of a speech rehabilitation course (which is not a one-time process, but long work, requiring sustained motivation) can be ensured by designing creative motivation, focusing on asserting and affirming life and creating new meanings. Results of the case study allow us to determine the importance of rehabilitation motivation for effective alaryngeal speech rehabilitation after laryngectomy. We can also confirm the critical role of meaning work of personality in case of serious illness or complex defect that demand significant efforts of the speech pathologist and the patient in the speech rehabilitation process.

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The use of artificial intelligence: the article is written without the use of artificial intelligence technologies.

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Article

Sclerotherapy Impact in Modern Treatment Methods of Children With Extracranial Venous Malformations

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Abstract:

Relevance. Venous malformation is an abnormal development of the collecting blood vessels based on the vascular wall formation disorder, which occurs during the peripheral vascular network differentiation. According to various sources, venous malformation prevalence ranges from 1 to 2 in 10 000 newborns. Head and neck VMs significantly reduce patients' quality of life, causing severe functional and aesthetic impairments. Sclerotherapy is an effective treatment method for children with venous malformations. In recent years, bleomycin has been the most commonly used sclerosant. It is a glycopeptide antibiotic synthesized by Streptomyces verticillus and belongs to cytostatic medications. It is successfully used for venous malformations sclerotherapy, also in children.

Purpose. The study aimed to improve the sclerotherapy method by combining the advantages of foam-form sclerotherapy and bleomycin.

Materials and methods. We provided experimental and clinical stages of the study. There were 48 samples of rats' external femoral veins morphologically examined in the experimental stage. We divided the rats into 2 groups depending on the administrated agent: the first group – 3% polidocanol (lauromacrogol 400), the second group – bleomycin-polidocanol mini-foam composition. The histological assessment identified the changes in the vein endothelium, necrosis of tissue structures, cell dystrophy characteristics. In the clinical stage we also divided patients into 2 groups following the same treatment protocols as in the experimental stage. The results assessment included presence or absence of clinical manifestations and magnetic resonance imaging malformation features.

Results. In the experimental stage the first group, in which the bleomycin-polidocanol mini-foam composition was used, demonstrated more pronounced irreversible changes in the venous vessel endothelium compared to the second group. In the clinical stage the second group where bleomycin-polidocanol mini-foam composition was used showed rather good and satisfied results than in the group where standard polidocanol technique was carried out.

Conclusions. The study revealed that the proposed method of venous malformation sclerotherapy using new bleomycin-polidocanol mini-foam composition is more effective than the polidocanol foam-form sclerotherapy. The new method is highly effective, minimally invasive, safe and can be considered an independent treatment method in children with head and neck venous malformations.

Keywords: venous malformation, sclerotherapy, bleomycin, polidocanol, vascular malformations, cytostatic agents, endothelium, rats, sclerosing solutions, quality of life.

1. Introduction

Venous malformation (VM) is an abnormal development of the collecting blood vessels based on the vascular wall formation disorder, which occurs during the peripheral vascular network differentiation. VMs are slow-flow vascular anomalies characterized with poor smooth muscle layer development. The VM endothelium is not prone to proliferation. However, clinical manifestations

of the disease are associated with local hemodynamic disturbances resulting from the inclusion of the malformed vascular bed into the circulation. Hemodynamic disturbances are characterized by local venous stasis with intravascular chronic coagulopathy development resulting in calcinates and phleboliths formation. The incidence of VM according to various data sources ranges from 1-2 cases per 10,000 newborns [1, 2] up to 1-4% of the population [3]. According to the U.S. consolidated data, venous malformations occur in 48% among all types of vascular malformations [4]. According to the literature, VMs are localized in the head and neck area with the frequency from 14.7% [5] up to 74% [6]. The venous malformations incidence among all vascular malformations in children is 21.5% [7]. The main pathogenetic mechanism of the disease is TEK gene mutation, locus 9p21.2 (short arm of the ninth chromosome). The TEK gene encodes the TIE2 protein, which is the intracellular domain of the tyrosine kinase receptor in endothelial cells; this protein functions as an angiopoietin I receptor. The TEK gene signaling pathway is the main factor in the formation of intercellular connections between the endothelium and the smooth muscle layer in venous vessels development. The TEK gene mutations are the major causes of an abnormal venous formation [8]. Clinical manifestations of head and neck venous malformations vary from the limited oral mucosa phlebectasis to the extensive diffuse angiomatosis spreading to several anatomical areas. Head and neck VMs, in addition to functional disorders, cause the aesthetic defects, thus, significantly hampering patient's social adaptation. The majority of authors recognize a surgical method to treat VM [9, 10, 11]. The authors note the angiomatous tissues radical excision difficulty due to the high risk of intra- and postoperative bleeding. Also, an excision of significantly sized malformation can be compromised due to the high aesthetic requirements of maxillofacial surgery [12, 13]. In addition, the frequency of VM's recurrences is high [14].

According to mentioned above the treatment tactic of patients with VM of head and neck should be pathogenetically reasonable and based on principles of:

1. Efficiency;
2. Minimal invasivness;
3. Safety.

The sclerotherapy method is fully corresponded to these criteria. Sclerosing therapy or sclerotherapy is an alteration on the venous malformation endothelium using a chemical substance to destroy its intima, followed by venous wall adhesion and, as a consequence, removal of pathological veins from the blood flow.

Sclerotherapy advantages are:

1) Selective effect on decompensated collective blood vessels (in case of endovascular agent injection);

2) Minimally invasive procedure;

3) Malformations management in complicated localization;

4) The procedure can be carried out without anesthetic assistance in elderly patients;

5) Absence of postoperative defects and scars.

Foam-form sclerosing therapy has been widely spread in clinical practice since 1993. It is based on the irregular bubbles dispersion with increased sclerosing agent concentration on the surface injection into the vessel lumen, and, as a result, has maximal sclerosing effect.

The described form has a number of advantages:

1) "Empty vein" effect by evenly displaced blood from the venous malformation lumen;

2) Sclerosing solution and the VM endothelium contact prolongation by keeping the agent in the vessel lumen until the bubbles decay, whereas the native agent form rapidly dissolves in the blood, losing its initial effectiveness;

3) Administrated agent's amount reduction;

4) Persistent pronounced vasospasm after the sclerosing solution foam-form injection into the vessel's lumen contributes to the development of sclerophlebitis, which is a predictor of VM persistent remission.

Considering foam-form sclerotherapy advantages, not all sclerosing agents are suitable for foam formation. Only detergents are suitable for this purpose due to its lyophilic center that reduces surface tension. However, recently, other pharmacological agent groups have become widespread. A large data amount about using bleomycin in the treatment of children with venous malformations is recorded in the foreign and domestic literature. Bleomycin is a glycopeptide antibiotic synthesized by Streptomyces verticillus and belongs to cytostatic medications. This agent is being successfully used for venous and lymphatic malformations sclerotherapy, also in children.

In order to improve the sclerotherapy method for venous malformations of the head and neck, we combined the advantages of foam-form sclerotherapy and the effectiveness of the bleomycin.

2. Materials and Methods

The presented mini foam composition is prepared of 3 components which are polidocanol (Aethoxysklerol 3%, Kreussler Pharma, Germany), bleomycin and an atmospheric air. 3% Aethox-

ysklerol and the same amount of bleomycin solution are mixed in a three-component syringe according to the Tessari method (Tessari L. 2000) with an atmospheric air in the second syringe. The optimal ratio of bleomycin-polidocanol-air is 1:1:4. The detergent component molecule of the foam composition (polidocanol) is a dipole with a lyophilic center and hydrophilic and hydrophobic sites at the opposite ends. Due to this feature, some of these molecules are fixed by the hydrophobic part to the membrane of endotheliocytes, causing denaturation of proteins and destroying the vascular endothelium with an extended exposure of the basal membrane. The second component of the mini foam composition (bleomycin) enhances the damaging effect on the malformation endothelium, complementing the total sclerosing effect and reducing the risk of disease recurrence by local angiogenesis suppression.

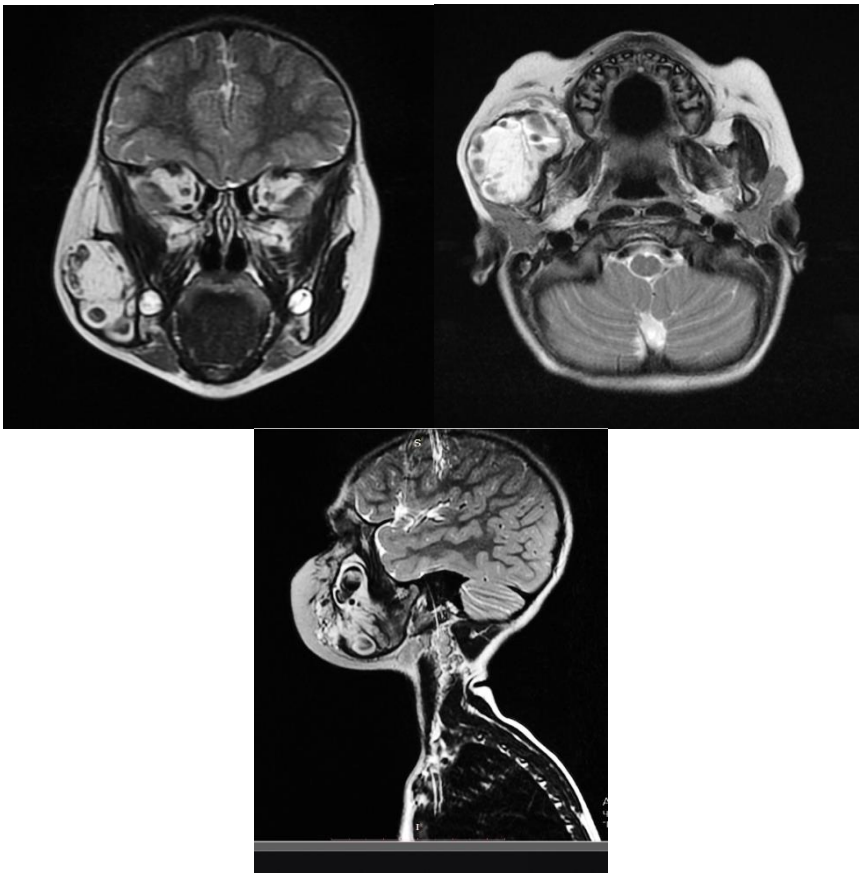

Figure 1. Magnetic resonance imaging of a patient with extensive venous malformation of the right parotid, buccal regions and right pterygopalatine fossa

The study was approved by the Ethics Committees of A.I. Evdokimov Moscow State Medical University of Dentistry and Medicine (MSMSU). In the period from 2016 to 2021 in A.I.Evdokimov MSMSU Clinical center of Maxillofacial and Plastic surgery we treated 62 patients 0 - 18 years of age diagnosed with venous malformation of head and neck. The diagnosis was based according to general examination data: interview, anamnesis, physical examination, functional tests (filling and compression symptoms, Valsalva maneuver) and additional methods of examination. All patients underwent Doppler color flow mapping ultrasound. Doppler color flow mapping should be the primary link in the diagnostic of this pathology, since it has several advantages: it is noninvasive, does not require special patient preparation and anesthesia. Also, ECHO-graphy combined with color flow Doppler is a rather informative technique in VM diagnostic: it allows not only revealing the vascular component of the malformation, but also determining the blood flow type and angioarchitectonics of the malformation. Ultrasonography also detected the presence of cavities sharply increasing in volume when performing compression tests. Thrombi, including those with signs of organization, and phleboliths were detected echographically.

Magnetic resonance imaging (MRI) is the most informative method to diagnose the venous malformations (Fig.1). This technique is highly informative to determine the malformation's size, localization and configuration. It also allows determining the volume of venous hyperemia in the affected area. No bolus contrast enhancement is required; the malformation is clearly visualized on T2-weighted image. At low blood flow rates, it is possible to detect signs of sedimentation. The

necessity of providing head and neck soft tissue MRI in venous malformations of all sizes and vocalizations is due to the probability of intra- and extracranial lesion foci, which may not manifest clinically. However, this highly informative technique has its disadvantages: the study is time-consuming and can be only performed under general anesthesia in young children.

Multi slice computer tomography (MSCT) angiography was additionally performed in 5 patients with extensive VMs. This method was not highly informative in VM diagnostic, a moderate accumulation of contrast agent in the venous cavities was detected 5 minutes after the injection. The method is also characterized by high radiation exposure and the need for intravenous injection of a contrast agent. In young children this study can be performed only under anesthesia support (Fig.2).

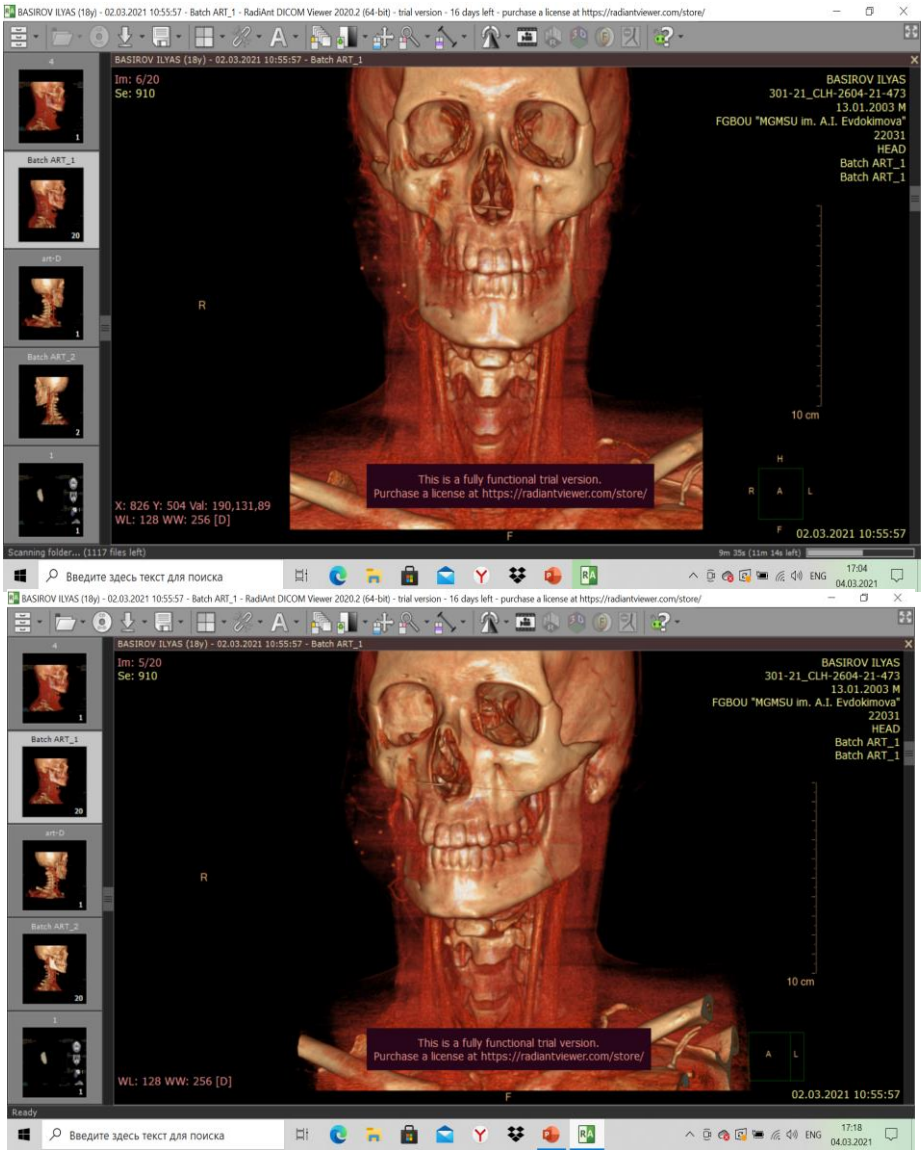

Figure 2. MSCT angiography of a 17-year-old patient with extensive venous malformation of the right side of the face. 3D reconstruction

All patients underwent sclerosing therapy: 41 patients were treated using the standard "foam-form" technique with 3% polidocanol solution and 21 patients - using the new bleomycin-polidocanol mini foam composition. The method was carried out as follows (FIg.3): under inhalation anesthesia, we performed puncture of one of the venous malformation cavities with an injection needle (two needles for extensive malformations) under ultrasound navigation; after the aspiration test, the foam was injected through one needle. The volume of injected sclerosant was calculated according to the formula: Vo = x A x B x C, where: Vo - malformation volume, cm; A - height, cm; B - width, cm, C-thickness, cm. In most cases, foam leaking through the second needle is determined, which is one of the signs of intravascular needle placement. The needle position does not change

throughout the procedure, the foam spreads in full volume through all the VM cavities, which is confirmed by intraoperative ultrasound monitoring. After the necessary volume of the drug is injected, the needles are removed and manual compression is performed for 5 minutes. The technique did not differ in the studied groups.

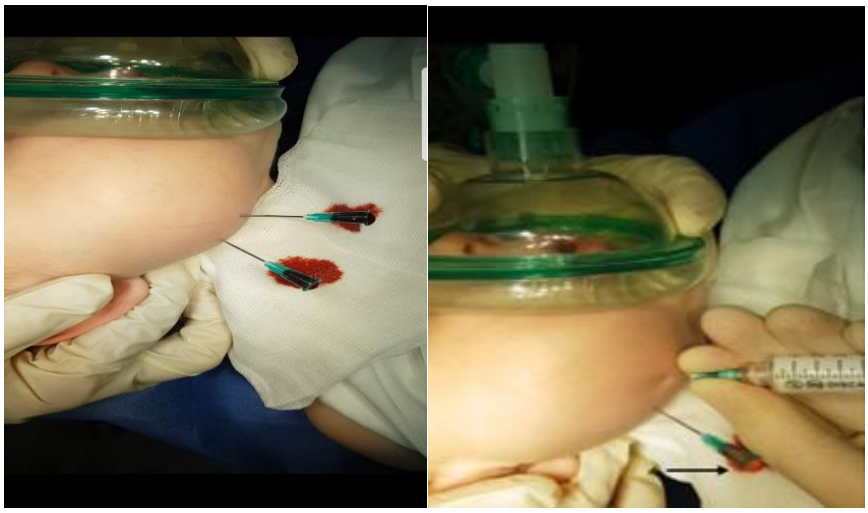

Figure 3. The process of performing VM sclerotherapy with the new bleomycin-polidocanol mini-foam composition. The arrow indicates the foam leaking through the second needle.

The number of procedures varied from 1 to 6. The time interval between the sclerotherapy procedures ranged from 30 days to 4 months, depending on the severity of the lesion, stage of treatment and social factors. An ultrasound was performed 30 days after the surgery in order to decide on the next stage of treatment. In the case of pathological vascularization absence according to the ultrasound findings, the patient underwent a control MRI scan. We performed MSCT in 12 patients on the third day after surgery. Numerous air bubbles evenly filling the entire volume of the malformation were visualized (Fig. 4). It should be noted that during paravasal injection of the foam form of the drug, air bubbles are concentrated strictly in the place of needle puncture. Thus, this method can be used as a postoperative control in the treatment of VM.

For morphological assesment of the proposed VM sclerotherapy efficiency, an experimental study was performed. Wistar laboratory rats of both genders with an average body weight of 180-220 g were used in the experiment. All experiments were performed according to the "Statute on legal and ethical principles of medical and biological research" (VAK Bulletin of the Ministry of Education of Russia. 2002. №3. P. 77-75); "Rules for work with experimental animals" (Appendix to the Order of the Ministry of Health of the USSR, August 12, 1977, N 755) and the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes", March 18, 1986. In order to assess morphological changes in the studied site we injected sclerosing agents into the intact tissues of laboratory rats: external vein of right and left hind limbs.

A total of 12 rats were involved in the experiment and divided into 2 groups depending on the injected agents: group 1 - 3% polydocanol (lauromacrogoal 400), group 2 - new bleomycin-polydocanol mini-foam composition.

The animals were weighed and the amount of administered drugs was calculated. Medetomidine 0.05 ml/100 g was administered intramuscularly in order to provide anesthesia and zoletil 100 5 mg/100 g intramuscularly was also administrated 10 minutes later. The lower extremities were fixed and a tourniquet was applied. 0.2 ml of sclerosing agents were slowly injected into the external femoral vein through an insulin needle. The needle was removed, hemostasis was performed by finger compression. For morphological study, animals were removed from the experiment by intramuscular injection of zoletil 100 10 mg/100 g on the 7th day after the drug administration. Histological evaluation included revealing changes in the endothelial layer of the venous vessel, necrosis of tissue structures and cell dystrophy.

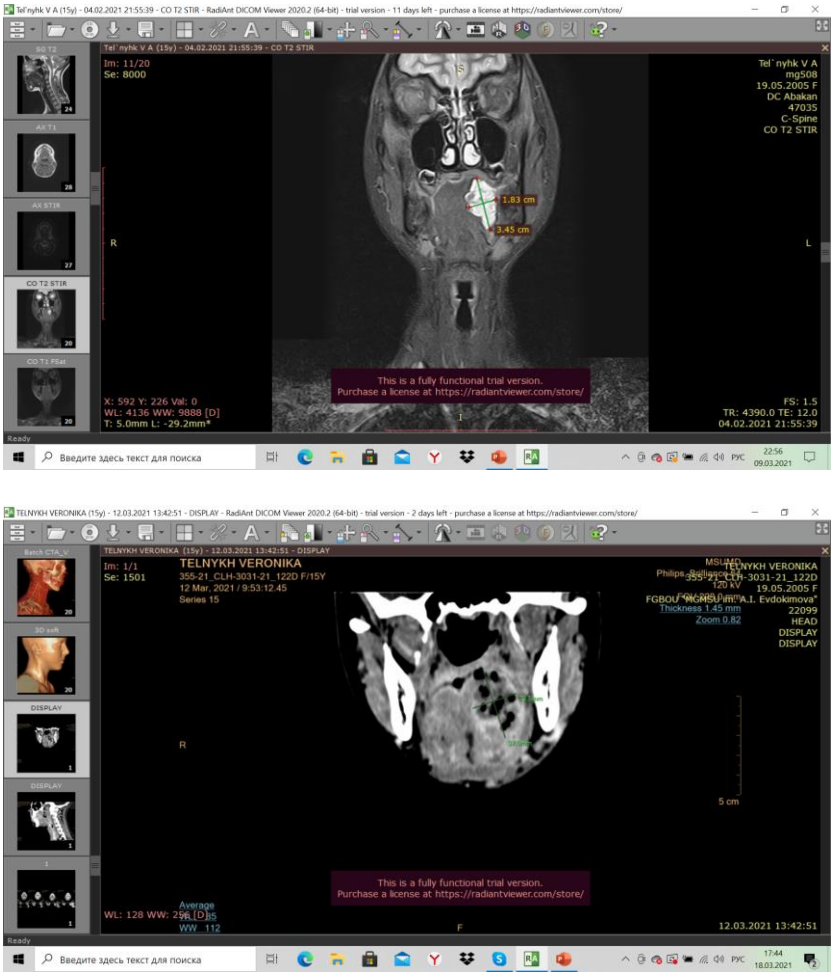

Figure 4. MRI scan of a 13-year-old patient with venous malformation of the tongue. MSCT of the same patient on the 2nd day after sclerosing therapy. Even distribution of gas bubbles over the entire volume of the malformation is visualized.

3. Results

3.1. Results of the clinical stage of the study.

The results were assessed as follows: absence of clinical manifestations and MRI features of malformation - good, clinical manifistation and malformation volume decrease according to MRI data - satisfactory, clinical manifestation persistence, absence of MRI dynamics - unsatisfactory. Good result was achieved in 33 patients (80%), satisfactory - in 6 patients (15%). In 2 patients (5%) we considered the result to be unsatisfactory. The results in the second group of 21 patients who underwent sclerosing therapy with bleomycin-polidocanol mini-foam composition were assessed in the similar way. The results were distributed as follows: good result was achieved in 19 patients (90.5%) and satisfactory result- in 2 patients (9.5%). We did not obtain unsatisfactory result in the group where bleomycin-polidocanol mini-foam composition was used. The results of the treatment of children are summarized in Table 1.

Bleomycin-polidocanol mini-foam composition in addition to its significant advantages such as minimal invasivness, selective effect on the pathological venous pool, absence of surgical trauma of the adjacent anatomical structures, has also the following advantages:

1.The combined effect of two sclerosing agents on the vascular endothelium significantly increases the sclerotherapy efficiancy;

2.Relapse probability decrease due to angiogenesis inhibition in the injection site of the composition;

3.This technique has been shown to be highly effective in large venous malformations (3 or more anatomical areas of the head and neck);

4.Surgeries that are necessary to achieve permanent irreversible sclerophlebitis of pathological venous vessels number decrease;

5.The total rehabilitation time of the child is significantly reduced (Fig.5).

Table 1. Sclerotherapy results

The agent	Average amount of sclerotherapy procedures	Obtained results			Total amount of patients
		Good	Satisfactory	Unsatisfactory	
Polidocanol foam-form	2.68	33(80%)	6(15%)	2(5%)	41
Bleomycin-polidocanol mini foam composition	1.46	19(90.5%)	2(9.5%)	0	21

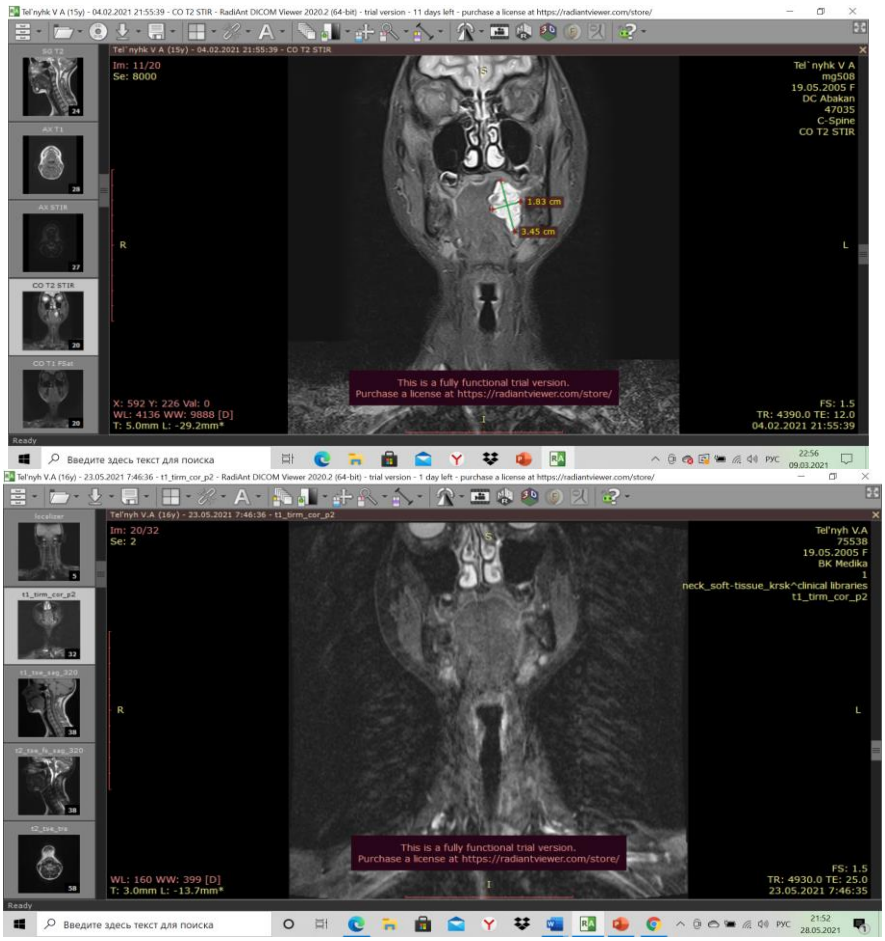

Figure 5. MRI of a 13-year-old female patient with venous malformation of the tongue. Before treatment (left) and after one session of sclerotherapy with the new bleomycin-polidocanol mini-foam composition (right - complete absence of pathological vascularization).

3.2. Results of the experimental stage of the study

Morphological study of 24 specimens divided into 2 groups depending on the injected drugs was performed: Group I - 3% polidocanol (lauromacrogol 400), Group II - bleomycin-polidocanol mini-foam composition. 12 specimens of external vein of Group I revealed different degrees of plasma impregnation and one case of vessel wall unwinding; the endothelium is preserved in 11

samples. In four specimens a collapsed lumen with "adhered" endothelium was detected. In 8 other samples the lumen was narrowed. In three samples a mixed clot was detected in the vein lumen.

12 specimens of external vein of Group II revealed different degrees of plasma impregnation and vessel wall unwinding; in 3 samples there was a collapsed lumen with "adhered" endothelium, and in the remaining 9 samples there was no endothelium and the vessel's lumen was dilated. There was a mixed clot in venous lumen in one specimen;

Comparative data by groups are presented in Table 2.

Table 2. Compatarive data of the groups

Changes characteristics in the vein	Specimens amount	
	Bleomycin-polidocanol foam composition	Polidocanol (lauromacrogol 400)
Complete absence of endothelium	18	2
Partial absence of endothelium	6	8
Totally preserved endothelium	0	6
"adhered" endothelium	6	8
Vein thrombosis	2	6

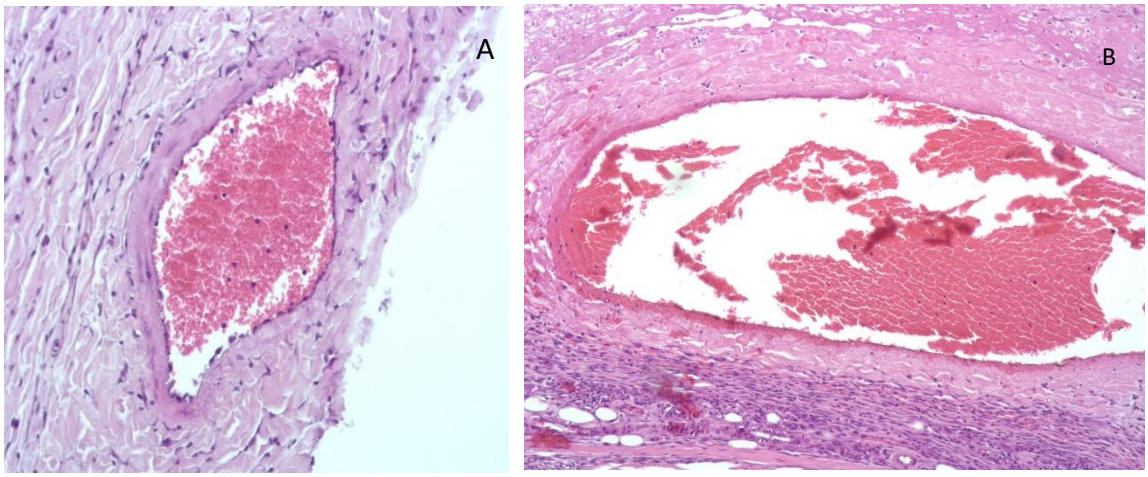

Figure.6. Comparison of external femoral vein specimens after polidocanol 3% (A) and new bleomycin-polidocanol mini-foam composition (B). Hematoxylin and eosin staining, magnification 200x. A – Partially preserved endothelium. B – Complete absence of endothelium

4 Conclusions

Clinical and experimental studies revealed that the proposed method of treatment of children with head and neck venous malformations using the new bleomycin-polidocanol mini-foam composition showed greater efficacy than "foam-form" sclerosing therapy using polidocanol. This method is highly effective, minimally invasive, safe and can be considered as a first-line method in the treatment of children with this pathology.

Author Contributions: Research concept and design - L.V. and O.Z., collecting and processing material - L.V, S.Y and A.M., writing and editing the text - L.V and A.M.

All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

The use of artificial intelligence: the article is written without the use of artificial intelligence technologies.

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Article

Mitochondrial Disorders and MRI of the Brain in Patients with Leukoencephalophathy with Brainstem and Spinal Cord Involvement and Lactate Elevation in Moscow Region

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Abstract: leukoencephalopathy with lesions of the brainstem and spinal cord and increased lactate levels (LBSL) is a hereditary autosomal recessive disease caused by a mutation in the DARS2 gene, with a heterogeneous lesion of the white matter of the brain involving the brainstem and spinal pathways, an increase in lactate in abnormal white matter. Objective. The purpose of the study is to evaluate the features of brain MRI and mitochondrial disorders in adult patients with PE-FMF. Material and methods. An observation of three adult patients from the Moscow region with a hereditary mitochondrial disease of leukoencephalopathy with damage to the brainstem and spinal cord and an increase in lactate level (LBSL) is presented. The diagnosis was confirmed by molecular diagnostics. An MRI examination of the brain was performed on an MRI tomograph with a magnetic field induction of 3.0 T For the cytochemical study of the activity of mitochondrial enzymes in peripheral blood lymphocytes, the method proposed by A.G.E. Pearse modified by R.P. Narcissov. Results. The clinical picture of the disease is similar to multiple sclerosis. MRI of the brain showed more pronounced diffuse changes in the white matter. In all patients, dysfunction of the respiratory chain of mitochondria was noted. Conclusion. Taking into account the data obtained, patients are shown energotropic therapy (idebenone and carnitine preparations). Thus, when doubtful cases in the diagnosis of multiple sclerosis, LBSL should be excluded.

Keywords: mitochondria; leukoencephalopathy with damage to the brainstem and spinal cord and increased lactate levels; LBS; multiple sclerosis; energotropic medicines.

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1. Introduction

Leukoencephalopathy with lesions of the brainstem and spinal cord and increased lactate levels (LBSL)) is a disease with a characteristic lesion of the white matter of the brain on MRI and MRI spectroscopy (MRS) (Scheper et al., 2007) [1]. Patients gradually develop progressive cerebellar ataxia, spasticity, and dysfunction of the spinal cord, sometimes with moderate cognitive impairment. The disease is caused by mutations in the DARS2 gene located in nuclear DNA on chromosome 1. The mode of inheritance is autosomal recessive.

LBSL – this new leukoencephalopathy, which was described by van der Knaap M. S. et al. in 2003 [2] in 8 patients. The authors revealed in these patients during MRS an inhomogeneous lesion of the white matter of the brain with the involvement of the brainstem and spinal pathways. Proton MRI showed elevated lactate levels in the abnormal white matter. Clinically, patients exhibited slowly progressive pyramidal, cerebellar, and spinal dysfunction. Autosomal recessive inheritance was considered likely. Three of the 8 patients were men. Among the 8 patients were 2 sisters, as well as a brother and a sister. Linnankivi T. et al. (2004) [3] described 5 more patients with this disease. MRS revealed a decrease in the content of N-acetylaspartate and an increase in the content of lactate in the white matter of the brain in all patients. Slowly progressive sensory ataxia and tremors were noted that appeared between the ages of 3 and 16 years, and a spastic distal increase in muscle tone in adolescence. One 13-year-old patient was asymptomatic. Two of

the 5 patients were brothers. Serkov S. et al. (2004)[4] also described 5 new unrelated patients. The clinical picture was homogeneous with the onset of the disease in childhood, a slowly progressive course, cognitive impairment, pyramidal and cerebellar symptoms. In some cases, dysfunction of the spinal cord has been identified. this new leukoencephalopathy, which was described by van der Knaap M. S. et al. in 2003 [2] in 8 patients. The authors revealed in these patients during MRS an inhomogeneous lesion of the white matter of the brain with the involvement of the brainstem and spinal pathways. Proton MRI showed elevated lactate levels in the abnormal white matter. Clinically, patients exhibited slowly progressive pyramidal, cerebellar, and spinal dysfunction. Autosomal recessive inheritance was considered likely. Three of the 8 patients were men. Among the 8 patients were 2 sisters, as well as a brother and a sister. Linnankivi T. et al. 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(2006) [5] described a sister and brother whose illness began at the age of 20 and 23 with unsteady gait and stiffness in the legs. The parents were not blood relatives. Isohanni R. et al. (2010) [6] studied the clinical features of 5 patients with LBSL reported by Linnankivi et al. (2004) [3] and described 3 new patients. Six patients were of Finnish origin. Overall, the phenotype was somewhat heterogeneous, with most patients having onset between the ages of 2 and 15 years. Most had a delay in motor development in childhood. In two cases it was normal. Tremor, ataxia, dysarthria and spasticity were most often noted in patients. For the first time, the authors described in patients with LBSL axonal polyneuropathy with weakness in the distal extremities and a decrease in vibration sensitivity. Four patients had no cognitive impairment, 4 had mild speech defects, learning problems. Two patients were described in detail. One of them at the age of 8 had seizures at night. MRI of the brain revealed changes in the white matter in the infra- and supratentorial regions. At the age of 15, he developed ataxia, extensor plantar reflexes, spasticity, and axonal neuropathy. Another patient, at 19 months of age, developed motor retardation with ataxia and muscular hypotonia. Spasticity and hyperreflexia appeared by the age of 2 years 3 months. He also had a slight speech delay. An MRI of the brain revealed pathology of the white matter of the brain in the supratentorial region. Miyake, N., et al. (2011) [7] reported 3 Japanese siblings with severe PE-FMF born to consanguineous parents. A homozygous mutation in the DARS2 gene (610956.0012) was identified. At the age of 3, a 21-year-old proband developed ataxia, then nystagmus, speech impairment, limb tremor, and decreased intelligence. He could only speak 1-2 words. Other features of the proband included atrophy and weakness of the limb muscles, joint contractures, hyporeflexia, and impaired deep sensation. His 2 brothers, who developed the disease before the age of 1, died in childhood from respiratory diseases. MRI of the brain in the proband revealed leukoencephalopathy of the cerebral hemispheres, cerebellum, brain stem and spinal cord. Synofzik M. et al. (2011) [8] reported on a 25-year-old female patient who had paroxysmal ataxia with gait disturbance during exercise for 3 years. Episodes of ataxia were observed up to 5 times a day and lasted from a few seconds to 5 minutes. In recent years, their frequency has increased to 23 times a day. The patient also experienced distal limb weakness, reduced vibration sensitivity, increased muscle tone in the legs, and hyperreflexia. But she never had permanent cerebellar ataxia or a spastic gait. An increase in the level of lactate in the blood serum was noted periodically. MRI of the brain revealed damage to the white matter of the cerebellum, deep sections of the white matter of the brain and the periventricular region with the involvement of the pyramidal tracts and pathways of the spinal cord. Treatment with acetazolamide resulted in a significant reduction in the frequency of seizures. Molecular genetic analysis revealed a homozygous mutation in the DARS2 gene (R609W; 610956.0013). A mutation in the known genes for episodic ataxia was ruled out. This observation showed that LBSL can occur with mild disturbances in the form of episodic ataxia. Nikolaeva E.A. et al. (2013)[9] described a 15-year-old girl with LBSL. In her blood, a decrease in the level of coenzyme Q10 was detected, in connection with which energotropic drugs were prescribed.

Most patients with LBSL have complex heterozygous mutations in DARS2 in association with a common splicing mutation in the acceptor splicing site of intron 2 [10]. Despite the same mutation, polymorphism is described in families with a difference in the onset of 36 years (Li) [11]. Tylki-Szymanska A, et al. (2014) [12] описали high outcome variation between two siblings. Yahia A. et al. (2028) [13] showed the presence of intrafamily polymorphism with an earlier and more severe manifestation of the disease and a lighter course despite the change in the white matter of the brain according to MRI data. Yazici Gencdal I. et al. [14] described a patient with a mild

course of the disease, which began with her at the age of 4, when a tremor appeared in her legs. At the age of 29, she had a slight spastic gait, impaired sensitivity in her legs, ataxia, but did not need help walking. Only isolated spastic paraparesis is possible [15].

Moroz A.A. et al. (2018) [16] described a wide range of pathological mutations in 9 adult patients with LSBL in the Russian population. Karpova M.I. et al. (2019) [17] described three patients with LSBL with onset in adolescence. Rudenskaya G.E. and Zakharova E.Yu. (2020) [18] described 6 Russian patients with LSBL with onset in the 2nd and 3rd decades of life. In 2 patients, the disease course was undulating, resembling multiple sclerosis.

Lin T.K. et al. [19] studied mitochondrial function in patients with LSBL by examining proteins of the respiratory chain complex in fibroblasts. In a patient with LBSL, oxygen consumption by cells and respiratory control coefficient were reduced; in addition, mitochondrial fragmentation was increased, while their tubular elongation and interconnection were reduced. Taken together, these data suggest that DARS2 mutations disrupt the translation of complex respiratory chain proteins encoded by mitochondrial DNA, hence causing cellular respiration dysfunction and hindering mitochondrial dynamics, which underscores the role of mtARSs in maintaining normal bioenergetics and mitochondrial dynamics. Stellingwerff M.D. et al. [20] found 2 MRI phenotypes: 1) early severe cerebral hypoplasia/atrophy (9 patients, 2) white matter abnormalities. Group 1 patients with antenatal onset, microcephaly and developmental delay were the most seriously affected. The DARS2 variants were heavier than the classic LBSL and heavier for Group 1 than for Group 2. Research is underway to develop LSBL gene therapy [21-23].

In view of the fact that the disease is rare, it is of interest to describe the features of MRI of the brain in patients. An increase in lactate in the affected white matter of the brain may indicate mitochondrial dysfunction in patients. The study of these disorders will contribute to the expansion of knowledge about the pathogenesis of the disease.

2. Patients and Methods

2.1. patients.

3 adult patients with LSBL from the Moscow region were examined. The diagnosis was confirmed by DNA diagnostics in the Laboratory of Hereditary Metabolic Diseases (headed by Doctor of Medical Sciences E.Yu. Zakharova) at the Medical Genetic Research Center.

2.2. MRI.

MRI of the brain was performed on a device with a magnetic field induction of 3 T. In the modes T1- and T2-WI, DWI in IP SE, TSE and FLAIR, images were obtained in the axial, coronal and sagittal planes.

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2.3. Cytochemical study of the activity of mitochondrial enzymes in peripheral blood lymphocytes.

For the cytochemical study of the activity of mitochondrial enzymes in peripheral blood lymphocytes, the method proposed by A.G.E. Pearse modified by R.P. Narcissov [13]. The activity of 4 mitochondrial enzymes involved in carbohydrate metabolism (lactate dehydrogenase, LDH), amino acid metabolism (glutamate dehydrogenase, GDH), fatty acid metabolism (α-glycerophosphate dehydrogenase, α-GPDH), and complex II of the mitochondrial respiratory chain (succinate dehydrogenase, SDH) was assessed (Fig. 1). 3 adult patients with PE-FMF from the Moscow region were examined. The diagnosis was confirmed by DNA diagnostics in the Laboratory of Hereditary Metabolic Diseases (headed by Doctor of Medical Sciences E.Yu. Zakharova) at the Medical Genetic Research Center. For the cytochemical study of the activity of mitochondrial enzymes in peripheral blood lymphocytes, the method proposed by A.G.E. Pearse modified by R.P. Narcissov [24]. The activity of 4 mitochondrial enzymes involved in carbohydrate metabolism (lactate dehydrogenase, LDH), amino acid metabolism (glutamate dehydrogenase, GDH), fatty acid metabolism (α-glycerophosphate dehydrogenase, α-GPDH), and complex II of the mitochondrial respiratory chain (succinate dehydrogenase, SDH) was assessed (Fig. 1). 3 adult patients with PE-FMF from the Moscow region were examined. The diagnosis was confirmed by DNA diagnostics in the Laboratory of Hereditary Metabolic Diseases (headed by Doctor of Medical Sciences E.Yu. Zakharova) at the Medical Genetic Research Center. The activity of 4 mitochondrial enzymes involved in carbohydrate metabolism (lactate dehydrogenase, LDH), amino acid metabolism (glutamate dehydrogenase, GDH), fatty acid metabolism (α-glycerophosphate dehydrogenase, α-GPDH), and complex II of the mitochondrial respiratory chain (succinate dehydrogenase, SDH) was assessed (Fig. 1).

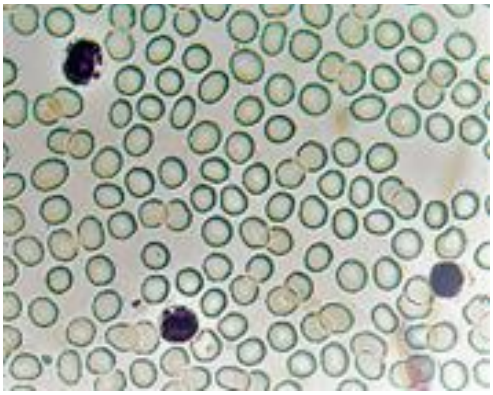

Figure 1. Detection of succindehydrogenase activity in lymphocytes by a quantitative cytochemical method (view under a microscope, magnification 600, dark granules along the cell periphery are the reaction product).

2.4. Lactate.

Using the ABL800 FLEX blood gas analyzer, the lactate level in heparinized whole blood was studied by the amperometric, ensematic method using a substrate-specific electrode. Lactate is determined in the blood on an empty stomach and after a load of carbohydrates at a dose of 1 g of dry glucose per kg of body weight.

3. Results

The diagnosis of LSBL in patients was confirmed by molecular diagnostics; mutations in paired DARS2 genes were identified. All examined patients with LSBL were females aged 37 and 39 years. The first symptoms of the disease appeared at 26, 28 and 37 years. The onset of the disease was acute in two cases and subacute in one. There was a violation of speech, writing, dizziness, absence of the left visual field, numbness of the extremities, gait disturbance. What was the reason to suggest the diagnosis of multiple sclerosis, given the defeat of the white matter on MRI of the brain. One patient was diagnosed with an unspecified demyelinating disease. In all cases, MRI of the brain revealed a symmetrical lesion of the white matter - diffuse focal lesions. Patient S. had bilateral diffuse-focal lesions of predominantly deep white matter at the level of the lateral ventricles with foci in the middle peduncles and hemispheres of the cerebellum, the medulla oblongata, throughout the spinal cord. Patient L. (previously described without MRI of the brain [25] showed extensive symmetrical pathological lesions without clear contours and borders, which spread along the cortico-spinal tract, at the level of the cerebellar peduncles and caudally to the posterior columns of the spinal cord. There was a similar signal characteristic of damage to the intratrunk portion and the mesencephalic pathway of the trigeminal nerve on both sides. The same changes were in the bridge. In the deep parts of the white matter of the hemispheres, paraventricular localization, different-sized foci were determined, prone to fusion (Fig. 2). Patient B. had periventricular and subcortical focal-confluent zones of increased MR signal.

The course of the disease was undulating in two cases and slowly progressing in one. On examination, one patient had a high arch of the feet. In the neurological status in two cases there was a lesion of the optic nerve. In one case, there was also involvement of the abducens nerve in the pathological process. Tendon reflexes in two cases were increased and in one patient with a pronounced violation of deep sensitivity, there were no knee and Achilles reflexes. Muscle tone in two patients was increased according to the spastic type. Vibration sensitivity in the toes was reduced in all patients. All examined patients showed instability in the Romberg position when closing their eyes. Missing during the finger-nose test was only in one case. All patients performed the heel-knee test accurately. Urinary incontinence was reported in one case. Sensitivity disturbance of the polyneuritic type was in one patient. The course of the disease was undulating in two cases and slowly progressing in one. On examination, one patient had a high arch of the feet. In the neurological status in two cases there was a lesion of the optic nerve. In one case, there was also involvement of the abducens nerve in the pathological process. Tendon reflexes in two cases were increased and in one patient with a pronounced violation of deep sensitivity, there were no knee and Achilles reflexes. Muscle tone in two patients was increased according to the spastic type. Vibration sensitivity in the toes was reduced in all patients. All examined patients showed instability in the Romberg position when closing their eyes. Missing during the finger-nose test was only in one case. All patients performed the heel-knee test accurately. Urinary incontinence was reported in one case. Sensitivity disturbance of the polyneuritic type was in one patient.

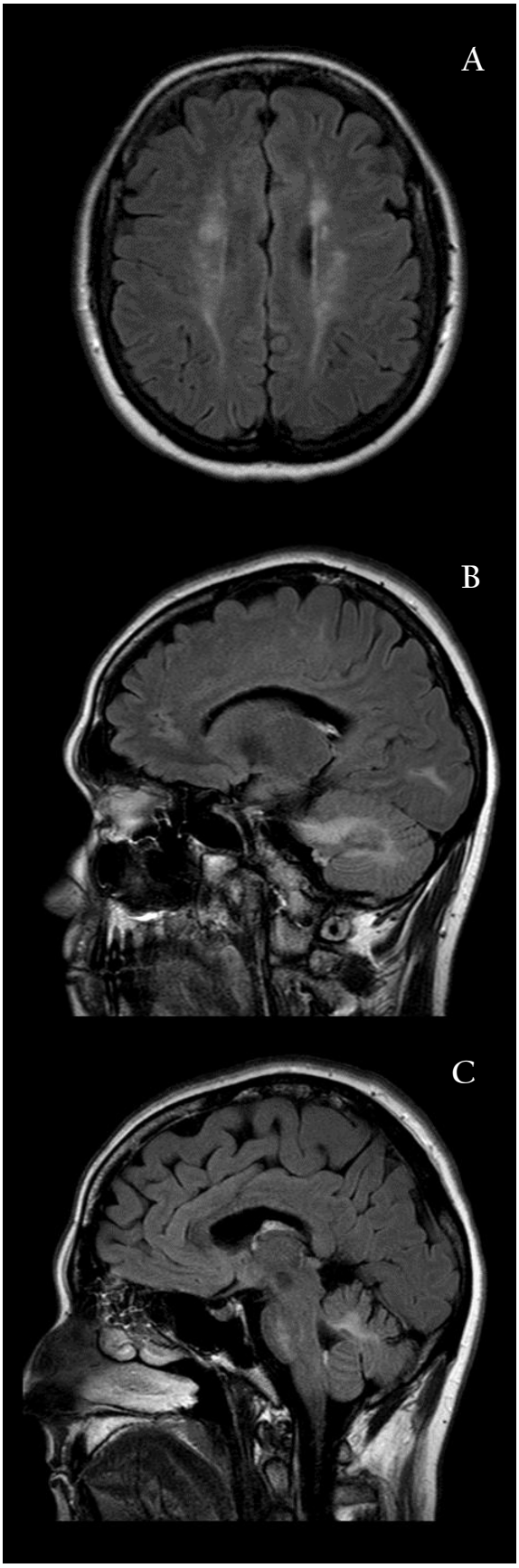

Figure 2. Brain MRI of patient L. with leukoencephalopathy with damage to the brainstem and spinal cord and increased lactate levels (a), b), c)).

The activity of mitochondrial enzymes of peripheral blood lymphocytes was changed in all the studied patients (Table 1). Dysfunction of the respiratory chain was found in 2 out of three patients. In one patient, SDH activity was reduced, in the other, it was compensatory increased. Violation of fat metabolism in mitochondria, determined by the activity of α-GPDG, was noted in two cases. In the third patient with normal values of SDH and α-GPDH, a decrease in GDH activity (impaired amino acid metabolism) was observed.

Table 1. Cytochemical activity of mitochondrial enzymes of peripheral blood lymphocytes (granules/lymphocyte (g/L)) with leukoencephalopathy, predominantly affecting the brainstem and spinal cord and elevated lactate levels in the Moscow Region

N	SDG	α-GPDH	GDH	LDH
1	15,2	5,7	7,3	19,1
2	24,7	5,6	-	-
3	18,8	9	8	16,9
Normal value (reference data)	18,5 – 19,0	9,0-12,0	9,0 – 12,0	10,0-17,0

The level of lactate in the blood was elevated only in one patient with a disease duration of 11 years. In the rest of the patients, blood lactate levels were not elevated over the course of up to 1 year and 12 years. After loading with carbohydrates, the value of the lactate index increased in all patients (Table 2).

Table 2. Blood lactate level (mmol/L) in patients with leukoencephalopathy with a predominant lesion of the brainstem and spinal cord and elevated lactate levels in the Moscow Region

N	Lactate	
	Before meals	After loading with carbohydrate
1	2,6	2,9
2	0,7	1,6
3	1,66	1,73
Normal value (reference data)	Up to 2,2	

4. Discussion

A new hereditary leukoencephalopathy described for about 20 years - LSBL was detected in three adult patients from the Moscow region with an initial diagnosis of multiple sclerosis and an unspecified demyelinating disease. The onset of the disease was acute and subacute. The course of the disease was undulating and slowly progressive. The pathological process involved the cranial nerves - the optic and trigeminal nerves. Cerebellar and pyramidal symptoms were noted. All patients had a violation of deep sensitivity in the lower extremities. In one case, there was a violation of pain sensitivity according to the polyneuritic type. In one case, urinary incontinence. On MRI of the brain, all patients had diffuse focal areas of legions of the white matter prone to fusion. In one case, an intra-stem lesion of the trigeminal nerve was also noted, in contrast to the study by Kassem H. et al. [26], which revealed this lesion in all patients.

In the examined patients with LSBL, the level of lactate in the blood serum was increased only in 2 out of 3 examined patients. After carbohydrate loading, lactate levels increased in all patients. A dysfunction of the mitochondrial respiratory chain was noted. In one case - a decrease in the activity of complex II and in one case - its compensatory increase. The activity of α-GPDH was significantly reduced in 2 out of 3 examined patients. Therefore, taking into account the data obtained, patients are shown energy-tropic therapy (idebenone and carnitine medicines). In a patient with normal SDH and α-GPDH values, the dose of these medicines may not be high.

Thus, the clinical picture in patients with LSBL is practically indistinguishable from multiple sclerosis. In differential diagnosis at the initial stage, probably only MRI of the brain can help, when more pronounced diffuse lesions of the white matter are detected. In addition, when diagnosing multiple sclerosis, it is probably necessary to perform a lumbar puncture in order not only to exclude the infectious nature of the disease (neuroborreliosis), but also to detect oligoclonal

antibodies in the blood and cerebrospinal fluid. There is not one type, but several types of borreliosis that cause neuroborreliosis. In the absence of antibodies to various types of Borrelia, the patient should be referred to a geneticist for DNA diagnosis of LSBL. It is possible to perform both the sequencing of a single DARS2 gene responsible for the development of LSBL, and the use of a panel for frequent mutations for the diagnosis of mitochondrial diseases. If a frequent mutation in the DARS2 gene is not detected using the Mitochondrial Diseases panel, sequencing of the DARS2 gene should be performed, since the panel detects mutations only in exons, and mutations in introns and the promoter region are not detected.

5. Conclusions

Presents patients with LSBL from the Moscow region. The disease is a genocopy of multiple sclerosis. Its diagnosis requires both MRI of the brain with the detection of diffuse foci in the white matter, and DNA diagnostics - detection of a mutation in the DARS2 gene or sequencing using the Mitochondrial Diseases panel to identify frequent mutations. Diagnosis of the disease is important for the management of such patients. They are not shown medicines that change the course of multiple sclerosis, but it is necessary to prescribe energy-tropic drugs. Identification of a mutation in the DARS2 gene in patients with LSBL will allow subsequent use of gene therapy if it is developed, given the intensive research in this area....

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Clinical case

Complex Rehabilitation of Patients with Defects and Deformities of the Maxillofacial Region Using the Method of Autografting of Adipose Tissue

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Abstract: the Central Research Institute of Oral and Maxillofacial Surgery has extensive experience in treating patients with and deformities of the maxillofacial region. This article presents clinical cases of lipofilling as an additional method in the complex reconstructive-surgical treatment and also as a method of choice for complete patients of this group.

Keywords: plastic surgery, lipofilling, defect, scar, deformity of the face

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1. Introduction

Soft tissue injuries of the maxillofacial region are one of the causes of disability due to the development of post-traumatic defects and deformities with functional disorders, sometimes requiring multiple recurrent onstructive and restorative operations and long-term social adaptation. More than half of the cases reveal extensive and deep injuries with the formation of true defects of organs and tissues [1]. Classical methods of elimination of defects of the maxillofacial region are: plasty with local tissues, autografting of free flaps of covering tissues or use of complex combined flaps, use of various kinds of materials for volume contouring [2].

Lipofilling is a method of surgical transfer of autologous adipose tissue from areas of excessive accumulation of fat in order to correct the volume and restore the contours of the so-called "zones of interest". [3]. The autologous fat transfer technique has over 100 years of history. The founder of this technique is considered to be the German surgeon G. Neuber, who in 1893 transplanted autofat into the area of periorbital cicatricial deformity resulting from osteomyelitis [4]. Thanks to the work of E. Hollander, E. Lexer and A. Pennisi, by the 1920s, the technique had reached the peak of its popularity. after which, due to a number of complications (liponecrosis, fibrosis, cyst formation, etc.), interest in it gradually faded away [3]. In the 1980s, interest in lipofilling gradually resumed due to the wide spread introduction of liposuction techniques into plastic surgery. The method got its "second breath" due to the works of American surgeon M. Birkall who in 1987 published the results of autologous transplantation of adipose tissue obtained after liposuction in order to increase and / or reconstruct breasts [5].

During the last decades the range of indications for injected adipose tissue transplantation has significantly expanded, which after the work of P. Zuk et al. in 2001 began to be considered as a rich source of multipotent mesohymal stem cells (MSCs) [10].

2. Patients and Methods

2.1. Lipofilling technique.

The results of the surgery largely depend on the technique of its performance. Lipofilling includes the standard stages: fat sampling, processing and injection of autogrease. Fat extraction is the main stage of lipofilling, which largely predetermines the effect of the intervention [11]. The most widespread method of fat extraction is the method described by S. Coleman (2006) [6]. An important part of the work is the technique of fat tissue aspiration, preparation of aspirated cells for transplantation [9]. The intervention can be performed under general or local anesthesia. The choice of donor areas is made before surgery individually for each patient.

In clinical studies, the loss of adipose tissue volume ranges from 30% to 60% within 4-6 months after surgery [7]. Thus, when calculating the required volume, the possible loss of adipose tissue should be taken into account. Therefore, most surgeons adhere to the so-called hypercorrection rule [8]. However, in some cases, hypercorrection is not possible due to a number of reasons (size of the defect, impaired microcirculation, loss of skin elasticity after radiation therapy, etc.), which implies an individual approach to the choice of treatment tactics and the need for repeated stages to achieve the desired effect.

2.2. Clinical case.

A 6-year-old patient was treated in "Central Research Institute of Oral and Maxillofacial Surgery" with the diagnosis: defect and scar deformity of the temporal, zygomatic and cheek areas on the left side. Condition after a traffic accident. The patient was admitted on the 7th day after the injury; there was a full-thickness soft tissue defect of the zygomatic region with exposure of bone tissue.

In this case, a dermal fascial flap on the temporal artery, characterized by an optimal ratio in terms of the volume and area of the defect, good blood supply and minimal damage to the donor area, was used to repair the defect (Fig. 1).

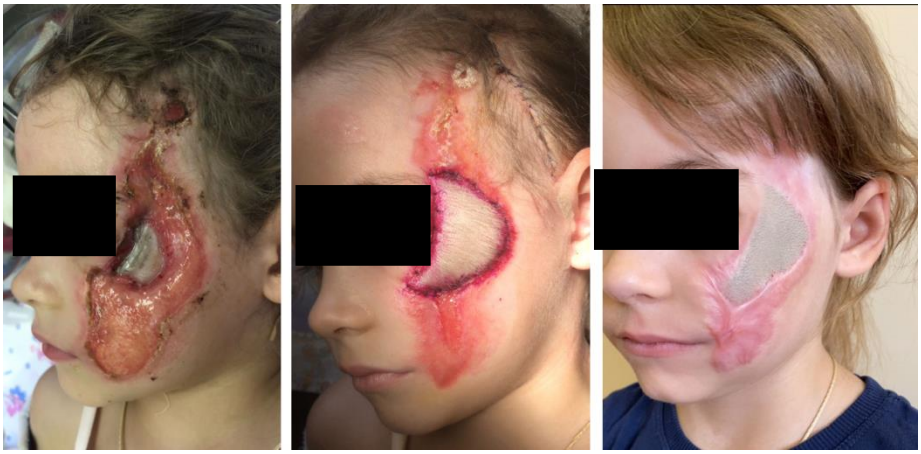

Figure 1. Defect repair of zygomatic area with application of dermal-fascial flap on temporal arter

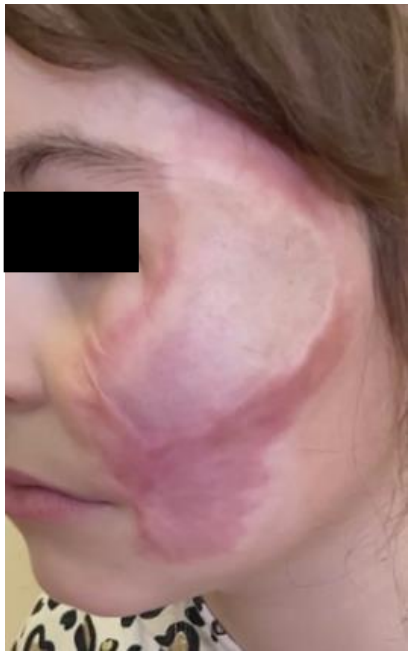

Figure 2. Patient after two stages of lipofilling

Then, to change the qualitative characteristics of the scar and soft tissue dermatension in the periphery, 2 stages of lipofilling were performed 6 months after surgery with a frequency of once every 4 months (Fig. 2).

At the moment the patient is at the stage of rehabilitation, laser resurfacing and correction of the color of the scar deformity is planned. A number of laser hair removal procedures are being planned for the hair.

2.3. Consider the second clinical case

A 34-year-old female patient diagnosed with posttraumatic deformity of the midface on the right side. Condition after a car accident (Fig. 2).

In the presence of a defect of the supporting structures of the maxillofacial region, the microsurgical stage for complete rehabilitation is a priority in most cases. In this patient, a microsurgical operation with a soft tissue-bone flap was planned in order to eliminate the defect and deformity of the midface on the right side. However, given the area of the scar tissue affected by the process, a series of autotransplantations of adipose tissue were performed in order to prepare conditions for subsequent transplantation of the recipient area tissue flap. Within a year after the first lipofilling, the required volume was achieved in the zygomatic and suborbital areas, which allowed us to restore the contour of the middle face and achieve a high aesthetic result without the need for complex microsurgery with the existing risk of flap rejection and prolonged postoperative rehabilitation of the patient.

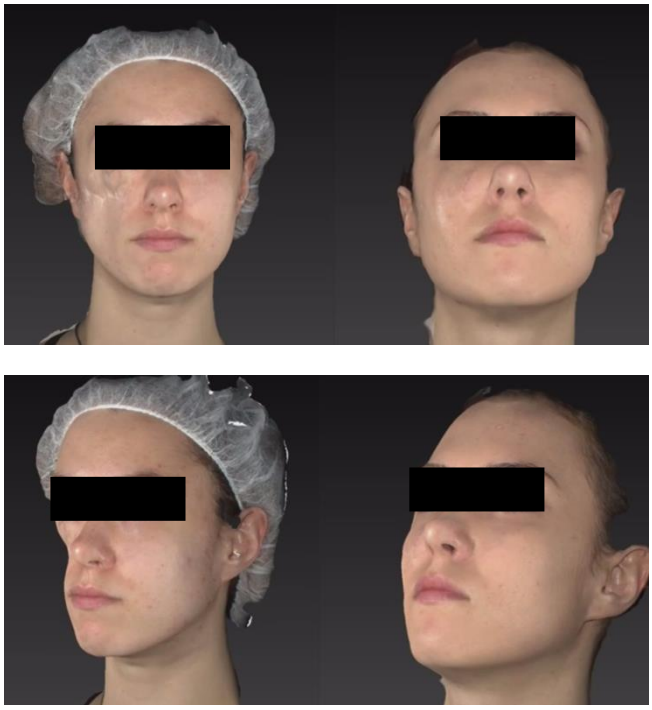

Figure 2. Patient before and after the four stages of lipofilling.

3. Conclusions

Inclusion of autotransplantation of adipose tissue into the algorithm of reconstructive and surgical treatment in cases of extensive defects and deformities of the maxillofacial region allows optimizing the results of complex treatment. The use of lipofilling as one of the methods of reconstruction in patients with posttraumatic deformities of the maxillofacial region is becoming increasingly popular due to the simplicity of the technique, low frequency of postoperative complications, satisfactory aesthetic results and regenerative effect on tissue. Lipofilling should also be considered as a full-fledged method when there is a need to change the qualitative characteristics of the skin and to correct minor deformities.

Thus, the lipofilling procedure should be considered an integral part of both stage rehabilitation and full-fledged independent treatment of patients with maxillofacial defects and deformities.

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data curation, K.L..; writing—original draft preparation, K.I. and G.M.; writing—review and editing, V.P., I.R. and E.S..; visualization, V.P.; supervision, K.L.; project administration, I.K. All authors have read and agreed to the published version of the manuscript."

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Article

Surgical Treatment of Epiretinal Membranes: a Comparative Analysis of Various Removal Techniques.

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Abstract: In most cases, vitreoretinal surgery is the only way to treat epiretinal membrane (ERM). For a long time, surgeons only removed epiretinal fibrosis. But relapse of ERM took place in 10% of cases. Internal limiting membrane (ILM) peeling reduced the number of relapses, but this membrane is connected closely with terminal legs of Müller cells and its removal leads to mechanical and functional damage of the latter. In addition, frequent cases of "dissociation of the optic nerve fiber layer" were noticed in the long term after ILM removal, which caused a deterioration in the functional state of the retina.

Purpose. The purpose of study was to conduct a comparative analysis of various methods of surgical treatment of epiretinal membrane.

Materials and methods. On the base of the National Medical Center of Ophthalmology 75 patients with epiretinal membrane were treated with vitreoretinal surgery.

All patients were divided into 3 groups. Patients of the first group were operated according to the standard procedure with the removal both ERM and ILM. The second group included patients after ERM removal without ILM peeling. The third group of patients were operated according to the original method – after ERM removal specific "debilitating notches" were performed on ILM.

A complete ophthalmological examination was conducted for all patients in the pre- and postoperative period (1,3,6,12 months after surgical treatment). There were no significant differences between groups in age, gender, preoperative BCVA, preoperative intraocular pressure, preoperative CMT on optical coherence tomography, and cataract status.

Results. Analysis of the results in the postoperative period revealed a significant improvement in BCVA at 6 months after surgery in the 2nd and 3rd groups of patients in comparison to the 1st group of patients.

Assessment of morphological parameters of the retina in the postoperative period showed a significant improvement of condition in epiretinal fibrosis in groups 2 and 3 at 6 and 12 months after surgery. The reduce of foveolar thickness was more noticeable in groups 2 and 3 during all the period.

In the postoperative period, a statistically significant improvement in central light sensitivity was revealed in patients of the 2nd and 3rd groups in comparison to similar parameters of patients of the 1st group at 3 months after surgical treatment. The same trend took place at 6 and 12 months after surgery.

Conclusion. Our results showed that surgical treatment of ERM without ILM peeling yielded a better functional result compared to a group where peeling was performed within up to 12 months of follow-up. In order to reduce the risks of ERM relapse, we have developed an innovative technique of "debilitating notches", which allows us to achieve higher functional results than traditional ILM peeling and reduces the risks of relapse.

Keywords: epiretinal fibrosis, epiretinal membrane, internal limiting membrane, vitreoretinal surgery, microperimetry.

1. Introduction.

Idiopathic epiretinal membrane (ERM) is a fairly common disease of persons over 50 years of age leading to the low vision functions development. According to various literary data, this pathology occurs in 2% of the population under 60 years of age and already in 12% in the age over 70 years. [1].

The pathogenesis of ERM is not well studied. A number of authors suggest that ERM may develop as a result of retinal microfractures wich forms after posterior vitreous detachment [2]. This process can activate the migration of fibroblasts, glial cells and astrocytes to the Internal limiting membrane (ILM), where they proliferate [3,4]. However, according to the latest hypothesis, the process of formation of ERM is more complicated. After syneresis (vitreous liquefaction) and vitreous collapse, as a result of abnormal posterior vitreous detachment (without sufficient divergence of attachment points on the vitreoretinal interface), the posterior part of the vitreous cortex (vitreoschisis) cleaves. As a result the outer layer of the posterior part of the vitreous cortex remains attached to the macula, causing the development of the membrane [5,6].

The main symptoms of this disease are: decreased visual acuity, metamorphopsia (as a result of "wrinkling" of the retina and its curvature), as well as micropsia, macropsia and monocular diplopia [7]. Unfortunately, in most cases, vitreoretinal surgery is the only way of treatment ERM. For a long time, surgeons only removed epiretinal fibrosis. But relapse of ERM took place in 10% of cases. Internal limiting membrane (ILM) peeling reduced the number of relapses, but this membrane is connected closely with terminal legs of Müller cells and its removal leads to mechanical and functional damage of the latter. In addition, frequent cases of "dissociation of the optic nerve fiber layer" were noticed in the long term after ILM removal, which leaded to a deterioration in the functional state of the retina [8,9].

Microperimetry is a relatively new method of research in ophthalmology, providing objective qualitative and quantitative information on the functional state of the macular region [10].

2. The purpose of the clinical study is to conduct a comparative analysis of various methods of surgical treatment of epiretinal membrane.

3. Materials and methods of research.

On the base of the Center of Ophthalmology of the N.I. Pirogov National Medical Center 75 patients with epiretinal membrane were treated with vitreoretinal surgery. All patients had a number of confirmed symptoms:

- epiretinal membrane attached to the foveolar pit according to OCT images;
- the presence of metamorphopsies, which were assessed based of subjective sensations and were tested by the Amsler grid;
- reduction of visual acuity;
- integrity of subfoveolar connection of internal and external retinal layers;
- Artifakia
- no vitreoretinal intervention in anamnesis

Exclusion criteria were:

- ERM of traumatic genesis
- macular pseudoholes
- concomitant ocular pathologies such as glaucoma, high-grade myopia, diabetic changes and retinal vascular pathology.
- eye cornea diseases in anamnesis, causing violations of the transparency of optical media.
- phakic eyes.

All patients were divided into 3 groups.

Group 1 (27 patients, 27 eyes). Patients of the first group were operated according to the standard procedure with the removal both ERM and ILM.

Group 2 (24 patients, 24 eyes). The second group included patients after ERM removal without ILM peeling.

Group 3 (25 patients, 25 eyes). The third group of patients were operated according to the original method – after ERM removal specific "debilitating notches" were performed on ILM.

The original methodic includes: after induction of posterior vitreous detachment and vitrectomy, ERM is painted and removed. Secondary, ILM is painted and assessment of its interface is carried out. In the places of the most pronounced deformation of the ILM and deformation of its interface, the ILM is removed locally, i.e. "weakening notches" are formed. After that the operation completes.

A complete ophthalmological examination was conducted for all patients in the pre- and postoperative period (1,3,6,12 months after surgical treatment). The examination included: biomicroscopy of the anterior segment of the eye; tonometry, b-scanning, spectral optical coherence tomography (OCT); and also subjective methods: questionnaire for assessing the level of complaints, visometry, examination with Amsler grid and microperimetry as the main functional research method.

There were no significant differences between groups in age, gender, preoperative BCVA, preoperative intraocular pressure, preoperative CMT on optical coherence tomography, and cataract status.

In OCT study, thickness of retina in the foveolar zone and average thickness of retina in the parafoveolar zone were determined.

To evaluate the central photosensitivity, a program of 37 points within 6 ° was used (0-3 ° from the point of visual fixation centered in the fovea region). In this study, the distance between luminous stimuli in the 1 ° projection from the fixation point was 0.5 °, the stimuli more distant from the center had a density of 1 °. Both studies were performed using strategy 42, a duration of 200 ms, a stimulus size of 0.43 ° (Goldmann III). The brightness of the stimuli ranged from 0 to 36 dB.

4. Statistical analysis.

Statistical processing of the results was carried out using the IBM SPSS Statistics 23 program. Paired samples t-test and Pearson correlation were used. Differences were considered statistically significant when $p < 0.05$. The results of descriptive statistics in most tables are presented as $M \pm \sigma$, where M is the mean and σ is the standard deviation.

5. Results.

Surgical intervention in all three groups of patients was performed in full, intraoperative complications were not detected, the early post-operative period in all cases was without any features. In one case in group 2, where ILM peeling was not performed, a recurrence of epiretinal fibrosis was detected and this patient was excluded from statistical account. The patient was re-operated with removal of the Internal limiting membrane.

All parameters of patients of all three groups were comparable.

Ophthalmological examination of all patients was carried out in postoperative period at 1, 3, 6 and 12 months after surgery.

Pre-operative BCVA in group 1 composed 0,37±0,12; 0,39± 0.15 in the 2nd group and 0,40±0,11 in the 3rd group. There was no statistical difference in functional parameters in all groups of patients (p = 0.73) and (p = 0.68).

The post-operative analysis of the results showed a significant improvement in BCVA in groups 2 and 3 compared with the data of group 1 at 6 months after surgery (p = 0.038) and (p = 0.041), respectively, and at 12 months after surgical treatment (p = 0.035) and (p = 0.037), respectively (Figure 1).

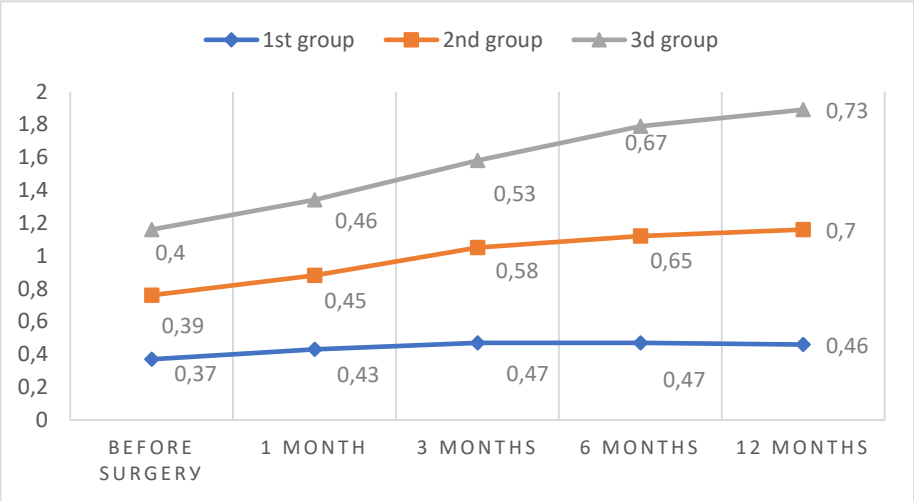

Figure 1. BCVA and its dynamics in patients after surgery, (M±σ)

When analyzing the morphological parameters of the retina in patients with epiretinal fibrosis, two parameters were evaluated: the thickness of retina in the foveolar zone (CRT - central retinal thickness) and the degree of its decrease during postoperative period (DCRT - decrease central retinal thickness).

Parameters of central retina thickness at the preoperative stage were statistically comparable in all 3 groups.

When assessing the morphological parameters of the retina in the postoperative period, a statistically significant improvement was revealed within 6 and 12 months after surgery in epiretinal fibrosis in groups 2 and 3. In Groups 2 and 3, there was more impressive reduction of foveolar thickness during the entire follow-up period. So in 6 months after surgical treatment, retinal thickness in group 2 decreased by 135,9±25mkm (p = 0.035), and in group 3 by 130,6±27 (p = 0.029) compared to similar data of group 1. The difference is statistically significant. The more pronounced dynamic of the central retinal thickness decrease had patients of the 2nd and 3rd groups, and it was associated with the lack of Müller cell microtraumatization due to ILM peeling in the central zone. (Figure 2, 3.)

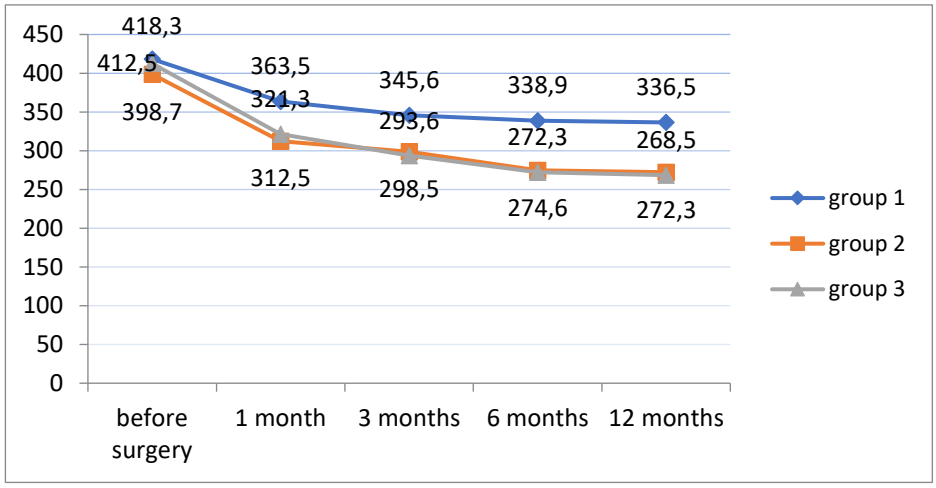

Figure 2. Central retinal thickness (CRT) and its dynamics in patients after surgery, (M±σ)

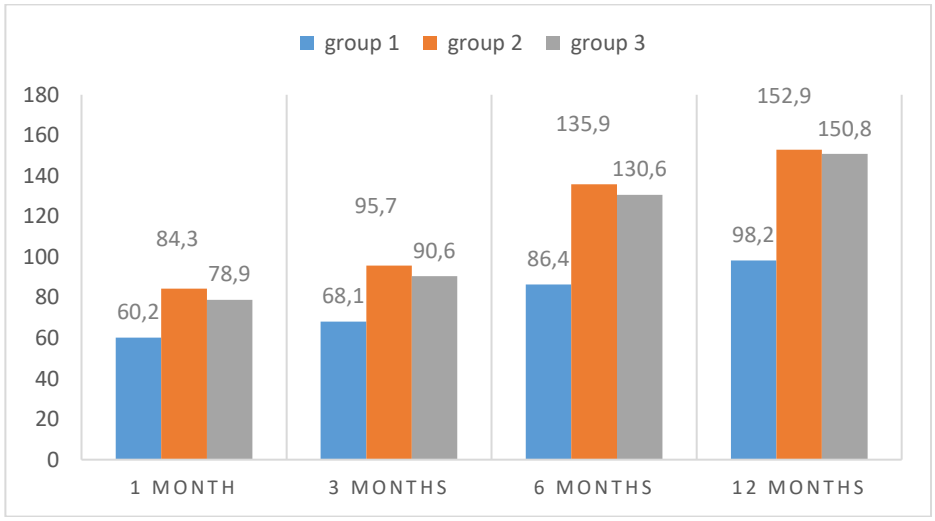

Figure 3. Retinal thickness reduction (DCRT) dynamics in patients after surgery, (M±σ)

Among the microperimetric parameters, the central and common light sensitivity of the retina was evaluated. All parameters were comparable at the pre-operative stage. There was a statistically significant improvement in central light sensitivity parameters of the 2nd and 3rd groups of patients in the postoperative period, compared to similar data of the 1st group within 3 months after surgical treatment. In addition, this trend continued at 6 and 12 months after surgery (Tables 1, 2).

Parameters	Group 1	Group 2	Group 3
Before surgery	23,45±2,76	22,96±2,55	23,73±3,35
1 month	22,58±2,53	23,10±2,23	23,65±3,43
3 months	22,72±1,78	25,50±1,51	25,73±1,12
6 months	22,65±1,14	26,72±1,47	26,34±1,15

12 months	23,11±1,23	26,98±1,43	27,11±1,90

Table 1. Microperimetric characterization of central light sensitivity before and after surgery, dB (M±σ)

Parameters	Group 1	Group 2	Group 3
Before surgery	23,73±2,23	22,43±2,83	22,89±2,49
1 month	23,58±2,43	23,10±2,54	23,71±1,87
3 months	23,52±1,78	24,80±1,89	24,73±1,45
6 months	23,14±1,14	24,70±2,17	24,78±1,89

Table 2. Microperimetric characterization of common light sensitivity before and after surgery, dB (M±σ)

Conclusion.

Our results showed that surgical treatment of ERM without ILM peeling yielded a better functional result compared to a group where peeling was performed within up to 12 months of follow-up. However, the absence of ILM peeling may increase the risk of epiretinal membrane recurrence. To reduce the chance of ERM recurrence, we developed an innovative technique for "weakening notches" at ILM. Using of this technology allows to achieve higher functional results compared to traditional ILM peeling and allows to reduce the risks of relapse. Thus, the obtained data confirm that the preservation of the Internal limiting membrane during the surgical treatment of epiretinal fibrosis is preferable.

Conflict of interest: The authors declare no conflict of interest.

The use of artificial intelligence: the article is written without the use of artificial intelligence technologies.

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Article

Familial Case of Porphyria with an Epileptic Seizure in the Moscow Region

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Abstract: Objective a clinical case of a 37-year-old patient with familial acute porphyria is presented (the patient's sister died at the age of 28 during an attack of acute porphyria). Material and methods: we used a qualitative urine test for porphyria with Erdich reagent and quantitative determination of porphyrins (porphobilinogen and delta-aminolevulenic acid on a spectrophotometer "Hitachi 3900". Results.The attack began with pain in the abdomen and lower back, tachycardia, arterial hypertension during menstruation. After taking ketorol and surgical intervention, tonic-clonic convulsions developed with involuntary release of pink urine. CT of the brain shows signs of ischemic cerebrovascular accident in the parietal region of the right hemisphere. There was a decrease in the level of hemoglobin in the blood and APTT. A urine test for porphyria was positive. Porphobilinogen and delta-aminolevulinic acid in the blood are elevated. After the appointment of glucose at a dose of 300 g of dry matter per day in an oral solution, the condition improved. Conclusion. The presented case demonstrates the difficulties in diagnosing and managing patients with acute porphyria, despite the awareness of the attending physicians about this disease. The patient developed an epileptic seizure and brain damage according to CT, which could be posterior reversible encephalopathy. To improve the efficiency of diagnosis and treatment of porphyria in all laboratories, a simple and cheap qualitative urine test for porphyria with Ehrlich's reagent should be organized and Hitachi 3900 spectrophotometers should be purchased at regional medical centers. Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Keywords: porphyria; epileptic seizure; porphobilinogen; delta-aminolevulinic acid; posterior reversible encephalopathy.

1. Introduction

Acute porphyrias are a group of genetically determined diseases associated with the heme biosynthesis cycle, having an acute, induced onset, a progressive nature of the course, which is based on excessive accumulation of metabolites of porphyrin metabolism [1]. An acute attack is provoked by various factors - starvation, alcohol intake, porphyrinogenic drugs.

In Finland, the prevalence of acute intermittent porphyria is 1:60,000 (Kauppinen R et al., 2002) [2]. J. Bustos et al. report a prevalence of acute intermittent porphyria of 1 per 2000 people [3]. In France, 1:1675 latent carriers of this disease were identified among healthy donors (Nordmann Y, 1997)[4]. In the genomic database, the number of cases of mutations in porphyria genes is approximately 1:1500 [5,6].

Porphyrins are involved in heme synthesis (Figure 1). In porphyria, due to a mutation in the genes encoding the enzyme involved in the synthesis of heme, under the influence of unfavorable factors, the metabolism of porphyrins is disturbed and their derivatives accumulate. All patients have elevated levels of porphobilinogen and delta-aminolevulinic acid in the urine.

Porphyria is a hereditary disease caused by a mutation in the genes involved in the heme formation cycle. 8 enzymes are involved in heme biosynthesis. Mutation in these genes involved in porphyrin metabolism leads to the accumulations of porphyrins - heme precursors (delta-aminolevulinic acid, porphobilinogen) under the influence of a provoking factor (starvation, taking drugs contraindicated in porphyria).

Porphyrins have a toxic effect on the nervous system. Initially, unmyelinated fibers of the autonomic nervous system are affected, which leads to dynamic intestinal obstruction due to spasm of some sections of the intestine and paresis of others. This is accompanied by pain in the abdomen. Pain in the chest and limbs are radicular . After 7-10 days, myelin fibers are affected and peripheral paresis develops according to the type of polyneuropathy.

Epileptic seizures are possible [8]. Usually these are tonic-clonic and focal seizures with impaired consciousness. Status epilepticus with seizures and partial continuous epilepsy are rare [9]. High probability of a lethal outcome of the disease with late diagnosis [10].

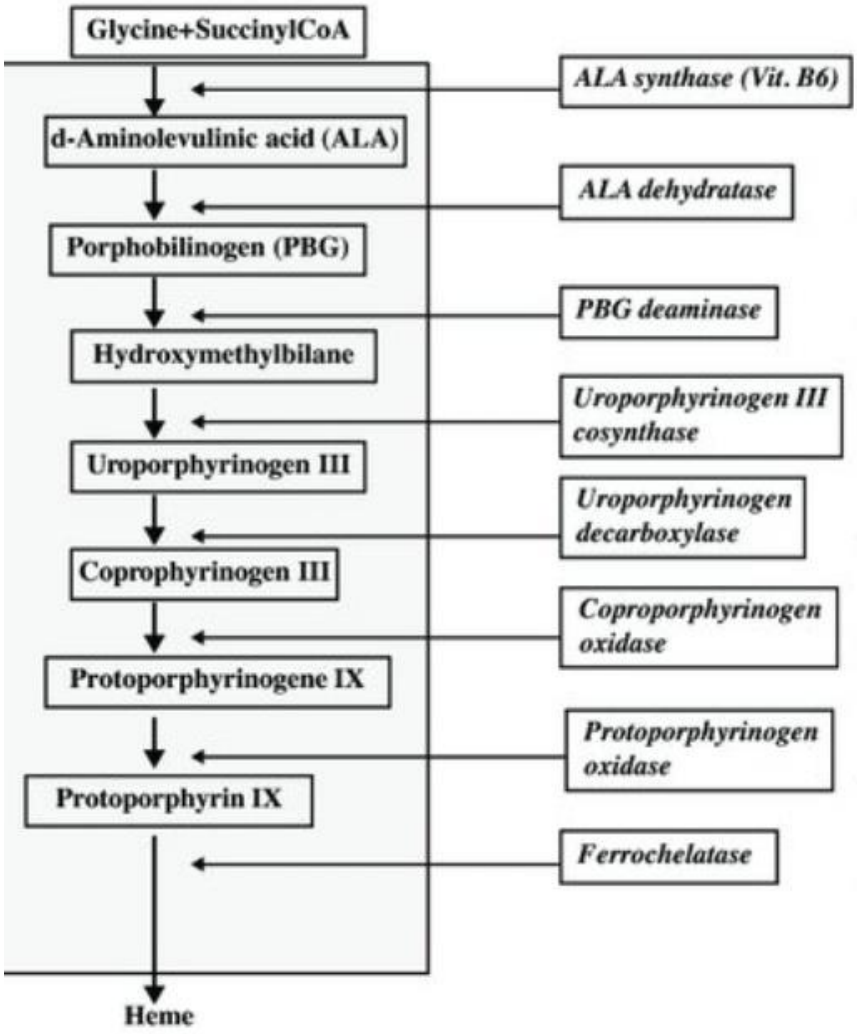

Figure 1. Metabolism of porphyrins [7].

Timely diagnosis of this pathology is important for the appointment of glucose (200-400 g of dry matter per day), as a blocker of the aminolevulinic acid synthetase enzyme. If this is not enough, heme arginate (normosang) is prescribed. It is necessary to clarify the possibility of prescribing drugs on the website of the National Research Center for Hematology of the Ministry of Health of Russia http://www.critical.ru/consult/pages/porphyria/prodlistsimple.htm. There is also a "porphyria drug" website.

It is important to examine the relatives of patients, since the disease is transmitted in an autosomal dominant manner and the children of patients, brothers and sisters are at high risk of developing acute porphyria. The latent phase of the disease in them can turn into a potentially life-threatening acute period [11]. There is also secondary porphyria in lead poisoning, alcohol surrogates. It is important to examine the relatives of patients, since the disease is transmitted in an autosomal dominant manner and the children of patients, brothers and sisters are at high risk of developing acute porphyria. The latent phase of the disease in them can turn into a potentially life-threatening acute period [11]. There is also secondary porphyria in lead poisoning, alcohol surrogates.

For the treatment of porphyria, glucose is used, which inhibits the activity of the enzyme aminolevulinic acid synthetase [12]. During the day, 200-400 g of dry matter glucose is prescribed. In the absence of improvement within three days, as well as in the case of a severe course of an acute attack of porphyria, intravenous heme arginate is administered at a dose of 3 mg/kg of body weight for 4-7 days. Heme arginate, according to the feedback principle, stops the development of metabolites of pores. And this leads to normalization of the patient's condition. Heme arginate is injected into 100-150 ml of physiological saline intravenously by drip rapidly, but not less than for 30 minutes in a dark glass container, protected from light system. Usually - 4 introductions. The central vein or vein of the forearm should be used.

A new medicine, gevosiran, has been developed to prevent acute attacks of porphyria. It disables the mRNA encoding aminolevulinic acid synthetase 1. The medicine provides prevention and reduction in the frequency of severe attacks of acute hepatic porphyria, controls chronic symptoms, and facilitates the course of the disease [13, 14]. New approaches are being developed for the prevention of acute attacks and the treatment of the disease, based on the stabilization of HMBS and the regulation of proteostasis [15].

Early identification of patients at risk of developing acute porphyria is important [16]. Timely laboratory diagnosis is important, including for presymptomatic carriers of the disease gene [17]. Timely diagnosis helps to prevent severe consequences of an acute attack of the disease [18,19].

Relatives of patients should be examined. Conduct DNA diagnostics to detect mutations in the genes encoding porphyria. The level of porphyrins in the urine of carriers of mutations in the porphyria genes should also be monitored.

It is also important to diagnose an acute attack of porphyria in a timely manner. The disease should be suspected if the patient has unexplained abdominal pain and at least one of the following: pain in the limbs, nausea, vomiting, anxiety, sleep disturbance, epileptic seizure, weakness in the limbs, dark or reddish urine, constipation or diarrhea, hallucinations .

An acute attack of porphyria requires a quick examination of the patient for his treatment. Therefore, it is important to identify carriers of the porphyria gene. When sequencing of newborns is included in the future, detection of mutations in porphyria genases in them will allow controlling the level of porphyrins in the urine, prescribing preventive treatment, and preventing an attack of acute porphyria. And, thus, reduce mortality in this disease.

It is important to provide medical institutions with affordable laboratory diagnostics of porphyria (urine test for porphyria with Erdich's reagent and quantitative determination of porphyrins in urine (delta-amnolevulinic acid and porphobilinrogen) using a Hitachi 3900 spectrophotometer.

2. Patients and Methods

2.1. Patient.

A women with porphyria from a family in which her own sister died during an acute attack of porphyria.

2.2. Urine test for porphyria with Ehrlich's reagent.

The diagnosis porphyria was clarified using a qualitative urine test for porphyria with Ehrlich's reagent. Ehrlich's reagent is a solution of p-dimethylaminobenzaldehyde 20 g/l in a mixture of glacial acetic and perchloric acids. When porphobilinogen interacts with Ehrlich's reagent, porphobilinogen aldehyde is formed, which has a red color.

During the determination of porphobilinogen, the patient's urine and Ehrlich's reagent are taken in a ratio of 1:1. The reaction should be considered positive if in the first 5 minutes after the addition of Ehrlich's reagent there was a sharp change in color (redness)

2.3. Quantitative determination of porphyrins in the urine

After qualitative urine test for porphyria with Ehrlich's reagent, followed by quantitative determination of porphyrins in the urine using a Hitachi 3900 spectrophotometer at a wavelength of 555 nm.

3. Results

A 37-year-old patient was admitted to the gynecology department with complaints of recurrent pain in the lower back, lower abdomen, increased blood pressure to 150/80 mm Hg. Art. The last 8 months there was an exacerbation of cystitis. The patient took monural, furadonin. The patient's sister died at the age of 28 during an attack of acute porphyria.

On examination, blood pressure was 150/70 mm Hg. Art., the number of heartbeats 150-160 in 1 minute, arrhythmia. The abdomen was soft, slightly painful in the navel. There was mucosaic

discharge from the genital tract (the last days of menstruation). Ultrasound of the abdominal cavity and small pelvis revealed no pathology. Acute salpingo-oophoritis was diagnosed. The patient received anti-inflammatory therapy - cefazolin, metronidazole, ketorol. But the pain persisted. Culdocentesis was performed under local anesthesia with novocaine, after which during the evening she felt weakness, "spots" before her eyes. The next day, tonic-clonic convulsions developed. There was involuntary urination, pink urine. In the blood test, hemoglobin is 105 g/l (normally 120-140 g/l), APTT is 14 seconds (normally 21.1-36.5 seconds). Acute intermittent porphyria was diagnosed.

The patient was transferred to the intensive care unit. Glucose was prescribed at a dose of 300 g of dry matter per day in oral solution. Condition of the patient was stabilizated, she was transferred to the therapeutic department.Drotaverine was prescribed to reduce abdominal pain. The patient also received ceftriaxone, metranidazole, B vitamins, omez, velferrum, bisoprolol, enalapril. Pain in the legs appeared 10 days after the onset of the disease. The patient was transferred to the neurology department. In the neurological department, she complained of weakness in the legs, pain in the abdomen, lower extremities, increased blood pressure. On examination, blood pressure was 130/80 mm Hg. Art., the number of heartbeats 82 in 1 minute on the background of enalapril and bisoprolol. The abdomen is of normal shape, painful on palpation. In the neurological status - cranial nerves without focal symptoms. The strength of the muscles of the limbs is reduced to 4 points. There was hypotonia of the muscles of the lower extremities. Tendon reflexes from the hands were brisk. The knee reflexes were reduced. The Achilles reflexes were absent. Violation of sensitivity by polyneuritic type. Finger-to-nose and heel-to-knee tests were performed with a slight overshoot.

ECG: atrial paroxysmal tachycardia 150 in 1 minute. A CT scan of the brain was performed. The CT picture may correspond to an ischemic type of cerebrovascular accident in the parietal region of the right hemisphere of the brain. Acute period? Atrophic changes in the cerebral cortex.

A qualitative urine test for porphyria with Ehrlich's reagent is positive. Quantitative determination of porphyrins in urine: porphobilinogen - 131.1 mg / l (normal 0.0 - 3.4 mg / l), delta-aminolevulinic acid 26.3 mg / l (normal 1.5-7.5 mg /l).

Diagnosis: acute porphyria. Epileptic syndrome (for the first time identified a single convulsive attack with loss of consciousness). Violation of cerebral circulation in the basin of the right cerebral artery according to the ischemic type of unknown statute of limitations. Polyneuropathy.

The patient received glucose at a dose of 300 g of dry matter dissolved in water, orally during the day, B vitamins (B1, B6, B12), gabapentin, enalapril, bisoprolol. The condition has improved. The patient was transferred to the National Research Center for Hematology of the Ministry of Health of Russia for treatment with heme arginate (normosang).

4. Discussion

The presented a patient whose disease began with abdominal pain during menstruation, increased blood pressure. After the surgical intervention and taking non-steroidal anti-inflammatory medicine tromethamin, the condition worsened, tonic-clonic convulsions appeared with involuntary urination of pink urine.

Taking into account the anamnesis (his sister died during an acute attack of porphyria) and the clinical picture of the disease (abdominal pain, tachycardia, pink urine), acute porphyria was diagnosed. After the start of glucose intake, the condition improved. Confirmatory laboratory diagnostics (qualitative urine test for porphyria with Ehrlich's reagent) was carried out on the 12th day from the onset of the disease (on the 2nd day of hospitalization in the neurological department). Due to the fact that laboratory confirmation of the diagnosis by quantitative determination of porphyrins in urine is carried out only at the National Research Center for Hematology of the Ministry of Health of Russia, this study was carried out after 1 week of hospitalization in the neurological department and on the 19th day from the onset of the disease. Since the treatment of the disease with glucose began already on the 7th day from the onset of the disease, the patient's condition did not worsen. But complete recovery required the introduction of heme arginate (normosang), for which the patient was transferred to the Federal State Budgetary Institution National Research Center for Hematology of the Ministry of Health of Russia. Discussion: a patient is presented whose disease began with abdominal pain during menstruation, increased blood pressure. After the surgical intervention and taking tromethzmin, the condition worsened, tonic-clonic convulsions appeared with involuntary urination of pink urine. Taking into account the anamnesis (his sister died during an acute attack of porphyria) and the clinical picture of the disease (abdominal pain, tachycardia, pink urine), acute porphyria was diagnosed.

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Changes on CT scan of the brain may be due to a stroke or it is a posterior reversible encephalopathy that occurs during an attack in acute porphyria [20, 21]. An epileptic seizure in patients with porphyria may be due to posterior reversible encephalopathy. The exact mechanism of posterior reversible encephalopathy syndrome is not fully understood. It is thought to be related to a problem with the blood vessels in the brain. There are several theories as to why these blood vessels may become inappropriately permeable and cause the surrounding brain tissue to swell. According to the "Vasogenic" theory, high blood pressure interferes with the normal ability of the blood vessels in the brain to maintain normal cerebral blood flow. Increased pressure damages the endothelial layer, the blood-brain barrier and leads to edema. The tendency to damage the posterior part of the brain can be explained by the reduced density of sympathetic innervation in the posterior circulation compared to the anterior circulation [22]. The "vasogenic" theory probably explains about 50% of cases of posterior reversible encephalopathy syndrome in which there was a significant increase in blood pressure [23.] . The "cytotoxic" theory suggests that edema is caused by direct damage to cells by toxins. "

5. Conclusions

The presented case demonstrates the difficulties in diagnosing porphyria. A patient with acute pain in the abdomen and lower back was hospitalized first in the gynecology department, then was transferred to the intensive care unit. After that, she was in the therapy department. And then she entered the department of neurology. The presence of the patient in various clinical departments is associated with the development of the pathological process in acute porphyria. The patient had an attack of pain during menstruation. Initially, the vegetative ganglia are affected, paresis and intestinal spasm occur. The patient has abdominal pain during menstruation, which can provoke the development of an acute attack of porphyria. The surgical intervention, the use of a non-steroidal anti-inflammatory drug led to the progression of the pathological process and the development of an epileptic seizure, after which the patient was transferred to the intensive care unit. When a change in the color of urine was revealed, and there was also information about porphyria in a sister, then the diagnosis was already clear. And the patient was transferred to the therapy department. Glucose was prescribed. But, probably, this was not enough, since the disease developed further, weakness appeared in the legs, polyneuropathy developed, which indicates damage to the myelin sheaths of peripheral nerves. However, unlike the patient's sister, she survived despite a severe attack of acute porphyria, as the diagnosis was made on time, although she had to be transferred to the federal center for the administration of heme arginate.

The presented case demonstrates the difficulties in diagnosing and managing patients with acute porphyria, despite the awareness of the attending physicians about this disease. Therefore, in order to improve the care of patients with porphyria, a number of organizational measures are needed. Acute hepatic porphyria (AHP) can cause severe neurological symptoms affecting the central, autonomic, and peripheral nervous systems. Due to their relative rarity and their chameleon-like appearance, delayed diagnosis and misdiagnosis, including Guillain-Barré syndrome, are common [24,25]. Physicians should be aware of porphyrias, which can cause unexplained gastrointestinal and neurological diseases [26]. Abdominal pain is a common reason for emergency room visits, with many patients not being definitively diagnosed based on their symptoms. Non-gastrointestinal causes, including porphyria, should be considered in the treatment of abdominal pain.

The availability of laboratory diagnostic methods is necessary to confirm the diagnosis of porphyria. The urine test for porphyria with Ehrlich's reagent is a screening test for the determination of indole compounds, which include porphobilinogen. In porphyria, porphobilinogen accumulates in large quantities and is excreted in the urine. Porphobilinogen is one of the main markers of an acute state (attack) in porphyrias, the pathogenesis of which is based on disturbances in heme synthesis caused by a deficiency of one of the enzymes of its synthesis and urinary excretion of precursors, protoporphyrins. Due to the fact that clinically acute conditions in porphyrias are characterized by a complex of therapeutic, neurological and psychiatric symptoms, such as abdominal pain, tachycardia, arterial hypertension, behavioral changes, epileptic seizures, coma, paresis of the respiratory muscles, etc., the determination of porphobilinogen in urine is most appropriate in neurological, psychiatric and surgical hospitals.

At the same time, with porphyria, the use of a number of widely used drugs (barbiturates, ethanol, chlorpropanide, sulfanides, etc.) is unacceptable, since they can cause an attack of por-

phyria. Therefore, the determination of porphobilinogen is the basis for timely diagnosis and adequate therapy, since at present there is a medicine hematin arginate (normosang) that can stop the attack in porphyrias.

A qualitative urine test for porphyria with Ehrlich's reagent is a cheap method that takes a small amount of time to perform. The test is a screening test and requires confirmation by a more expensive and time-consuming method, the quantitative determination of porphyrins in urine using a Hitachi 3900 spectrophotometer.

Ehrlich's reagent is a solution of p-dimethylaminobenzaldehyde 20 g/l in a mixture of glacial acetic and perchloric acids. When porphobilinogen interacts with Ehrlich's reagent, porphobilinogen aldehyde is formed, which has a red color.

During the determination of porphobilinogen, the patient's urine and Ehrlich's reagent are taken in a ratio of 1:1. The reaction should be considered positive if in the first 5 minutes after the addition of Ehrlich's reagent there was a sharp change in color (redness) (Figure 2).

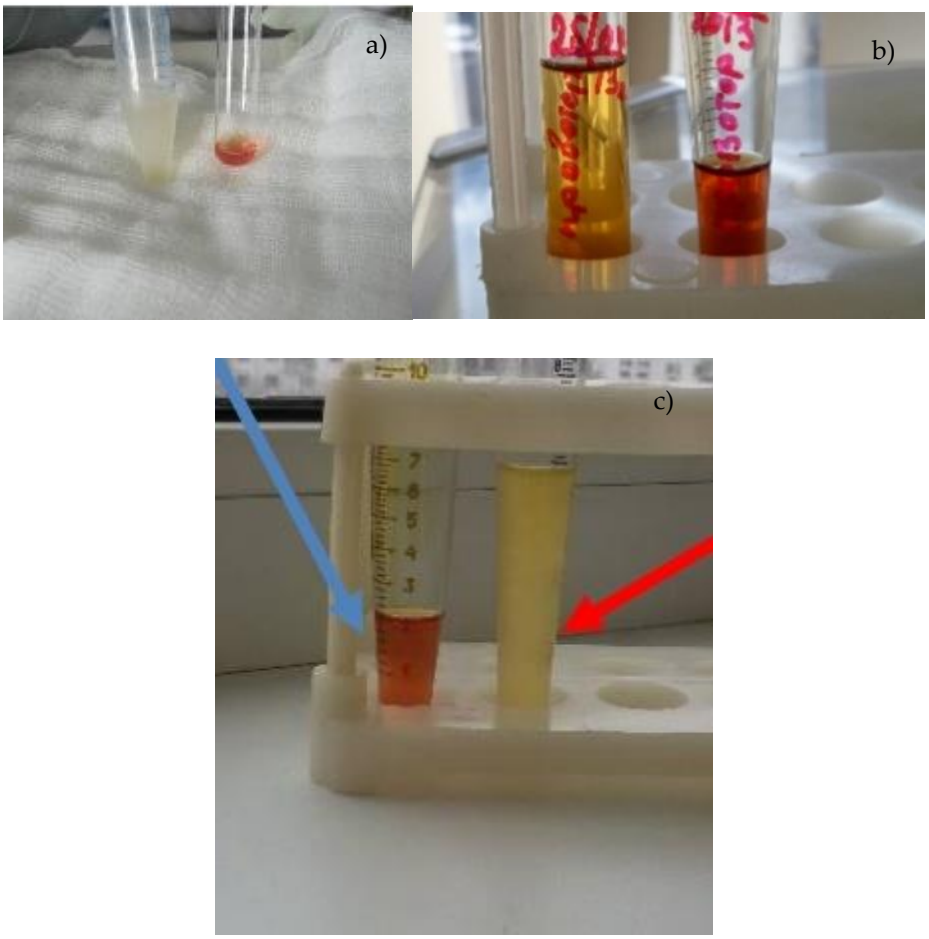

Figure 2. Positive qualitative urine test for porphyria with Ehrlich's reagent (a, b, c)

A urine test for porphyria with Earlhill's reagent should be in the structure of all medical institutions. If laboratory diagnosis is carried out centrally, it is necessary to ensure that urine is frozen and delivered in a cooler bag with a cooling element, since porphobilinogen is rapidly destroyed and this can lead to the fact that porphyria will not be diagnosed.

To quantify porphyrins in urine, a Hitachi 3900 spectrophotometer is used. Total porphyrins are determined in daily urine and delta-aminolevulinic acid and porfibilinogen are determined in single urine. Porphobilinogen is rapidly degraded. Therefore, the determination of delta-aminolevulinic acid may be more informative for the diagnosis of porphyria. Urinary porphyrin quantitation can be used to monitor urinary porphyrin levels by detecting porphobilinogen alone.

The method for the quantitative determination of porphobilinogen and delta-aminolevulinic acid in urine is based on their separation by absorption (absorption) of solutions on columns with

an ion-exchange resin (ion-exchange column chromatography), followed by the use of Erlichp's reagent and measurement of the results on a spectrophotometer at a wavelength of 555 nm to detect porphyrins .

Given that the spectrophotometer is an expensive device, it is advisable to place it in medical centers. It is necessary to organize the delivery of urine for examination in a cooler bag with a cooling element, so that there is no destruction of porphyrin metabolites and the diagnosis of porphyria is not missed. Daily urine should be collected in a refrigerator so that the metabolites of the porphyrins are not destroyed. Single urine and a small amount from daily urine can be frozen and stored for a long time for further research.

In connection with the development of preventive medicine, the most significant effect will be the identification of carriers of the porphyria gene among newborns with the expansion of mass screening of newborns using the sequencing method. If carriers of mutations in the porphyria genes are identified, recommendations will be given on the contraindication of the use of drugs that worsen the course of porphyria. Recommendations will also be given on the exclusion of alcohol in the future, that fasting should be avoided. Carriers of mutations in the porphyria gene will be warned to monitor the level of porphyrins in the urine, if they increase, it is necessary to take glucose to prevent an acute attack. These patients will be prescribed gevosiran to prevent acute attacks of porphyria. At present, when sequencing has not yet been included in the list of mass newborn screening methods, it is necessary to expand the information of doctors about porphyria and make the diagnosis and treatment of patients with an acute attack of porphyria accessible.

To improve the efficiency of diagnosis and treatment of porphyria in all laboratories, a simple and cheap qualitative urine test for porphyria with Ehrlich's reagent should be organized and Hitachi 3900 spectrophotometers should be purchased at regional medical centers. Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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Article / Clinical case

Features of Vestibular Changes in Patients with Vestibular Schwannoma. Historical Background and the Current State of the Problem.

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Abstract: The problem of vestibular disorders is one of the most urgent in the practice of a neurologist and otorhinolaryngologist. Dizziness patients can also ask for help specialists of any profile. Typical complaints require to conduct an appropriate examination and prescribe treatment. Due to the acute manifestation and rapid progression of symptoms, the patient's quality of life is significantly decreased and the ability to work is impaired. Vestibular disorders are even increased with age. Among the elderly, such complaints presented in about 48% of patients, almost every second one. Depends on the cause, vertigo can be of peripheral (otological), central and functional (psychological) origin. Often, the patient's condition assessed as serious and required immediate medical manipulations. For this reason, any specialist, to whom patient complains of dizziness, must be able to competently conduct an examination and perform the most complete examination. However, the lack of uniform standards for vestibular testing can lead to diagnostic errors and the choice of incorrect medical tactics. The article provides an overview of the literature data on the examination of patients with complaints of dizziness. An integral part of the diagnostic search for dizziness is the collection of complaints and anamnesis, a standard otorhinolaryngological examination, as well as audiometric and vestibular otoneurological tests. There is not much literature about vestibular testes in patients with vestibular schwannomas, here in this paper we present the literature dats and our experience in this topic.

Keywords: vertigo, dizziness, vestibulometry, computed videonystagmography, caloric test, vestibulometry, video head impulse test, acoustic neuroma, vestubular schwannoma.

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1. Introduction

Dizziness is one of the most common reasons for seeking medical help. Patients with vestibular disorders are found in the practice of a doctor of any specialty [1]. It is reported that 15-30% of the adult population experience debilitating symptoms of dizziness and balance disorders, which are accompanied by the risk of falling as the most frequent and alarming consequence. With age, vestibular manifestations increase, and the frequency of their occurrence in women is 2-3 times higher than that in men. Among the elderly, such complaints are made by about 48% of patients, namely, almost every second. Depending on the cause, dizziness may be of peripheral (otological), central and functional (psychological) origin [2].

Often vestibular disorders are acute. Dizziness can be accompanied by nausea, vomiting, intolerance to head movements, the appearance of nystagmus, instability when walking and balance disorders. The symptoms of peripheral and vestibular dysfunction partially coincide, and only a thorough history collection and a comprehensive physical examination help to conduct a qualitative differential diagnosis. Thus, the most common form of acute peripheral vestibular dysfunction is vestibular neuritis. In 25% of cases, the causes of severe imbalance of central origin are ischemic stroke of the posterior cranial fossa and demyelinating diseases [3].

The lack of standardization of vestibular testing can lead to diagnostic errors and incorrect choice of patient management tactics. In addition, it should be noted that most neurological and ENT rooms do not have sufficient equipment for the most qualitative and complete vestibular testing. Prolonged diagnosis due to prolonged examination of a patient with dizziness not only worsens his quality of life and leads to disability, but is also dangerous from the point of view of a possible rapidly developing severe pathology up to a threat to life.

2. Purpose: to highlight the historical aspects and the current state of the problem of examining patients with complaints of dizziness and share their own experience.

3. Results

An integral part of the diagnostic search for vertigo is the collection of complaints and anamnesis, standard otorhinolaryngological examination, as well as audiometric and otoneurological tests. To systematize and objectify complaints detected in patients with vestibular disorders, various scales, tests and questionnaires were created. The most common of them are the "Vertigo and Mnestic Functions Assessment Scale" (DHI), the "International Classification of Functional Disorders" (ICF) and the Karnowski Index [4, 5].

Often vestibular disorders are accompanied by tinnitus and hearing loss, which can serve as one of the criteria for diagnostic search. For this reason, a qualitative surdological study is necessary, which consists in assessing the indicators of tonal threshold bone and air conduction and conducting tuning fork tests. For example, in vestibular schwannoma, the intelligibility of spoken speech in the affected ear is usually markedly reduced, does not always correlate with the size of the tumor and may be disproportionate to the measured degree of hearing loss [6]. Interestingly, the absence of unilateral sensorineural hearing loss is not a reason to exclude the diagnosis of neoplasm: scientists describe at least 4.2% of cases of large acoustic neurinoma that do not affect hearing acuity [7].

Before the widespread use of magnetic resonance imaging, tympanometry, impedance audiometry and the Bekeshi test were considered to be among the most accurate methods of diagnosing cochlear pathology. Despite the limited accuracy of the research results, they allow us to assume the presence of the disease, the possible level of lesion and determine the further tactics of the patient's management. The most diagnostically valuable are the results of the study of auditory evoked potentials, which can be used as an additional screening measure in patients with unilateral hearing loss. In the latter case, magnetic resonance imaging makes it possible to indicate with maximum accuracy whether the symptoms are caused by brain neoplasm, circulatory disorders or some other cause [8, 9].

The safety of the function of the vestibular analyzer and cranial nerves is checked in the process of otoneurological examination. The corneal reflex, sense of smell, skin and taste sensitivity, chewing muscle tone, pharyngeal reflex, swallowing, phonation, facial expressions are evaluated [10, 11, 12]. Vestibular examination includes checking oculomotor reactions, as well as stato-coordination and statokinetic tests. The sampling should be carried out taking into account the general well-being of the patient. The study should be stopped immediately in case of a sharp deterioration of the patient's condition and provide him with the necessary assistance. With regard to the diagnosis of developing vestibular schwannoma, it should be remembered that dizziness may be the only symptom even if normal indicators recorded during audiometry are maintained.

When checking oculomotor reactions, the presence of spontaneous nystagmus, its direction, and the change in intensity in the absence of eye fixation are evaluated [12]. To exclude focusing on any subject, N. Frenzel in the middle of the 20th century proposed a device consisting of a combination of magnifying glasses and a lighting system that allows detecting eye movements better than with traditional examination [13]. With the help of N. Frenzel glasses, it is possible to register a hidden nystagmus. The doctor can also detect it without this device with the patient's upper eyelids closed by placing fingers on them and catching rhythmic eye movements. However, such a technique significantly limited the researcher in describing the characteristics of spontaneous nystagmus. In addition, rectangular saccadic oscillations can be detected in this test, the direction of which is not determined due to the almost equal deviation of the eyeballs by 0.5-5 degrees in both directions. These symptoms can be observed in smokers, with severe psychoemotional stress, progressive supranuclear paralysis of the eye and some cerebellar syndromes [12, 14].

Devices similar to N. Frenzel glasses have been proposed and improved by many scientists studying nystagmus [15-18]. The concept of the level of damage to structures is given by differential diagnosis of peripheral and central nystagmus, as well as an assessment of the preservation of the function of oculomotor systems – optokinetic, vestibular, saccades, smooth tracking [19]. Available methods for examining a patient with complaints of dizziness are caloric and rotational tests. These diagnostic methods are convenient to use as screening methods, since they suggest a violation of the function of the peripheral part of the vestibular analyzer without its quantitative assessment. Statocoordination and statokinetic tests (Romberg, index, Fischer-Vodak, marching) they can also be carried out during routine examination and are most informative in acute developing processes. At the same time, they have low information content in chronic diseases that

cause dizziness, due to compensation at the expense of the healthy side (for example, in long-term developing tumors) [20, 21].

Modern scientific approaches and technical capabilities have defined a new direction in the diagnosis of vestibular dysfunction using computer technology. Thus, static and dynamic equilibrium is studied using computer stabilometry, which allows not only to quantify the function of the vestibular analyzer, but also to store data in electronic form with the possibility of subsequent dynamic observation [21]. Electronystagmography is also widely used to examine a patient with dizziness. With the help of this technique, the movements of the eyeballs are graphically recorded, and according to the results obtained, it is possible to objectively evaluate the work of the vestibular analyzer. In addition, electrostagmography, being one of the most convenient and accessible approaches, is recommended for examination not only of adults, but also of children as the most gentle method of diagnosis, including in the absence of obvious otoneurological symptoms [22]. Electrooculography and video oculography are similar to this technique, with the help of which not only the fact of the presence of nystagmus is recorded, but also the movements of the eyeballs are recorded in order to allow their further detailed analysis [21].

One of the most modern, accurate and informative methods for assessing vestibular function is computer videonistagmography. The technique is characterized by high sensitivity and specificity and consists in a comprehensive objective automated analysis of oculomotor reactions, caloric and rotational tests. A significant advantage of this method is the ability to fix disorders of the function of the vestibular analyzer at the subclinical stage before their manifestation. Computer videonystagmography can be used to assess neurological dynamics in patients with neoplasm of the place-cerebellar angle before and after surgical and radiosurgical treatment, as well as during conservative therapy [23, 24].

The data of audiometry and otoneurological tests, which make it possible to identify a violation of vestibular function and to assume a probable pathological process, must necessarily be compared with neuroimaging methods for the most accurate diagnosis. In particular, such a technique is magnetic resonance imaging with a high degree of resolution (1.5 Tesla). If there is a suspicion of the formation of a place-cerebellar angle (in particular, a vestibular suture), contrast enhancement is used, in particular gadolinium. This method makes it possible to most accurately determine the size and localization of the tumor, its relationship with nearby structures, the presence of a cystic component. Magnetic resonance imaging with a low degree of resolution (0.2 Tesla) it also allows you to visualize a neoplasm (in particular, neurinomas less than 2 cm in size). However, for the most accurate diagnosis, preference should be given to a study with a high degree of resolution and contrast should be used [25, 26].

Computed tomography in bone mode also has sufficient information. In particular, according to the results of this study, in patients with acoustic neurinoma, the expansion in the area of the external auditory canal is visualized, as well as the anatomical topography of the structures of the temporal bone. However, neuroimaging methods, despite the highest accuracy and specificity, are still not routine, due to the high cost and the need for appropriate equipment, and with frequent use they are associated with the risk of increased exposure [27]. However, magnetic resonance imaging is recognized as the "gold standard" for the diagnosis of organic pathology of brain structures and should be prescribed if a disease of the central nervous system is suspected, which the doctor could assume according to other studies. For example, when treating patients with vestibular schwannoma as a screening method, preference should be given to magnetic resonance imaging performed in the turbo spin-echo mode, which has high sensitivity (100%), specificity (96%) and has not shown a single false negative result. In addition, this method is non-invasive and less expensive compared to contrast examination, which can always be performed to clarify the diagnosis and in case of complications [28].

Thus, due to the variety of conditions that cause dizziness, including an acutely developing pathology that poses a direct threat to life, at each stage of diagnosis, the patient needs a universally accessible and most detailed examination. However, at the stages of examination preceding neuroimaging, the search for the cause of dizziness may cause difficulties in correlating clinical manifestations with the alleged focal pathology. Due to the high specificity, accuracy, and accessibility, the use of KVNG at various modern diagnostic levels will optimize and make it economically more profitable to recognize the causes of dizziness, determine further tactics for managing patients with dizziness and monitor the course of treatment of the disease in dynamics.

4. Clinical case

As an example, let's give a clinical case. The otoneurologist was contacted by patient V., a 53-year-old man, complaining of dizziness, noise in the left ear, hearing loss on the left. The patient noted the first manifestations about six months ago, however, she did not attach importance to

the symptoms. During the last month, the dizziness intensified, which significantly affected performance, and the patient sought medical help at the polyclinic, from where he was referred to an ENT doctor, a surdologist and an otoneurologist. During a standard otorhinolaryngological examination, no data for acute ENT pathology were revealed. According to the results of audiometry, chronic sensorineural hearing loss of the left II degree was diagnosed.

As a screening otoneurological test, vestibulometry was performed using the VO 425 Interacustic device (Denmark). The technique consists in the automated diagnosis of labyrinthine hyporeflexia, which was recorded when performing the test of impulse movements of the head. To conduct the study, the patient wore special glasses equipped with cameras and illumination, ensuring the impossibility of focusing the gaze. The data obtained during the tests were processed using a standard program and displayed on a personal computer screen in the form of graphs and numerical expressions characterizing the operation of each semicircular channel. This study is the only one in the world that provides the fastest detection and assessment of the degree of damage to the vestibulocular reflex in response to stimuli in the high-frequency range, which is natural for head movements, simulating daily activity. The indisputable advantage of conducting vestibular testing using this device is its greatest comfort for the patient (sufficient speed of head pulses is provided even when turning no more than 20 degrees), as well as accessibility, maximum accuracy and speed of complex interpretation of the results.

Otoneurological examination of patient V. revealed the absence of spontaneous nystagmus, as well as pathological changes in the vestibulocular reflex and in the tangential deviation test. However, according to video pulse testing, hyporeflexion of the lateral and posterior semicircular canal on the left and the anterior semicircular canal on the right was noted (Fig. 1).

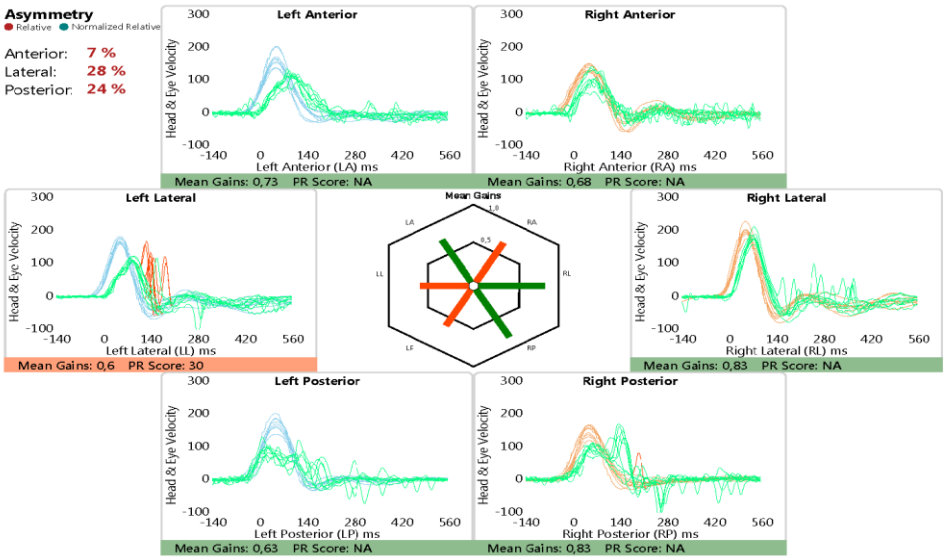

Figure 1. Graphical representation of the responses of semicircular channels to high-frequency stimuli.

The data of the video pulse test demonstrate peripheral vestibular disorders on the left, with satisfactory central compensation. To clarify the diagnosis, patient V. underwent magnetic resonance imaging, which showed the presence of a developing neoplasm of the vestibulocochlear nerve on the left (vestibular schwannoma) (Fig. 2).

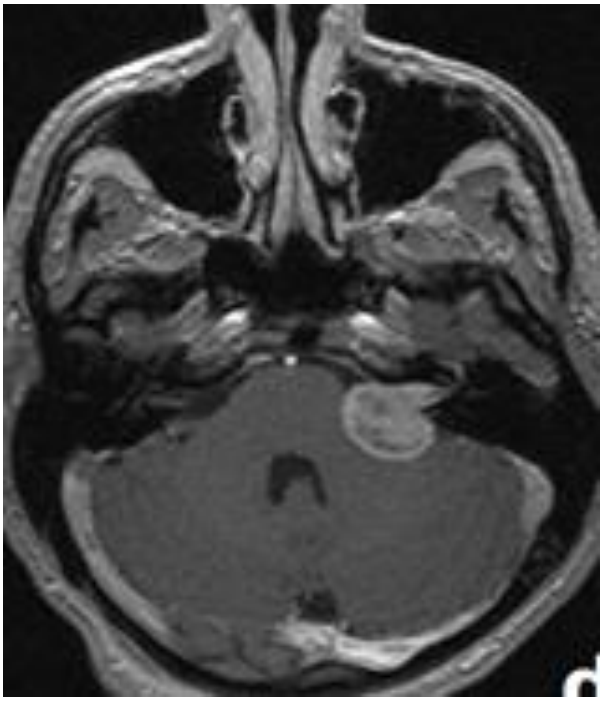

Figure 2. MRI in T1-weighted mode of patient V. 53 years old.

In the area of the internal auditory canal on the left, with a spread to the place-the cerebellar angle, an unevenly accumulating contrast agent is detected, with clear, even contours, up to 2.5 cm in diameter, presumably vestibular schwannoma.

Further tactics of examination and treatment For follow-up and therapy were explained to the patient. Patient B. was referred for consultation to a neurosurgeon and a neuroradiologist to resolve the issue of the possibility of radiohirrug treatment or the feasibility of surgical removal of the tumor.]. PBM therapy [7, 8, 17 - 19]...

5. Conclusions

Thus, vestibulometric examination of patients with complaints of dizziness is timely, accurate and allows to determine the presence and degree of peripheral vestibular pathology. An integrated approach to the diagnosis of the pathological process provides a competent definition of further management tactics for patients with vestibular dysfunction, and in particular patients with vestibular schwannomas, which avoids severe complications and prolonged disability.

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The use of artificial intelligence: the article is written without the use of artificial intelligence technologies.

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Review

Etiopathogensis of Macular Diseases in Terms of Glymphatic Fluid Circulation

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Abstract: This article is an analysis of theoretical aspects of etiopathogenesis of the macular zone of the eye in terms of glymphatic circulation of tissue fluid. To date, a lot of data has been accumulated on functional and structural changes of the macular zone in normal and in various pathologies. The genesis of macular edemas along with subretinal and choroidal neovascularisation could be highlighted and understood from a different point of view if assuming the presence of the glymphatic para- and perivascular fluid flow within the retina, channels in the vitreous body and the choroid. Clinical features of the various eye diseases including hereditary, highlight the paravascular glymphatic outflow routes. As a result of the data analysis, a new theory of disease development in the macular region has been developed for the first time, which explains the pathogenetic mechanisms of occurrence and progression of macular pathology based on the principles of glymphatic current.

Keywords: pseudophakic cystoid macular oedema, macular hole, Irvine-Gass syndrome, glympha intra-ocular fluid, transient macular oedema, age-related macular degeneration, serous retinal detachment

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1. Introduction

The etiopathogenesis of Irwin-Gass syndrome or pseudophakic cystic macular oedema (CMO) is not completely clear. It is generally believed that seepage from parafoveolar capillaries, which is recorded on fluorescent angiography (FA), leads to the formation of intraretinal cysts mainly in the outer nuclear layer. But macular oedema, observed in such hereditary diseases as X-linked retinoschisis, retinitis pigmentosa and Goldman-Favre syndrome, as a rule, manifests itself without seepage according to FA data [1]. The same absence of dye leakage from the parafoveolar capillaries is observed in maculopathy on the background of hypotension [2] and in drug-induced oedema from the action of nicotinic acid [3], drugs of the taxane group [4] and cefuroxime [5]. However, it should be noted that in hereditary degenerative diseases, the pattern of percolation in FA in the macular zone is similar to that observed in aphakia and posterior uveitis [6]. Despite a big step forward in the treatment of wet age-related macular degeneration due to anti-VEGF drugs, there are still unresolved issues concerning the etiopathogenesis of age-related macular degeneration (AMD), relapses of neovascularization and the so-called accumulation of intraretinal fluid [7,8]. There is also no single concept of etiopathogenesis of macular ruptures to date. Glymphatic pathways of fluid circulation in the posterior segment of the eye can answer many questions related to these conditions. **Aim** of this study is to highlight the macular disorders in terms of glymphatic fluid flow and to generate new theoretical concept of macular diseases.

2. Methods: literature review and analysis.

3. Results

3.1 Glymphatic circulation pathways in the eye

Lymphatic outflow is provided mainly by the conjunctival collectors [9] with the participation of the so-called uveolymphatic pathway [10,11]. At the end of the 20th century, a consensus was reached according to which the vitreous body, the interstitium between the glial cells of the optic nerve, the soft meninges between the septa of the optic nerve, the perivascular spaces and the subarachnoid space of the optic nerve, all together constitute a single pre–lymphatic space [12]. Perivascular channels in the adventitia of cerebral vessels (Virchow-Robin spaces) were described in 1859. In 2012, Iliff and colleagues "rediscovered" these spaces in the form of a single network of interconnected paravascular spaces of arteries and veins that circulate interstitial fluid with the excretion of metabolic products along the processes of astrocytes [13]. So, a new point of view on the exchange of interstitial fluid in the brain arose due to the so-called glymphatic system, which provides fluid exchange between paravascular spaces, nervous tissue and subarachnoid space with the participation of circadian rhythm and pulse wave [13-15]. It has been experimentally shown that the glymphatic outflow pathways of the eye include the vitreous body, the paravascular spaces of the retinal vessels and the suprachoroidal space [16]. Wang and co-authors (2020) proved that in mice with experimental glaucoma, fluid from the vitreal cavity enters directly into the interaxonal space of the optic nerve and moves centripetally, whereas in healthy mice, fluid is absorbed into the paravenous spaces of the retina, from where it flows along the axons of ganglion and amacrine cells along the gradient of hydrostatic pressure and is absorbed into the venous capillaries of the optic nerve membranes [16]. It is important to note that the interaxonal current in the optic nerve in rodents practically stopped when atropine and pilocarpine were instilled and was more pronounced in the light than in the dark [16]. Clinical ophthalmologists have suggested that interstitial glymphatic current in the thickness of the retina is involved in the pathogenesis of microcystic maculopathy at the level of the inner nuclear layer with the participation of Muller cells [17], as well as in the pathogenesis of paravascular posterior uveitis [18,19].

Clinical manifestations of diabetic maculopathy and retinopathy involving the vitreous body also confirm the great importance of glymphatic intraocular fluid circulation in their pathogenesis. We assumed that the fluid normally enters the premacular bag from the anterior segment of the eye through the central channel and is absorbed along the pressure gradient into the thickness of the retina in the fovea along with tissue fluid secreted by the macular choriocapillary lobule [20]. Further, this fluid flows in the thickness of the glymphatic spaces of the inner layers of the retina, where only the superficial and intermediate vascular networks are surrounded by perivascular astrocytes. The deep vascular plexus is surrounded only by the processes of Muller cells, therefore, excess tissue fluid from the outer layers of the retina is normally excreted through the retinal pigment epithelium (RPE), and with its excess into the vitreous body and into the glymphatic spaces of the inner layers of the retina and into the venous collection of the optic nerve sheaths, as was shown by experiment on rodents [16]. Venules predominate in the capillary network of the optic nerve disc, and there are also many astrocytes in this zone, which suggests the function of glymphatic outflow of tissue fluid in the optic cup area.

3.2 Pseudophakic CMO

The frequency of pseudophakic CMO is from 1 to 10%, which is similar to the frequency of transient macular oedema in the early stages after cataract surgery due to the toxic effect of cefuroxime 3.5% [21]. It is assumed that the etiology of the first one is associated with inflammatory factors and an imbalance between the rate of capillary filtration and the rate of fluid outflow from the retina through the perivascular interstitium. The second one is associated with dysfunction of the RPE proton pump and retention of the outflow of tissue fluid between the outer layers of the retina and choriocapillaries (see Fig.1).

It is likely that pseudophakic CMO and central serous chorioretinopathy or detachment (SRD) have common etiopathogenetic pathways of disorder of the water transport function of RPE [22-24]. A defect in the RPE was found between the optic disc and the macula in the FA in a patient with transient macular oedema from cefuroxime, while the authors noted the similarity of the OCT picture of the condition they described with Vogt-Koyanagi-Harada syndrome [5]. It is interesting to note that neovascularization in Vogt-Koyanagi-Harada syndrome is most often located in this zone – juxta-papillary between the optic disc margin and macula, where the perforant artery penetrates into the thickness of the retina.

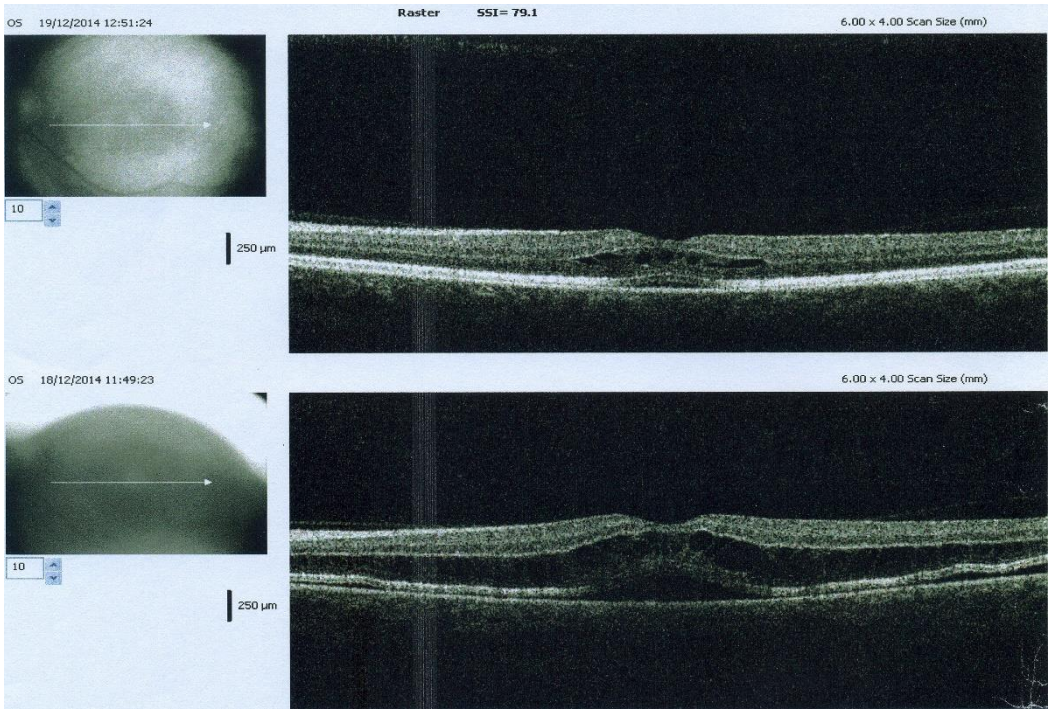

Figure 1. OCT picture of acute transient oedema after cataract surgery.

In pseudophakic CMO, anatomical and functional recovery is possible in 80% of cases, but in chronic CMO, in addition to cavities in the outer retina, histologically observed: perivascular infiltration by inflammatory cells, Muller cell oedema, mitochondrial oedema in the pre-laminar axons of ganglion cells, astrocyte degeneration and occlusion of surface capillaries of the retina [25,26]. The hydrostatic pressure gradient over the fovea is 3 times higher than over the optic nerve disc [20], which provides a flow of tissue fluid along papillomacular bundle into the lymphatic spaces of the optic nerve in addition to the difference in osmotic pressure of this fluid between the fovea region and the periphery of the retina. This may explain the pathogenesis of pseudophakic CMO and the observed histological changes. The largest and thickest choriocapillary lobule is located under the macula, the RPE cells are the widest and tallest here, and the elastic sieve-like layer of the Bruch membrane is the thinnest here [27].

In pseudophakic CMO, glymphatic flow in the macula probably fails because of weakened fluid flow through the central channel into the premacular sac and increased fluid secretion from the choriocapillaries or because of retention of its outflow towards the choroid. As a result, fluid accumulates in the outer retina. It does not have time to be transported by Muller cells into the vitreous body due to the presence of an ionic gradient limit and accumulates around retinal vessels for outflow through perivascular glymphatic spaces. The opening of the endothelium of retinal capillaries is probably compensatory and adaptive in order to improve the outflow of accumulated tissue fluid in the outer retina. With normalization of the functioning of the proton pump, the described imbalance of flow of tissue fluid from the choriocapillaries is restored. This is confirmed by the positive effect of carboanhydrase inhibitors in the course of cystic CMO. Muller cells, forming a framework in the foveolar zone, contain receptors for carboanhydrase inhibitors on their membrane, regulate the composition of extracellular fluid due to voltage-dependent ion channels, and also due to the presence of glutamate and GABA receptors, regulate depolarization of neurons and intracellular calcium levels [28].

Thus, we assume that it is the activation of the perivasal lymphatic outflow of fluid that causes the appearance of a cystic pattern and the leakage of the dye during FA. Only in this case there is an outflow of tissue fluid into the perivascular space and further into the paracellular spaces of the optic nerve. That is why diffuse macular oedema in uveitis is a poor prognostic sign, because there is no activation of the outflow of interstitial fluid. It which accumulates excessively in the thickness of the retina due to RPE dysfunction. The absence of normal tissue metabolism leads to the death of retinal neurons, followed by a decrease in central vision.

The lens contains melanopsin [29], a protein that is also expressed in the macular retina on specialized melanopsin-containing ganglion cells involved in the regulation of circadian rhythm through the suprachiasmatic nucleus and epiphysis. Also, in the thickness of the retina in the outer nuclear and ganglion layers, MT1 melatonin receptors are expressed [30]. The absence of which leads in mice to an increase in intraocular tone by 5 mmHg at night and to the death of up to 30%

of ganglion cells with age [31]. The protein dystrophin, also expressed in the macular zone and in the thickness of the lens, also affects the intraocular pressure. The absence of this gene in mice leads to a decrease in intraocular tone and is also associated with Alzheimer's disease. It is known that the transmembrane protein BEST 1 belongs to the family of calcium-activated anion channels regulating transepithelial transport of chlorides, is associated with the β-subunit of Ca2+ channels and is located on the basolateral membrane of the RPE [32].

Thus, there is a circulation of tissue and intra-ocular fluid (IOF) in the thickness of the retina, the optic nerve and the central channel of the vitreous body. At the same time, at night, there is an outflow of tissue fluid in the thickness of the retina from the macular zone towards the optic nerve along a pressure gradient, probably mainly in the thickness of the ganglion nerve fibre layer. This glymphatic outflow, which occurs only at night, depends on pressure gradients, head position, pulse pressure and the coordinated functioning of aquaporin-4 and G-protein receptors in the glial spaces of the retina. In the brain, for example, perivascular glymphatic spaces expand at night in order to increase the inflow of cerebrospinal fluid, followed by outflow together with tissue glymphatic fluid [33]. It has been established in rodents that aquaporin-4 on Muller cells and astrocytes is highly expressed, mainly along the border between the inner limiting membrane (ILM) and vitreous body. In the process, networks in the inner and outer plexiform layers opposite the capillary networks and is less expressed on fibrous astrocytes of the optic nerve and its soft sheaths [34].

The relationship between cataract surgery and macular pathology has been noticed for a long time. It was found that in the early stages (maximum values after 1 month) after uncomplicated cataract surgery, there is a thickening of the ganglion cell complex-the inner plexiform layer [35]. CMO in patients with ophthalmohypertension in the background of prostaglandin intake can occur on the artiphakic eye even 9 months after cataract surgery [36] and even 24 months later [37], as well as against the background of drug withdrawal in refractory operated glaucoma [38]. I.e., in some circumstances, there is a direct relationship between the values of IOP and the thickness of the retina in the macular area. We also observed appearance of CMO in several clinical cases when using prostaglandin analogues in patients with artiphakia, which resorbed when they were cancelled with an increase in IOP. Given the presence of prostaglandin receptors in the retina [39], these observations are quite understandable.

3.3 AMD

Deposition of pigment granules from RPE in the thickness of the neuroepithelium occurs in maculopathy against the background of tamoxifen [40], as well as in the late stages of age-related macular degeneration. It is known that retinal vessels radially diverge on average of 8.9 ± 0.23 around the foveola, and arterioles are usually located above the venules [41]. There are more diverting venules in the parafoveolar zone than arterioles. I.e., there are about 8 channels located radially around the foveola, and one vertical from the central channel of the vitreous. Moreover, the latter plays one of the leading roles in the pathogenesis of macular diseases, since posterior vitreous detachment (PVD) is reliably a factor of protection against both pseudophakic cystic macular oedema [42] and AMD [43]. It has also been found that in diabetes mellitus, partial PVD contributes to increased proliferation, and full PVD causes a stop of the proliferative process [44].

In patients with AMD, when stimulated by a light wavelength of 488 nm, increased emission is observed with autofluorescence at the level of the Bruch membrane and subretinal deposits, in contrast to the control group without AMD [45]. This indicates an altered chemical composition of the intercellular fluid in this zone, probably due to a primary change in the outflow rate of the interstitial fluid, followed by the activation of inflammatory factors on such metabolic products as beta-amyloid, etc.

The macula has a high density of green and red cones that express carbohydrase, but in the foveola there are only blue cones that do not express carbohydrase receptors [46] and a special type of Muller astrocytic cells on the roof of the foveolar fossa. These data may indicate that through the foveola, there is normally an outflow of tissue and intraocular fluid towards the RPE and into the thickness of the retina at night and an influx during the day from the choriocapillaries to cool the RPE and remove metabolic products.

Carboanhydrase inhibitors in some patients with primary glaucoma cause choroidal effusion, which may indicate a significant outflow of intra-ocular fluid through the retina into the suprachoroidal space in these patients, especially given the presence of carboanhydrase receptors in the RPE and glia [47]. It is known that the perichoroidal space, behind on the nasal side of the eyeball, ends 2-3 mm from the exit point of the optic nerve. On the temporal side – at the central fossa of the retina, and in front – at the attachment point of the ciliary body to the scleral spur. The lymphatic vessels of the conjunctiva are maximally developed from below-inside the eyeball and have nasal-ventral and temporal-dorsal polarization [8]. The number of vorticose veins collecting blood from the choroid clearly does not allow taking the entire volume of tissue fluid, and part of the tissue fluid goes through the suprachoroidea and sclera into the lymphatic collectors of the face

and neck [9]. But the central region of the retina has an additional, autonomous glymphatic outflow of tissue fluid along the glial spaces of the retina itself into the thickness of the optic nerve and its para-sheaths space.

The shape of the drusen with the convex side up indicates that the delay of tissue current and fluid stasis occurs precisely in the direction from under the RPE towards the vitreous body. The etiopathogenesis of AMD is unknown for certain changes in the structure of choriocapillaries, etc., although much is clear about the pathogenesis of this disease, including activation of the complement system and cytokines. We assume that the triggering moment of AMD is not just physiological photo-oxidative stress in the central zone of the retina, namely, a decrease in the rate of hydrodynamic flows in the macula and the occurrence of fluid stasis. A decrease in the metabolic rate in this zone and the accumulation of detritus: intralaminar basal deposits, soft and dry drusens also occur. Figure 2 shows the accumulation of fluid in the perithyroidal pocket, which is located between the Bruch membrane and hyperreflective deposits in the thickness of the detached retinal pigment epithelium which correlates with the activity of the neovascular membrane in AMD [8]. The process of neovascularization in AMD itself may be the primary adaptive factor for eliminating excess interstitial fluid accumulating in this zone through newly formed "fenestrated" vessels. It has been proven that endothelial vascular growth factor (VEGF) is the main element for the pathogenesis of wet AMD, and it also reduces the hydraulic bandwidth throughout RPE [48].

Thus, we assume that a decrease in the hydrodynamic parameters of the rate of transition of HCV into the interstitial fluid of the inner layers of the retina, as well as a decrease in the rate of tissue fluid exchange between the choriocapillary lobule and the outer layers of the retina are the main glymphatic components of the etiopathogenesis of age-related degenerative diseases of the macular zone. The hydrostatic pressure gradient between the vitreous, sensorineural and pigment epithelium, calculated in the area of the foveolar fossa, is about Δ 5 mm Hg. [20], which is confirmed by experimental data [49], therefore, even a slight decrease in the rate of inflow of IOF through the central channel into the macular sac and/or a decrease in the rate of fluid outflow through the RPE towards the choroid can lead to stasis of the interstitial fluid in this zone. The main reason for the decrease in the rate, is probably age-related in the production of IOF by ciliary processes and altered regulation of the transport of tissue fluid in the macula. A change in osmotic gradients between the external hematophthalmic barrier and the interphotoreceptor space, leading to fluid stasis under RPE and "intoxication" by products of the exchange of choriocapillaries, RPE cells and photoreceptors, also occurs. It is important to note that damage to ganglion cells in AMD occurs much more significantly in the exudative form of AMD than in the non-exudative form.

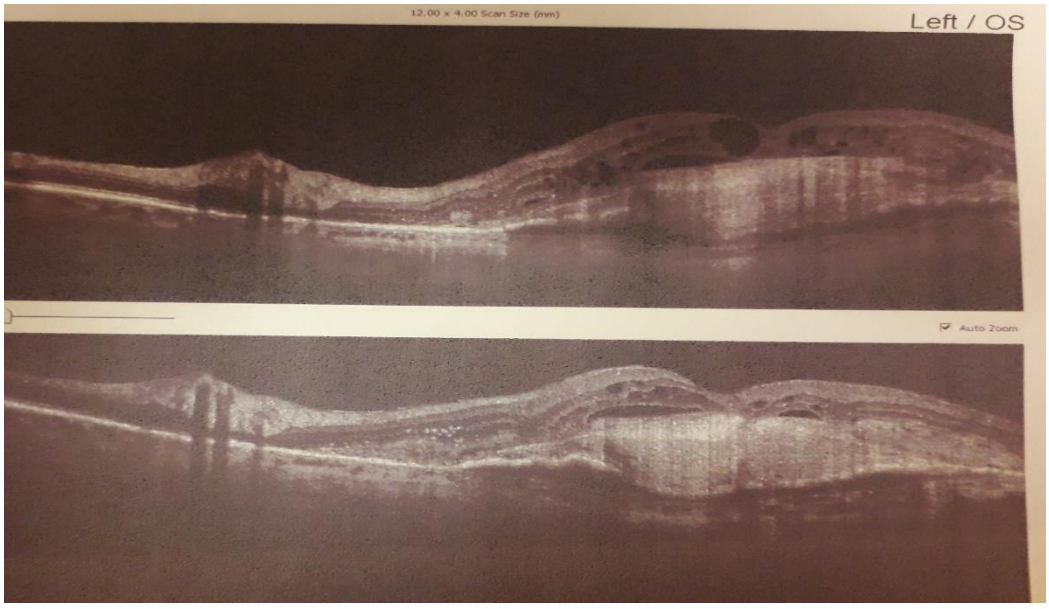

Figure 2. OCT picture of a patient with a wet form of AMD after 3 injections of anti-VEGF therapy with the presence of a prechoriodal pocket and accumulation of fluid around the scar

Age-related cataract is also probably associated with impaired circulation of IOF around the lens capsule and the Bergson space towards the posterior segment of the eye. The development of

age-related posterior capsular cataracts in the native vitreous body may indicate either the presence of excess oxygen in IOF behind the lens, which occurs predominantly preretinally in the posterior segment of the eye, or the stasis of the fluid washing the lens in the Bergson space. This is probably due to the low throughput of the foveolar radial outflow path of glymphatic fluid, as well as direct reverse absorption to the choroid through the RPE.

Confocal microscopy of cadaveric eyes revealed an additional silent vessel in the avascular zone of the retina in 2 out of 9 cases, which adds to the understanding of the etiopathogenesis of the wet form of AMD [41].

3.4 Macular rupture

To date, there are several theories of the development of macular ruptures. The theory of Gass (1973), based on the disorder of the skeleton functions of Muller cells located Z-shaped in the thickness of the macular zone, is complemented by the traction theory. Alpatov (2005) proved that cystic retinal oedema with subsequent trophic disorder forms the basis of structural and functional disorders around the rupture, and epiretinal membranes can also form at the last stage of rupture formation, after the development of complete PVD [50].

The initial or first stage (1a) of idiopathic age-related macular rupture presupposes the elevation of the neuroepithelium under the foveola. i.e., the influx of fluid from under the RPE secreted by the choriocapillary lobule exceeds its absorption rate into the thickness of the retina. Further excess inflow of tissue fluid can lead to the formation of intraretinal cysts when local compensation pathways are activated by Muller cells and ILM astrocytes, but eventually leads to a divergence of the retina in the radial direction. It is known that macular ruptures most often primarily manifest in the morning. During the night, fluid accumulates in the thickness of the retina, which could not be "pumped" along the perivasal outflow pathways, as well as due to a violation of the physiological process of vertical outflow of tissue fluid towards the choroid due to a violation of the transport function of the RPE. Therefore, an excess of tissue fluid is formed, aiming to "go down the sides" into the thickness of the retina, while the entry point is the foveola. Hydrodynamic flows of interstitial fluid rushing along the gradient of hydrostatic pressure towards the optic disc along the axons of the ganglion cells of the papillo-macular bundle and below in the plexiform layers are normally carried out due to the processes of Muller cells and glial astrocytes, as well as convection. But when certain conditions are combined: degenerative glial changes and/or functional disorders (failure of regulation by the dopamine-melatonin system in the retina, decreased blood flow in the macular choroidal lobule, etc.), these outflow pathways are disrupted, and a macular rupture occurs.

OCT images of the macular zone of the operated macular rupture show that fluid accumulation in the early postoperative period (up to 1 month) occurs in the same "spaces" as in CMO: in the cystic cavities in the outer plexiform and nuclear layers (Fig. 3 and 4) and directly under the foveola (see Fig.3).

Thus, convection in the foveolar zone, which increases during the day under the influence of light and chemical reactions, leads to the formation of cysts with violations in the glymphatic outflow at night against the background of a malfunction in the functioning of the RPE. The dopamine-melatonin system of macular RPE and neuroepithelium performs a regulatory role and depends on circadian rhythms on the day-night principle. At night, the outflow of tissue fluid goes through the glymphatic paravasal spaces of the retina and optic nerve (central vascular bundle and venules of meningeal membranes). During the day, under the influence of light, the glymphatic current flows along the axons of ganglion cells and mainly through retinal veins, as well as through the capillary network of the choroid, ciliary body and optic nerve into venous and lymphatic collectors. The production of a residence permit occurs in the ciliary processes and choriocapillary lobules mainly at night and in the morning in order to activate the circulation of tissue fluid with which it is mixed.

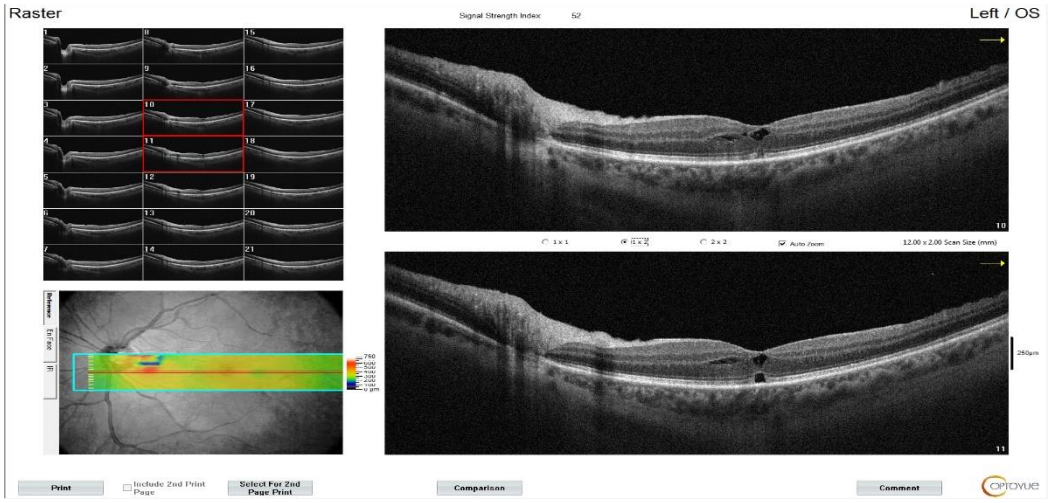

Figure 3. OCT picture of the macular interface in the early postoperative period of macular rupture surgery.

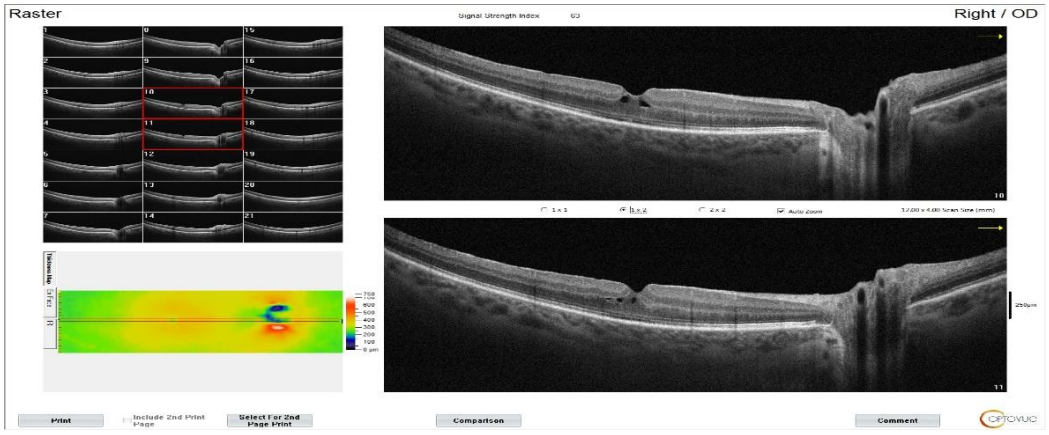

Fig. 4. OCT picture of operated macular rupture with cavities in the outer layers of the retina in the early postoperative period

In the macular zone there is a "crossroads" regulated by the dopamine-melatonin system through the suprachiasmal nucleus, which, thanks to the RPE, Muller cells, glial astrocytes and paravasal spaces, provides a bidirectional fluid flow in the thickness of the retina in two planes: longitudinally radial and transversely through the thickness of the retina. A schematic representation of the circulation of tissue fluid in the central zone is shown in Fig. 5.

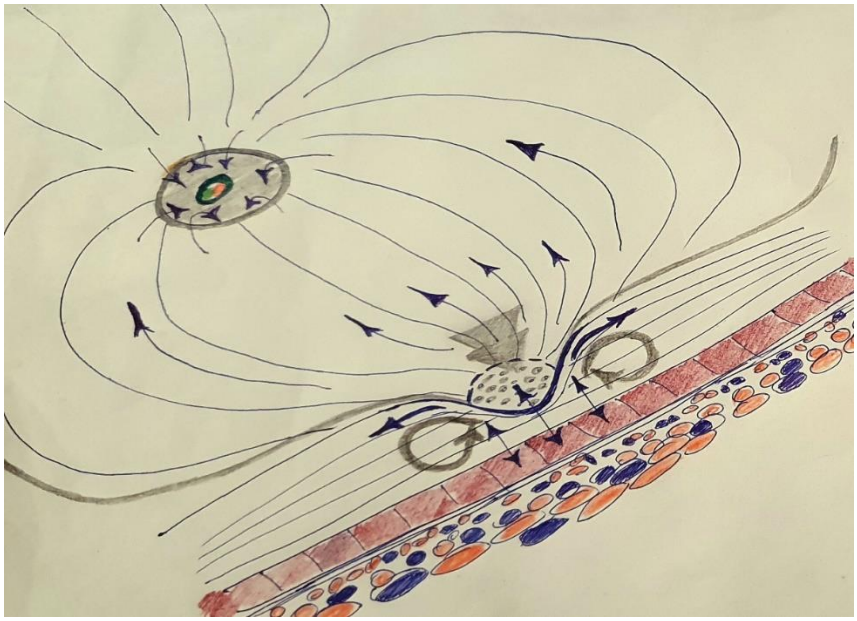

Fig. 5 Schematic representation of tissue fluid circulation in the central area of the retina. The blue arrows represent the interaxonal fluid flow (along the surface capillary network). The gray thick arrow above the foveola is the HCV current from the central channel through the thickness of the retina. Gray arrows around the foveola in the thickness of the retina – the direction of fluid flow under the action of convection.

4.1 Hydrodynamic theory of the development of macular diseases

1. Idiopathic degenerative/age-related macular ruptures from a hydrodynamic point of view can be explained by a violation of the flow of tissue fluid through the thickness of the retina at the point of entry into the fovea both from the premacular bag and from under the RPE. In this case, a rupture in the fovea occurs with a sharp increase in the flow rate of the interstitial fluid in the thickness of the retina in the radial direction against the background of an increase in the contractile activity of the processes of Muller cells. Macular rupture is detected, as a rule, in the morning after sleeping in a horizontal position, in particular, and on the first day after phacoemulsification, which confirms the hypothesis of a radial-longitudinal glymphatic flow of tissue fluid in the inner layers of the retina in the macula.

2. Age-related macular degeneration manifests itself with a decrease in the flow rate of lymphatic tissue fluid in the thickness of the retina and from under the REM in this area. A decrease in the flow of glymphatic fluid occurs with age with a decrease in heat production in the retinal pigment epithelium, which leads to a decrease in convection and circulation of tissue fluid in the foveolar zone, accumulation of metabolic products and deposition of retinal and subretinal druzens. The fact that in macular ruptures, as a rule, there are no concomitant macular druzens indirectly confirms paragraphs 1 and 2.

3. Epiretinal fibrosis occurs with a decrease in the rate of outflow of IOF diffused from front to back towards the retinal RPE and choriocapillaries along the posterior hyaloid membrane into the thickness of the inner layers of the retina. Stagnation of tissue fluid, coupled with an increase in the concentration of proinflammatory factors and protein fractions that have passed through the external hematophthalmic and/or hematopoietic barriers, leads to the deposition of inflammatory products on the surface of the posterior hyaloid and/or internal boundary membranes. Thus, idiopathic epiretinal fibrosis occurs as an "attempt" to suspend the amount of diffused fluid from the vitreous body into the thickness of the retina and RPE, as well as in the opposite direction during inflammatory and infectious processes of the posterior segment.

5. Conclusions

In the posterior segment of the eye, in addition to a slight fluid flow from front to back towards the RPE, there are two ways of tissue fluid flow: the first is radial, which is caused by fluid flow along the axons of ganglion cells along the paravasal pathways of the superficial capillary network into the thickness of the axons of the optic nerve. The second is longitudinal in the outer layers of the retina, draining into the paravascular glymphatic spaces of the optic nerve and to a lesser extent under the RPE in the choriocapillaries. The first one functions mainly at night in a

horizontal position under the influence of gravity and hydrodynamic gradients of the bags and channels of the vitreous body and the pressure of the cerebrospinal fluid, and the second direction of the tissue fluid flow occurs during the day and is due to the electrochemical potential of the visual act, i.e. heating of the retina in the macular zone and the difference in temperatures in different parts of the retina, i.e. convection. Gravitational (gravispin) forces and the hydrodynamics of a charged fluid are two forces that cause the circulation of the interstitial and IOF.

Thus, the totality of data on various eye diseases, as well as the revealed clinical features of their course based on the latest scientific data and glymphatic flow in the nervous tissue allowed us to make assumptions about the presence of new physiological patterns of fluid flow in the posterior segment of the eye and formulate a new concept of the development of macular diseases.

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The use of artificial intelligence: the article is written without the use of artificial intelligence technologies.

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