Optic neuritis in various demyelinating diseases

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The discovery of antibodies against aquaporin-4 (AQP4) and against myelinoligodendrocyte glycoprotein (MOG) confirmed the existence of two disease entities distinct from multiple sclerosis (MS) – neuromyelitis optica spectrum disorders (NMOSD) and myelinoligodendrocyte glycoprotein-associated disease (MOGAD). Demyelinating optic neuritis (ON) can be either idiopathic (iDON) or a manifestation of MS, NMOSD (AQP4-ON) or MOGAD (MOG-ON).

Objective: to determine the clinical features of ON and to evaluate the diagnostic value of optical coherence tomography (OCT) in demyelinating diseases of the central nervous system.

Material and methods. The study included 43 patients with demyelinating ON who were divided into three groups according to the underlying disease (NMOSD, MOGAD and MS/iDON). We assessed visual acuity (VA) in the acute phase and analyzed VA and average values of retinal nerve fiber layer thickness (RNFL) and retinal ganglion cell complex (RGC) thickness using OCT data 6 months after the onset of ON.

Results. ON was observed in the onset of the disease in 75% of NMOSD patients, 62% of MOGAD patients and 86% of MS/iDON patients. In the MOGAD and NMOSD groups, bilateral ON was predominantly observed. In 65% of patients with MOGAD (MOG-ONr), a recurrent course of ON was observed. VA was significantly lower in patients with AQP4-ON in acute phase and comparable to the MOG-ONr group in the long-term phase. VA in the onset of MOG-ON with a single episode was comparable to that of MS/iDON (p=0.2), but recovery was less pronounced (p=0.03). The most significant thinning of the RNFL and RGC complex was observed in the AQP4-ON and MOG-ONr groups. In AQP4-ON and MOG-ON groups, restoration of VA up to 0.5 and higher was observed significantly more frequently in the group of patients receiving pulse therapy with glucocorticoids (p=0.018).

Conclusion. The study showed the most pronounced structural and functional disturbances in the long-term phase of AQP4-ON and MOG-ONr. MOG-ON was characterized by a high frequency of relapses with the influence of this factor on VA and thinning of the retinal layers in the long-term.

Keywords: optic neuritis; neuromyelitis optica spectrum disorders; a disease associated with the presence of antibodies against myelin oligodendrocyte glycoproteins; multiple sclerosis; demyelinating diseases; optical coherence tomography.

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Optic neuritis (ONt) can develop both at the onset and during the chronic phase of CNS demyelinating diseases. In 2022, a new classification was proposed and diagnostic criteria for ONt were formulated to improve the quality of diagnosis of this pathology [1]. Taking into account the peculiarities of the course of ONt, it is proposed to distinguish "typical" and "atypical" ONt [2]. Idiopathic ONt or ONt associated with MS belong (IDON/MS) to "typical" ONt and are characterized by unilateral lesions, involvement of the anterior portions of the optic nerve (ONv) with the lesion extent not more than $^{2}/_{3}$ of the ONv length, insignificant edema of the optic disc (OD). Patients with "typical" ONt usually complain of a sensation of para-orbital or retrobulbar pain, color vision impairment, and decreased VA. Visual function impairment in most cases has a favorable prognosis and regresses partially or completely within one month. In "atypical" ONt, cases of painless simultane-

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ously or sequentially developing bilateral lesions of the ONv prevail, with the involvement of more than half of the ONv length, including chiasma and optic tracts. Visual function may decrease to loss of light perception and loss of visual acuity may progress over two weeks, which is often associated with a poor prognosis for visual function recovery, even with glucocorticoid treatment [2]. The atypical course of ONt suggests a demyelinating disease other than MS with known serologic markers. Over the last 15 years, two new glial antibodies have been identified, AQP4-IgG (antibodies IgG to aquaporin-4, AQP4) and MOG-IgG (myelin oligodendrocyte glycoprotein, MOG) [3]. Thus, two new forms of autoimmune demyelinating diseases of the CNS have been identified - disease associated with antibodies to myelin oligodendrocyte glycoprotein (MOG-antibody-associated disease - MOG-AD) and neuromyelitis optica spectrum disease (NMOSD), which according to diagnostic

criteria are divided into seropositive and seronegative variants depending on the presence of antibodies to aquaporin-4.

NMOSD is an orphan disease accompanied by autoimmune-mediated damage to the CNS and rapidly leading to severe disability. The regions of the Far East and Southeast Asia have the highest prevalence of NMOSD (prevalence 3.36 and 3.56; morbidity rate 0.41 and 0.65 per 100 000 population in 2016 and 2017, respectively). Data on the prevalence of the disease in Russia are scarce, but the high geographic clustering of the disease in Asian countries is relevant for Russia, given the diversity of ethnicities in Russia, including Mongoloids [4]. MOG-ON is a demyelinating disease of the CNS, identified as a separate nosological form distinct from MS and NMOSD. International diagnostic criteria for MOG-ON were published for the first time in 2018, and adjusted in 2023. The incidence rate of MOG-ON worldwide ranges from 0.16 to 1.4 per 100 000 [5].

The most important goal is the timely detection of ONt, which in some cases is the first manifestation of a demyelinating CNS disease. ONt as the initial and the only manifestation of NMOSD is observed in 37-93% of patients. Isolated ONt is the most frequent manifestation of MOG-ON (54-59%) [6]. Recognition of clinical features that helps to distinguish typical MS-associated ONt from "atypical" ONt in NMOSD and MOG-ON is of primary importance for determining the tactics of examination and treatment of the patient. Despite an increase in the number of articles devoted to this topic, there is still insufficient awareness of specialists about clinical and paraclinical signs of "atypical" ONt, which leads to a high frequency of untimely or ineffective selection of therapy and disability of young patients [7]. Over the last 2 years, the modalities of laboratory and instrumental diagnostics of ONt have expanded, and the value of retinal optical coherence tomography (OCT) for differential diagnostics of various types of ONt has been demonstrated. OCT is a noninvasive, fast and accurate method for visualization of the retinal nerve fiber layer (RNFL) and individual retinal layers in the macular zone. A number of studies in recent years showed that evaluation of structural changes in the retina is highly informative in the examination of patients with CNS demyelinating diseases [8]. The use of OCT allows to assess the degree of axonal loss by measuring RNFL thickness and neuronal damage by measuring the RGCC. Many studies have shown OCT signs of acute ONt characteristic of various demyelinating diseases. ONt in the MOG-AD is known to be associated with the most frequent and severe edema of the OD at the onset of ONt compared to other demyelinating diseases (OD edema is present in 86% of cases) [9]. In MS-associated ONt, the OCT demonstrates normal but, in some cases, asymmetric values of RNFL and RGCC thickness in the first 4-8 weeks from the onset of ONt. There may also be thickening of the RNFL associated with edema of the OD, but much less than in MOG-AD [10]. In MOG-AD, most studies show greater thinning of the RNFL and RGCC in the acute period of ONt compared to MS [11]. However, the above signs are often not recorded due to the fact that OCT in the acute period of ONt is performed in only a small number of patients. Nevertheless, the degree of partial ONv atrophy that develops in the long-term period of ONt may also differ depending on the specific demyelinating disease. The thickness of the peripapillary RNFL and RGCC should be assessed not earlier than 6 months after ONt, when all structural changes at the level of these ONv structures have occurred [12].

The aim of this study was to determine clinical features of ONt and evaluate the diagnostic significance of OCT in CNS demyelinating diseases.

Materials and methods. Forty-three patients with demyelinating ONt (main group) and 20 healthy control participants were included in the study. The main group included patients with NMOSD (AQP4-ON) (8 patients, 15 eyes – group 1), MOG-ON (21 patients, 34 eyes – group 2), MS/IDON (14 patients, 16 eyes – group 3). In the MOG-ON group, cases of ONt were divided by the type of the course into cases with a single episode of MOG-ON and remitting episodes (MOG-ONr).

Inclusion criteria were: time interval of OCT performance – at least 6 months since the last exacerbation of ONt; AQP4-IgG and MOG-IgG seropositivity in the respective groups. Patients with MS met the McDonald 2017 criteria [13]. MOG-ON was diagnosed based on the diagnostic criteria adopted in 2015 by the International Panel for NMO Diagnosis (IPND) [14]. MOG-ON was diagnosed based on the 2018 international recommendations [15].

Demographic (sex and age at the time of ONt onset) and clinical data (duration of the disease, number of eyes with ONt symptoms, number of episodes of mono- and bilateral cases of ONt; information on the therapy with registration of steroidrefractory cases), data of ophthalmologic examination in the acute and long-term (at least 6 months later) periods of ONt were collected in all patients. The data were analyzed for each eye separately.

The examination of the final VA with maximum correction was performed using the Sivtsev–Golovin table. OCT of the retina and optic nerve was performed using Spectral Domain OCT RTVue-100 (Optovue Inc., USA). Patients underwent crossline scans, retinal thickness maps in MM5 mode, scanning of the optic disc (ONH and 3D Disc protocols) and thickness maps of the RGCC: RGCC, nerve fibers and inner plexiform layer (GCC protocol – Ganglion Cell Complex). The mean values of RNFL (Avg. RNFL) and RGCC thickness (Avg. RGCC) in the remote period of ONt (at least 6 months later) were compared. In addition to the mean values of RNFL, this index was assessed separately by sectors.

Laboratory diagnostics for serum MOG-IgG and AQP4-IgG was performed on the basis of "Scientific Center of Neurology" by indirect immunofluorescence with cellular presentation of antigen.

Clinical characteristics of the patients are summarized in Table 1.

Statistical analysis was performed using Statistica 6.0 software. Variables were presented as mean values and standard deviations or medians and interquartile range. Qualitative variables were presented as absolute values and percentages. Normality testing of the distribution was not performed due to the small sample size (n<30). To compare quantitative data in two unrelated samples, nonparametric Mann–Whitney U-test and Kruskal–Wallis analysis of variance were used. Chi-square test was used to compare nominal variables in two unrelated populations, and Fisher's exact test was used if there were limitations for its use. Correlation analysis was performed using Spearman's rank correlation coefficient due to the lack of assumption of normality of distribution. P-value 0.05 was considered to be statistically significant. The efficiency of OCT parameters for differential diagnosis of typical (MS/IDON) and atypical ON (AQP4-ON, MOG-ON with a single episode of ONt, MOG-ONr) was evaluated using ROC curves.

Results. The analysis of demographic parameters (Table 1) revealed the predominance of the female sex in all observation groups and no significant difference when comparing the age of ONt onset in these diseases; however, the minimum and maximum indices showed a large variation in the group of patients with NMOSD (8.2/53.2 years) and MOG-ON

(3.0/60.3 years). ONt was the initial symptom of the disease in 75% of patients with NMOSD, 62% of patients with MOG-ON, and 85.7% of patients with MS/IDON.

As presented in Table 2, the prevalence of bilateral ONt was observed in the MOG-ON and NMOSD groups. ONt exacerbations occurred in 65% of patients with MOG-ON and were not observed in other groups. There were no significant differences in the frequency of pain with eyeball movement in all three groups. Patients were comparable in terms of disease duration.

Comparison of VA in CNS demyelinating diseases is presented in Table 3. In the AQP4-ON group, VA in the acute period was significantly lower compared to all studied groups. In the long-term period, the final VA in AQP4-ON was comparable to MOG-ONr (p=0.06). VA at the onset of MOG-ON with a single episode and in MS/IDON was comparable (p=0.2), but the recovery was less pronounced (p=0.03). There was a complete recovery of VA in patients with MS/IDON in the remote period of ONt.

The results of OCT in CNS demyelinating diseases are summarized in Table 4. The lowest thickness of RNFL was found in the AQP4-ON group and in the MOG-ONr group. Similar structural differences were found in the thickness of the RGCC.

A strong direct correlation between VA and the thickness of RNFL (K=0.59; p<0.001) and RGCC (K=0.58; p<0.001) was revealed in the late phase in the group of patients with AQP4-ON and MOG-ONr. However, this correlation was absent in the group of patients with a single episode of MOG-ON.

In order to determine the most significant index and sensitivity and specificity of OCT parameters in the late phase in the differential diagnosis of typical and atypical ONt, ROC analysis was performed. We obtained the results demonstrating that atypical ONt can be predicted with sensitivity of 82.4% and specificity of 62.5% if the thickness of RNFL in the nasal sector is less than or equal to 77.8 $\mu m.$

Discussion. In this study, ONt was the initial symptom of CNS demyelinating disease in the majority of patients. The prevalence of bilateral ONt was found to be higher in NMOSD and MOG-ON compared to MS/IDON. Our findings are in line with the results obtained by other authors [16]. According to our findings, AQP4-ON and MOG-ON differ in their course, prognosis of ONt recovery, and response to treatment. MOG-ON has

 Table 1.
 Clinical and demographic characteristics of patients

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Parameters	NMOSD	MOG-ON	MS/IDON			
Number of patients/eyes with ONt, n	8/15	21/34	14/16			
Gender (female/male ratio), n	6:2	16:5	9:5			
Age of onset of ONt, years: M±σ min-max	33,1±16,8 8,2-53,2	30,0±13,5 3,0-60,3	29,3±9,4 18,1–54,5			
Duration of disease after ONt, years: M±σ min-max	3,6±5,7 0,2–17,0	4,4±4,7 0,4–17,1	2,1±4,2 0,02–13,0			
Number of patients with ONt at the disease onset, n (%)	6 (75)	13 (61,9)	12 (85,7)			

Table 2.Characteristics of the course of ON in various
demyelinating diseases, n (%)

Parameters	NMOSD (n=8) 1	MOGAS (n=21) 2	MS/IDON (n=14) 3	р
Remitting type of ONt	-	14 (65)	-	
Bilateral ONt	7 (87,5)	13 (62)	2 (14)	$\begin{array}{c} P_{1-2} = 0,37 \\ P_{1-3} = 0,0015 \\ P_{2-3} = 0,0069 \end{array}$
Retro-orbital pain	2 (24)	10 (48)	9 (64,2)	$\begin{array}{c} P_{1-2} = 0,4 \\ P_{1-3} = 0,183 \\ P_{2-3} = 0,49 \end{array}$

Table 3.	VA i	in demy	velinating	ON
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Parameters	AQP4-OH	MOG MOG-OH 2a	G-ON MOG-OHp 2b	MS/IDON 3	р
VA in the acute phase: M±σ min–max	0,0006±0,001 0-0,005	0,2±0,25 0,001-0,7	0,08±0,17 0-0,7	0,3±0,41 0,01-1,0	$\begin{array}{c} p_{1-2a} = 0,0002\\ p_{1-2b} = 0,0001\\ p_{1-3} = 0,000009\\ p_{2a-3} = 0,2\\ p_{2b-3} = 0,002\\ p_{2a-2b} = 0,04 \end{array}$
VA in the long-term period $M\pm\sigma$ min-max	i: 0,2±0,39 0-1,0	0,9±0,28 0,1-1,0	0,5±0,45 0-1,0	1,0±0	$\begin{array}{c} p_{1-2a} = 0,0005 \\ p_{1-2b} = 0,06 \\ p_{1-3} = 0,000005 \\ p_{2a-3} = 0,03 \\ p_{2a-3} = 0,00006 \\ p_{2a-2b} = 0,01 \end{array}$

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OCT parameters	AQP4-OH 1	MOG MOG-OH 2a	G-ON MOG-OHp 2b	MS/IDON 3	р
RNFL, μm	64,7±13,6	90,5±3,71	72,3±18,0	93,6±12,5	$\begin{array}{c} p_{1-2a} = 0,0005 \\ p_{1-2b} = 0,3 \\ p_{1-3} = 0,000005 \\ p_{2a-3} = 0,6 \\ p_{2b-3} = 0,007 \\ p_{2a-2b} = 0,005 \end{array}$
RGCC, μm	65,9±11,4	85,0±11,3	65,2±10,6	85,4±10,4	$\begin{array}{c} p_{1-2a}=\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!\!$

Table 4.OCT indicators for demyelinating ON

a favorable course with a high potential for VA recovery in most cases. However, some cases of MOG-ON are characterized by a high frequency of exacerbations, especially after glucocorticoid withdrawal, with cumulative structural and functional damage to the ONv with each subsequent exacerbation of ONt. In this regard, the prognosis of VA recovery in MOG-ON patients with a single episode of ONt and remitting course of ONt is different. The final VA in our patients with MOG-ONr was significantly lower than in patients with a single episode of MOG-ON and did not differ from that in AQP4-ON, which indicates the need for timely prevention of exacerbations to reduce the disability of patients [17].

NMOSD is a severe disabling neuroinflammatory disease characterized by episodes of ONt and transverse longitudinal myelitis extending to more than 3 vertebral segments. AQP4-ON is characterized by a severe decrease in VA and extensive ONv lesions extending to the optic chiasm and optic tracts, poor response to glucocorticoid therapy, and persistent visual deficits [18]. Our results confirm the presence of significant structural and functional changes of the ONv in NMOSD after the first episode of ONt. Outcomes after a single episode of AQP4-ON and MOG-ONr were comparable.

Along with brain MRI and targeted orbital examination, which allow to clearly visualize focal changes in the ONv structure, OCT has no less diagnostic value, as it allows to assess structural changes in the inner retinal layers arising from the

ONv. When analyzing the OCT results of the patients included in this study, the lowest thickness of RNFL and RGCC was detected in the NMOSD group, which is consistent with the data of similar works [19]. At the same time, the OCT parameters did not differ in patients with AQP4-ON and with MOG-ONr, which is the result of the influence of the number of ONt episodes on the severity of structural damage to the retina and ONv. There was also no difference of structural indices in patients with MS/IDON and MOG-ON patients with a single episode of ONt, which confirms the favorable course of a single episode of MOG-ON and necessitates therapy aimed at prevention of ONt exacerbations. The absence of cor-

relation of VA with OCT parameters in the group of patients with a single episode of MOG-ON is a hallmark of MOG-ON, showing dissociation of severe structural damage to the ONv and preserved VA. The mechanisms of this process have not been determined and require further studies of the pathophysiology of MOG-ON [20].

OCT maps of the patients included in the study showed that there was a predominantly decreased thickness of the RNFL in the temporal sector in MS/IDON, whereas moderate to severe thinning of the RNFL was observed in all peripapillary sectors in MOG-ON. Differences in the degree of RNFL thinning were most prominent in the nasal sectors, remaining within the normal range in almost all eyes of MS/IDON patients.

Conclusion. The majority of patients included in the present study showed symptoms of ONt at the onset of CNS demyelinating diseases. AQP4-ON had the most severe course with damage to the ONv and unfavorable prognosis of VA recovery. The peculiarity of MOG-ON was a high frequency of ONt exacerbations, with an obvious influence of this factor on VA in the late period and on the degree of loss of the RNFL and RGCC. Early diagnosis of atypical ONt using modern diagnostic methods, timely initiation of therapy in the acute period of ONt, as well as prophylactic therapy between exacerbations is crucial to prevent blindness and loss of VA in young patients. OCT can be used as an auxiliary diagnostic tool for differential diagnosis of demyelinating ONt.

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Conflict of Interest Statement

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