Consensus of expert advices on routing, diagnosis, and management of patients with neuromyelitis optica spectrum disorders

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Neuromyelitis optica spectrum disorders (NMOSDs) are autoimmune inflammatory disorders accompanied by central nervous system damage, widespread immune-mediated demyelination, and axonal damage, involving mainly the optic nerves, spinal cord, and area postrema. The diagnostic capabilities, administration and routing of patients, and therapeutic approaches to this disease need to be improved. During several expert councils held in 2019–2021 in different regions of the Russian Federation, we discussed multiple issues related to various aspects of medical care for patients with NMOSDs. As a result, the experts developed further steps necessary to improve the medical care to these patients: to write and publish clinical guidelines for the diagnosis and treatment of NMOSDs; to consider the possibility of optimizing the NMOSDs diagnostic program including the aquaporin-4 antibodies (AQP4-IgG) testing; to evaluate the implementation of a set of measures aimed at including the corresponding laboratory investigations into the system of state guarantees (together with the institutions of the Ministry of Health of Russia), if there is clinical and economic feasibility; to include the issues of timely NMOSDs evaluation in educational programs initiated by the scientific medical community, in order to raise awareness of primary care neurologists in relation to the clinical and neuroimaging signs of probable NMOSDs; to assess the possibility of introducing routing schemes for patients with NMOSDs at the regional level; to work out a decision on the collection of NMOSDs epidemiological and clinical data in the Russian Federation.

Keywords: *neuromyelitis optica spectrum disorders; neuromyelitis optica; aquaporin-4; expert advice.*
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Introduction

Neuromyelitis optica (NMO) is an autoimmune inflammatory disease of the central nervous system, in which there is widespread immune-mediated demyelination and axonal damage involving mainly the optic nerves and spinal cord. In 2014, during development of the International Consensus Diagnostic Criteria (ICDC), it was decided that the term «neuromyelitis optica» should be included in the single descriptive term «neuromyelitis optica spectrum disorders», or NMOSD. NMOSD prevalence rate in the world varies from 0.1 to 5 cases per 100 thousand people [1].

Currently, in the Russian Federation, it is difficult to identify patients with NMOSD due to the objective difficulties of diagnostics, absence of wide access to testing of the disease biomarker (antibodies to aquaporin-4 – AQP4-IgG), lack of suspicion and detailed information about the disease among both neurologists and radiologists, as well as lack of clinical recommendations on diagnostics of this group of patients. Management of patients with NMOSD is carried out in the absence of available and registered pathogenetic therapy. Due to high relevance of the issues of identification, recording and management of patients with NMOSD expert councils were held in 2019–2021 to address the identified problems and possible solutions.

Evolution of the Definition of Neuromyelitis Optica and Neuromyelitis Optica Spectrum Disorders. Laboratory Diagnostics

Originally, the term «neuromyelitis optica» was understood as a monophasic or recurrent disease in which bilateral optic neuritis and transverse myelitis occur simultaneously [2]. In 2004, disease-specific antibodies, Class G immunoglobulins, which selectively bind to aquaporin-4 (AQP4), were identified in the blood serum of NMOSD patients [3]. Detection of antibodies to aquaporin-4 in about 70% of patients with NMOSD has demonstrated the diversity of the disease spectrum, elevating NMO into a distinct nosological entity and dividing patients into aquaporin-4 seropositive and seronegative [3,4].

It is important to understand that clinical characteristics, immunopathogenesis and therapy do not differ depending on which term was used in diagnostics – NMO or NMOSD. In addition, it should be noted that patients with incomplete forms of NMO often begin to conform to the classical understanding of NMO over time [5, 6]. The historically preserved term NMO remained inside the term NMOSD. The revised criteria emphasize that clinical, serological and neuroimaging data must be integrated to diagnose; the diagnosis cannot be based solely on revelation of AQP4-IgG antibodies.

Since development of optic neuritises and/or myelitis is also possible in case of multiple sclerosis (SS), the practical significance of differentiation of two demyelinating diseases lies in the fact that approaches to their treatment are fundamentally different: multiple sclerosis disease modifying drugs (MSDMD) can provoke exacerbations in patients with NMOSD [5].

In 2014, an international expert group consensus thus made it possible to diagnose AQP4-IgG seropositive NMOSD in patients with central nervous system damage who have not yet developed clinical signs of optic nerve or spinal cord involvement in the pathological process with AQP4-IgG seropositive antibodies to aquaporin-4 (AQP4-IgG). The reasons for this decision were as follows: (1) no data were obtained on the biological differences between patients with NMO compared to NMOSD (using the 2006 and 2007 definitions) in AQP4-IgG-seropositive patients; (2) NMOSD in AQP4-IgG-seropositive patients begins by affecting areas of the nervous system other than the optic nerve or spinal cord often preceding the subsequent typical clinical NMO syndromes; (3) modern immunotherapeutic approaches are the same for recurrent NMO and NMOSD, regardless of serological status on AQP4-IgG antibodies.

Taking into account the diverse clinical picture, in many cases, the onset of NMOSD may prompt patients to consult various specialists: neurologists, gastroenterologists, rheumatologists, ophthalmologists, etc. Due to a lack of suspicion of NMOSD, the diagnosis is often delayed and patients may remain symptomatically treated by non-specialists for long periods of time. In routine clinical practice in the Russian Federation, the timeliness of performing serum AQP4-IgG testing in a variety of clinical situations remains a problem. This may be due to a number of objective reasons, including the possibility of testing, and insufficient awareness of doctors about the indications for its implementation [7].

For verification of the diagnosis, a laboratory test to detect antibodies to aquaporin-5 in serum by cell-based assay, using indirect immunofluorescence, is optimal, but the less sensitive immunofluorescence method (ELISA) for this diagnostic task has been used more frequently so far. To ensure high affordability of laboratory diagnostics with proper sensitivity and specificity characteristics in relation to antibodies to aquaporin-4, it is required to include AQP4-IgG test by indirect immunofluorescence in the nomenclature of medical services provided to the citizens of the Russian Federation under compulsory medical insurance, as well as in clinical recommendations for NMOSD. These steps require preparation of clinical, epidemiological and economic justifications for inclusion of AQP4-IgG test in the program of state guarantees of provision of free medical care to Russian Federation citizens [5].

Epidemiology of NMOSD in Russia and Globally

NMOSD refers to orphan diseases, since the total prevalence rate of NMO in all geographical regions can make about 1.82 per 100,000 persons of population [1, 8].

There are currently no accurate data on the epidemiology and clinical course of NMOSD in the Russian population, nor is there a mechanism for regular epidemiological data collection. There is no NMOSD registry at the state level and in the Russian Federation regions, and therefore the issue of collection of statistical data on the epidemiology, demographic and clinical characteristics of patients with NMOSD is relevant.

There is virtually no data on the prevalence of the disease in Russia [2]. In 2019–2021, the first observational epidemiological study was performed to determine the clinical and epidemiological characteristics of NMOSD. A cross-sectional interval study was conducted in 25 Russian Federation entities having different geographical locations. Based on the obtained data, the predicted number of patients in the Russian Federation may range from 660 with a low degree of

prognosis to 6,179 with a high degree of prognosis, which corresponds to spread of 0.45 to 4.21 per 100,000 persons of population [5].

Data on the number, demographics and clinical characteristics of patients with NMOSD and NMO observed in 2020-2021 by neurological specialists in different regions were presented at the expert council meetings.

According to the presented data, the average onset age most often corresponds to similar world data (30–40 years and older) [9]. The frequency of seropositive forms also corresponds to international data and makes approximately 65–70% of the total number of cases; however, in some Russian Federation regions this indicator is lower due to unavailability of anti-AQP4-IgG test. Unfortunately, it takes an average of 2.5 to 5 years from the onset of the disease to diagnosis. The average level of disability assessed by the EDSS is above 4.0–5.0 in most cases, reflecting the severity of the disability.

Taking into account the presented data, it seems relevant to search for solutions for timely diagnosis of NMOSD and improvement of availability of diagnostics for AQP4-IgG antibodies. These steps will make it possible in the future to start pathogenetic treatment promptly after the onset of disease in patients with ASONM and ONM and to keep disability rates low in these patients. Within the expert councils, the need of update of the problem of NMOSD and closer interaction, exchange of experience between specialists in order to reduce the time of diagnosis was discussed. Nevertheless, the epidemiological data on NMOSD in the Russian Federation are disaggregated since there is no system for recording patients with NMOSD at the state level and most regions of the Russian Federation have not developed routing rules for patients with NMOSD.

Patient's Path with NMOSD: Routing

Routing of patients with suspected NMOSD remains an unsolved problem. Given the common pathogenetic and clinical features between nosologies such as multiple sclerosis and NMOSD and the demyelinating and autoimmune nature of both pathologies, the vast majority of NMOSD patients end up being referred to specialized centers that provide care for patients with multiple sclerosis.

At the state level, the system of care for MS patients is represented by a network of specialized centers, regulated by regional or city orders, which serve to improve the organization of specialized medical care for MS patients. Neurologists working in these centers (interdistrict MS centers, regional, republican and city MS centers, MS offices) in daily clinical practice treat patients with various neurological autoimmune demyelinating diseases (including, but not limited to, NMOSD, acute multiple encephalomyelitis, MOG-associated central nervous system damage and other conditions). However, the almost universal lack of indication in these

The results of neurologists' observations of patients with NMO and NMOSDs in different regions, presented at a series of expert councils in 2020–2021

Region, institution	Number of patients		Average onset	Time to	Antibodies	EDSS level,
	all	number of women, %	age, years, mean ±SD	diagnosis, years, mean±SD	to AQP4, n (%)	mean, points
E.V Popova, IDMS of SBHI CCH No. 24, Moscow	21	16 (76)	42.8±10.8	4.9±6.9	14 (67)	3.88
D.S. Kasatkin, Clinical Hospital No. 2 (Center of Demyelinating Diseases), Yaroslavl	6	5 (83)	52.5	Not determined	4 (67)	4.73
S.V. Kotov, SBHI MR MRCRI named after M.F. Vladimirsky, Moscow region	23	16 (70)	35.5	Not determined	0	5
A.A. Sokolova, District Center of Multiple Sclerosis, Khanty-Mansiysk	10	8 (80)	37	Not determined	7 (70)	4.6
T.N. Trushnikova, Regional Center of Multiple Sclerosis, Perm	15	14 (93)	35.7	Not determined	13 (87)	4.6 (for 9 patients with NMOSD)
F.A. Khabirov, SAHI RCDC for demyelinating diseases of the Ministry of Health of the Republic of Tatarstan, Kazan	35	24 (69)	43.4	Not determined	17 (49)	5.4/3.8 (Anti-AQP4 +/– respectively)
S.A. Sivertseva, Tyumen Regional Center of Multiple Sclerosis, Tyumen	52	41 (79)	46.2	Not determined	7 (13)*	5.4
K.Z. Bakhtiyarova, RCH named after Kuvatov, Multiple Sclerosis Center, Ufa	35	25 (71)	39	Not determined	5 (14)**	5.3
N.A. Malkova, Regional Center of MS and other AID NS, Novosibirsk	19	10 (53)	37.5	Not determined	14 (73%)	<6.5 in 84% (16 patients)

Note. *24 patients were not examined. ** All patients were not examined. N – number of patients; SD – standard deviation; IDMS – Interdistrict Department of Multiple Sclerosis; SBHI – State Budgetary Healthcare Institution; CCH – City Clinical Hospital; SBHI MR MRCRI named after M.F. Vladimirsky – State Budgetary Healthcare Institution of Moscow Region «Moscow Regional Clinical Research Institute named after M.F. Vladimirsky»; RCDC DD of MH of RT – Republican Clinical Diagnostic Center for Demyelinating Diseases of the Ministry of Health of the Republic of Tatarstan; RCB – Republican Clinical Hospital

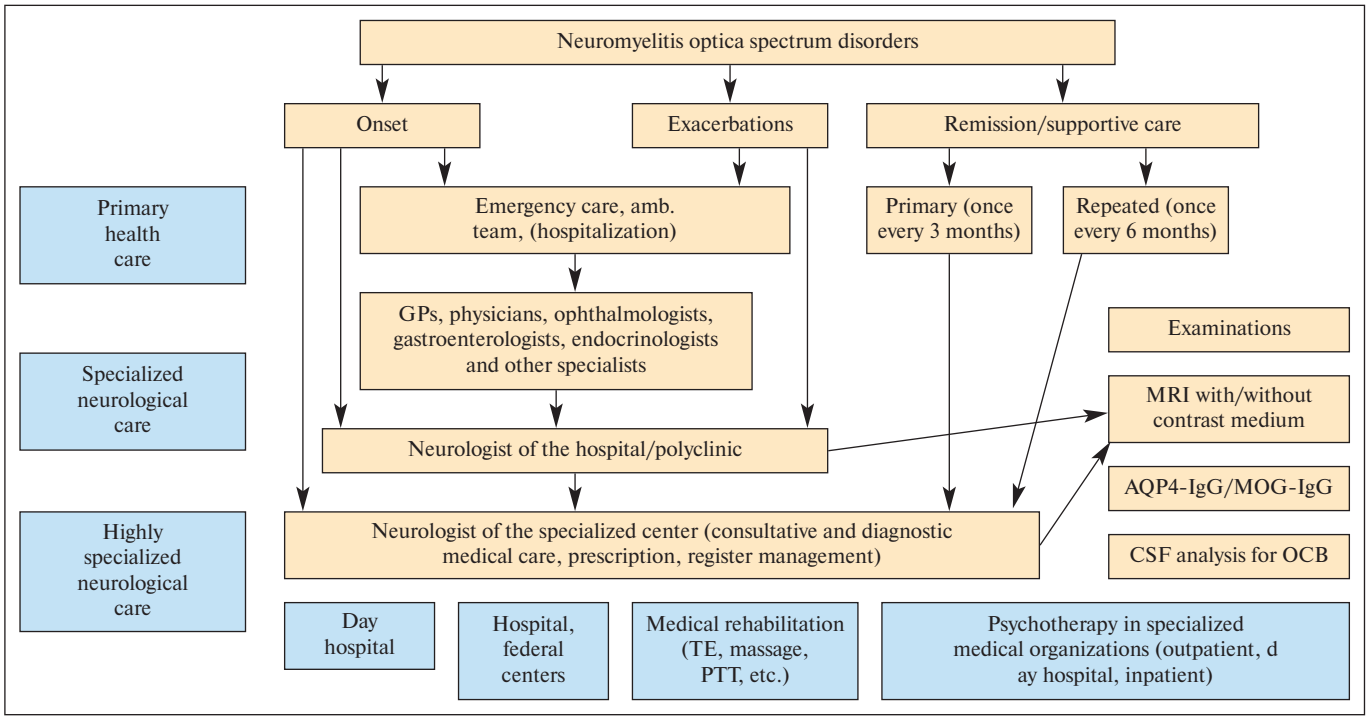
orders for the routing of patients with NMOSD to these specialized centers prolongs the time to diagnosis, does not guarantee the patient's registration in such a center and makes it difficult to provide the patient with the necessary pathogenetic therapy. The solution of the problem currently seems to be in development of the routing scheme for these patients and in update of regional orders regarding specialized centers for MS patients, inclusion of patients with NMOSD in the list of patients who have the right to apply to, be monitored and get treatment in these centers.

Taking into account the above, it was proposed within the expert council to develop the routing scheme for patients with NMOSD. The aim of this step is to ensure rapid diagnosis of patients, clear procedures for their examination and treatment, and a basis for improved epidemiological data collection on patients with NMOSD and approaches to their management.

During the Expert Council on December 10, 2020, the experts' answers to a questionnaire with formulated proposals on routing of patients for familiarization and expression of the level of agreement with a particular statement were evaluated. The scale of agreement ranged from 0 to 10 points, where 0 points: no agreement; 1–3 points: low level of agreement; 4–6 points: average level of agreement; 7–10 points: high level of agreement. Responses were received from 14 experts. The following statements got the maximum level of expert agreement:

1) Patients with the established diagnosis of neuromyelitis optica spectrum disorder/neuromyelitis optica/Devic disease (hereinafter - NMOSD) should be registered at a dispensary, monitored by a neurologist, if possible in a specialized center (office) for MS/demyelinating diseases/autoimmune diseases, as well as in other centers that deal with the management of patients with MS. *Agreement level: 9.9 out of 10.*
2) Therapy of exacerbations of patients with NMOSD should be carried out in hospital conditions in specialized departments (neurological, resuscitation and intensive care units, neuro-intensive care units, intensive care wards at the neurological department) using pulse therapy with corticosteroids and/or plasmapheresis. *Agreement level: 9.7 out of 10.*
3) A routing scheme for the NMOSD patient flow over the age of 18 according to the purpose for which they seek medical care is shown in Figure 1. *The agreement level was 8.9 out of 10.*
4) Diagnosing is based on Diagnostic criteria of neuromyelitis optica spectrum disorders, developed in 2015 by the international group under the supervision of D.M. Wingerchuk (given in Russian in the works of A.N Belov et al. [8], T.O. Simaniv et al. [5]. *Agreement level: 9.9 out of 10.*

The resulting patient routing and management scheme can be used at the regional/federal level as a basis for regulatory documentation on routing and the procedure of provision of specialized medical care to patients with NMOSD and other autoimmune diseases of the central nervous system (Figure 1).



Routing scheme for neuromyelitis optica spectrum disorders patients flow over the age of 18 according to the purpose for which they seek medical care (Appendix 1)
TE – therapeutic exercise; MRI – magnetic resonance imaging; OCB – oligoclonal bands; CSF – cerebrospinal fluid, amb. – ambulance; PTT – physiotherapy treatment; AQP4-IgG – Class G immunoglobulins to aquaporin-4; MOG-IgG – Class G immunoglobulins to myelin oligodendrocyte glycoprotein.

Pathogenetic Therapy

As of September 2021, there is no commercially available and registered pathogenetic therapy in the Russian Federation that modifies the course of the disease in case of NMOSD. Azathioprine, mycophenolate mofetil and rituximab, used off-label for the prevention of exacerbations, do not always achieve satisfactory results in terms of both efficacy and safety of therapy. There are no clear recommendations for the duration and dose selection for drugs used off-label.

In a survey of expert council members, low levels of satisfaction with the effectiveness (2.75 out of 5), safety (2.75 out of 5) and accessibility (2.1 out of 5) of existing therapies were found. Thus, there is currently a need in the scientific and medical community for effective, safe and accessible therapy. Experts discussed the need for clinical guidelines from the professional community, approved by the Ministry of Health, which would improve the provision of specialized medical care for this disease.

A number of clinical studies have been carried out in recent years which have investigated the use of a number of drugs in NMO and NMOSD. In particular, a therapy aimed at inhibiting the interleukin-6 pathway has been shown to be effective and safe in NMOSD [11], and study results have been published on a complement component inhibitor C5[12]. The therapy has already been registered and is available in several countries worldwide, and registration of a drug aimed at suppressing the interleukin-6 pathway is also expected to take place soon in Russia.

Conclusion

In view of the issues described above, a number of provisions aimed at improving the diagnosis, monitoring, recording and treatment of patients with NMOSD were formulated and recorded during the expert councils held:

1. To write and publish harmonized clinical guidelines on the diagnosis and treatment of NMOSD;
2. To consider the possibility of optimization of the NMOSD diagnostic program with inclusion of testing for antibodies to aquaporin-4 (AQP4-IgG), in those patients whose symptoms and clinical picture suggest the probability of NMOSD; to evaluate the implementation of a complex of measures aimed at inclusion of the appropriate laboratory test in the system of state guarantees (together with the institutions of the Ministry of Health) subject to clinical and economic feasibility;
3. To include issues of timely diagnosis of NMOSD in educational programs initiated by the scientific medical community in order to raise awareness of primary care neurologists regarding clinical and neuroimaging signs of probable NMOSD;
4. To evaluate the possibility of implementation of the routing schemes for patients with NMOSD at the regional level;
5. To develop a solution on collection of epidemiological and clinical data in respect of NMOSD in the Russian Federation.

Appendix 1.

This article is based on the results of work of four expert councils on routing, diagnosis and management of patients with neuromyelitis optica spectrum disorders. Expert councils were held on June 13, 2019 (St. Petersburg), December 10, 2020 (online event), May 15, 2021 (St. Petersburg), June 26, 2021 (online event).

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