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# Overview of the Current Situation and Challenges about Neuromyelitis Optica Spectrum Disorders in the Republic of Macedonia

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## Abstract

**BACKGROUND:** Neuromyelitis optica spectrum disorders (NMOSD) are rare, progressive inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination targeting optic nerves and spinal cord. Prior establishment of diagnostic criteria, patients were often misdiagnosed which led to delayed/inappropriate treatment and disability. Current practice involving immunotherapies is insufficient. Recent data are encouraging since the novel treatments allow effective prevention.

**AIM:** The primary objective was to evaluate the current situation to identify challenges and develop intervention that might improve the current state as secondary objectives.

**METHODS:** Standard questionnaire containing 22 questions was developed. Collected data were analyzed and descriptive report was created.

**RESULTS:** Current estimated prevalence is approximately 20 NMOSD patients; trend is unknown due to unavailability of patient registry. Six neurologists from one health-care institution are responsible for the whole management. Despite physician's insufficient experience, ~80% of them are willing to switch patients into innovative treatments once available. Aquaporin-4-IgG testing is not routinely available resulting in ~30% testing rate. Approximately 80–90% of patients are on maintenance treatment with immunosuppressant, corticosteroids are used for acute relapse. Lack of novel innovative medications is evident.

**CONCLUSION:** Current NMOSD management is challenging with significant unmet needs. Highest priorities that might provide improvement are: AQP4-IgG testing availability, establishment of patient registry, and availability of novel treatments.

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## Introduction

Over a century ago, the first clinical descriptions of neuromyelitis optica (NMO) spectrum disorders (NMOSD, previously known as Devic disease or NMO), were documented by Devic and Gault [1], [2]. NMOSD are inflammatory disorders of the central nervous system (CNS) characterized by severe, immune-mediated demyelination, and axonal damage predominantly targeting the optic nerves and spinal cord. It was previously believed that NMOSD and multiple sclerosis (MS) represented one disease entity, with variable phenotypes and expression. Recent evidence indicates that NMOSD is distinct from classic relapsing-remitting MS with respect to pathogenesis, imaging features, biomarkers, neuropathology, and treatment. Now, NMOSD is recognized as a distinct clinical entity based on unique immunologic features. The discovery of a disease-specific serum NMO-IgG antibody that selectively binds aquaporin-4 (AQP4) has led to increased understanding of a diverse spectrum of disorders. In NMOSD, floric demyelination and inflammation involve multiple spinal cord segments and the optic nerves with associated

axonal loss, perivascular lymphocytic infiltration, and vascular proliferation [3] whereby necrosis and cavitation typically involve both grey and white matter [4]. The pathophysiology of NMOSD is thought to be primarily mediated by the humoral immune system [3], [5], [6], [7]. Several lines of evidence support an autoimmune pathogenesis for NMOSD. The most important of these was the identification of a NMOSD disease-specific autoantibody, AQP4 autoantibody [8]. Serum AQP4 autoantibody titers at the nadir of clinical attacks have been shown to correlate with the length of longitudinally extensive spinal cord lesions [9], [10]. In addition, serum anti-AQP4 titers have been shown in several studies to correlate with clinical disease activity, decline after immunosuppressive treatment, and remain low during remissions [9], [10], [11]. Additional data support the autoimmune pathogenesis since NMOSD is frequently associated with some systemic autoimmune diseases mediated by pathological antibodies; as hypothyroidism, pernicious anemia, ulcerative colitis, myasthenia gravis, and idiopathic thrombocytopenic purpura; and non-organ-specific disorders such as lupus erythematosus (LE), antiphospholipid antibody syndrome, and Sjögren syndrome [12], [13], [14].

NMOSD is a rare disorder. The prevalence in various studies ranges from 0.5 to 10/100,000 [15], [16], [17], [18], [19], [20], [21] and recognized gender, ethnic, and geographic disparities [22], [23]. The incidence of NMOSD in women is up to 10 times higher than in men [24], [25], [26]. The median age of onset is 32–41 years, but cases are described in children and older adults [11], [15], [24], [25], [26].

Hallmark of NMOSD includes acute attacks of transverse myelitis (often causing limb weakness, sensory loss, and bladder dysfunction) or optic neuritis (bilateral or rapidly sequential) leading to severe visual loss with a typically relapsing course [1], [2], [3], [24], [26], [27]. Attacks most often occur over days, with variable degrees of recovery over weeks to months [28]. CNS involvement beside that of the spinal cord and optic nerves is also recognized in NMOSD patients.

NMOSD must be distinguished from MS, which is the most common disorder likely to cause CNS demyelination. Furthermore, acute disseminated encephalomyelitis and other autoimmune diseases such as LE and Behçet disease may rarely have similar presentations. According to the Revised 2015 Diagnostic Criteria for NMOSD, diagnosis is based on the presence of cardinal clinical characteristics, AQP4 antibody status, and magnetic resonance imaging neuroimaging features [29].

The rationale of the treatment of acute and recurrent relapses in NMOSD is based on evidence that humoral autoimmunity plays a role in the pathogenesis and is driven by the high attack-related disability, poor prognosis, and overall high risk of mortality if left untreated [11], [30]. All suspected NMOSD patients should be treated for acute attacks with high-dose intravenous corticosteroids (methylprednisolone 1 g daily for 3–5 days). For patients with severe symptoms, whose are unresponsive to corticosteroids, the suggested rescue treatment is plasma exchange started quickly [11], [31], [32]. Due to devastating nature of the disease, long-term maintenance therapy should be started as soon as possible after the first attack, since attacks may be frequent and neurological disability can accumulate rapidly [31], [33]. There are no data for optimum duration of immunosuppressive maintenance therapy, but guidelines suggest continuing for 5 years to cover period with the highest relapse risk (2–3 years after presentation) [34]. At present, there are no approved medications for the acute or maintenance treatment of NMOSD. Current practice includes off-label use of immunotherapies for prevention or relapse treatment.

There is no randomized, controlled trials that would confirm effectiveness and tolerability of these off-labeled treatments.

A number of potential NMOSD pharmacological therapeutic targets have been identified, including interleukin-6 (IL-6), B cells, and complement. At present,

there are ongoing Phase III trials investigating satralizumab (IL-6 inhibitor), eculizumab (C5 inhibitor), inebilizumab (CD19 mAb), and RC 18 (B cell activating factor inhibitor).

The natural history of NMOSD is one of the stepwise deteriorations due to accumulating visual, motor, sensory, and bladder deficits from recurrent attacks (relapses) which worsen over days to a nadir and recover over several weeks to months with significant sequelae. The predictors of a worse prognosis include the number of relapses within the first 2 years, the severity of the first attack, older age at disease onset, and an association with AQP4 antibody status. The mortality rates are high in NMOSD (ranges from 25% to 50%), most frequently secondary to neurogenic respiratory failure, which occurs with extension of cervical lesions into the brainstem or from primary brainstem lesions [11]. Progress in the diagnosis, treatment, and care of NMOSD patients is expected to decrease the mortality rates.

The primary objective of our study was to evaluate and clarify the current situation in NMOSD, while the secondary objectives were to identify the challenges, unmet needs and develop a potential intervention with aim to improve the current state.

## Methods

A standard questionnaire was developed and specifically designed for this work, in cooperation with neurologists with experience in this field with aim to ensure relevance and easy comprehension. The survey contained 22 questions, divided in five sections related to NMOSD prevalence, current physician awareness and knowledge, AQP4 antibody testing, current treatment approach, and funding mechanism. This observational survey was conducted by four local neurologists with experience in demyelinating diseases, at University Clinic of Neurology in Skopje, Republic of Macedonia, over a period of 1 month, from April to May 2019. Collected data were analyzed and final report was prepared which consisted descriptive answer for each question.

## Results

A group of four neurologists with experience in the field of this area answered to all questions and results divided in five sections are as follows:

### **NMOSD incidence and prevalence**

Due to unavailability of an official patient data registry in our country and regular patient's visits, the

NMOSD incidence and prevalence are approximate. According to the clinics archives stored at the University Clinic of Neurology, the current estimated prevalence is approximately 20 patients. At present, there are patients in diagnostic procedure.

### ***Physician awareness and knowledge/ experience***

All required processes and management (diagnosis, prescription, treatment, and follow-up) of NMOSD patients are performed at the PHO University Clinic of Neurology, Skopje, which is the only public tertiary institution for diagnosis and treatment of demyelinating diseases. NMOSD market in our country is split between public and private, with significant predominance of public by 98%. Six neurologists are currently active in diagnosis and treatment working with NMOSD patients at University Clinic of Neurology. However, they are not fully dedicated only to NMOSD, they also cover other neurological areas, such as MS, myasthenia gravis, and epilepsy. Although the small number of NMOSD patients, the neurologists are aware and have sufficient knowledge about the disease nature. Their level of awareness about IL-6 as a new mechanism of action and experience with IL-6 in NMOSD treatment is very low. However, despite these knowledge gaps, around 80% of neurologists treating NMOSD patients in the country would be open to treat their patients (switch) innovative treatment options.

### ***AQP4 antibody testing***

At present, AQP4 antibody testing is not available in any public institution in the country. Hence, patient's blood samples are sent to private laboratories, which in turn send them abroad, sometimes questioning the reliability of the results. This process is not regularly organized and it is costly and paid out of the pocket. These issues impact on AQP4 testing rate which currently is around 30% of all population with demyelinating diseases (e.g., NMOSD).

### ***Treatment approach***

At present, NMOSD treatment rate is approximately 80–90% of all diagnosed patients. Almost all patients (95%) are treated with immunosuppressant, most of them with azathioprine (only 5% with mycophenolate mofetil) as first-line maintenance treatment. High-dose intravenous methylprednisolone is used in treatment of acute attacks. Patients with severe symptoms, which failed to corticosteroid treatment, plasma exchange are offered/ treatment option. Other medications (e.g., rituximab, and tocilizumab) are not in clinical use due to off-label limitation, and eculizumab/satralizumab is still not registered in Republic of Macedonia. Despite,

lack of various treatment options currently around 80% of all NMOSD patients are on maintenance treatment with available immunosuppressant. Since immunosuppressive drugs are the only approved and available treatment option, physicians are not able to switch from 1 L into 2 L maintenance if needed. At present, there is no ongoing clinical trial in our center for investigating new treatment options. At the same time, physicians are experience since they participated in few multicentric clinical trials for MS or other neurological diseases.

### ***Funding mechanism***

Reimbursement and/or funding process of rare/orphan disease in our country is managed through a special funding mechanism organized and leads by the Ministry of Health. Ministry of Health is responsible for allocating funds for the treatment of rare diseases through a Rare Disease Program. To be funded, the medicine needs to proof certain level of evidence acceptable by the Ministry of Health as pricing strategy, business case model, and condition list/ process or similar. In this process, a dedicated patient association group (PAG) for rare diseases and alliance of PAGs for rare diseases have ability and capacity to shape the local healthcare policies, are able to influence in decision making process (approval and/or reimbursement). They have certain level of influence in the whole process throughout direct negotiation with the authorities, dissemination of information through social media, patient conference/meetings, etc. A dedicated PAG for NMOSD is not present yet.

## **Discussion**

Despite latest improvements, significant unmet medical needs in the management of NMOSD are remaining. The current unmet needs can be divided in four sections: Knowledge (consistent and appropriate patient referral, appreciation of consequences of NMOSD relapses), diagnosis (further, robust validation, and adjustment of current NMOSD diagnostic criteria, AQP4-IgG-negative specific clinical, and neuroimaging features), maintenance treatment (robust evidence base for recommended drugs, approved drugs to treat NMOSD with a more favorable benefit/harm/risk balance), and improved symptom control (increased effectiveness in primary disease control to reduce secondary symptoms and disability, integrated multidisciplinary team approach for management to reduce/prevent relapses and disability) [35], [36], [37], [38], [39].

The whole management of NMOSD in republic of Macedonia, starting from diagnosis, treatment prescription until follow-up of patients, is done in the only

qualified center, PHO University Clinic for Neurology in Skopje. This center represents a public health-care institution at tertiary level with the low number (6) of neurologists dealing not exclusively with NMOSD. Recent published article, reported that 87% (13/15) of patients reported concern that their physicians' were not knowledgeable about NMO and this had a potentially serious impact on outcomes [36]. Furthermore, patients believed that a delayed diagnosis was due to lack of knowledge of physicians at initial consultation and lack of patient support at early stages of diagnosis, and full consequences of the condition and relapses were not well communicated [36]. Taking this into account, we believe that appropriate tailored education will raise the level of knowledge that will help them to arise into local and/or regional NMOSD experts. Furthermore, improved local and regional habitat conservation plan coordination is needed to support patients with NMOSD and/or patient organization(s).

To make efficient clinical and policy decision-making process at a national and institutional level, continuous examination of the disease trends in populations over time including incidence/prevalence rates and prognoses is critical. Recommendation from developed neurology centers in EU is that having an electronic patient data registry can support and overcome current situation. Their experience is showing that patient data registries can additionally support and enable a more effective use of limited resources; explore the impact of the disease and treatment on patients, including health-related quality; assess the clinical outcomes; support the health technology assessment process by providing data on the cost effectiveness of treatments, etc. Patient data registries are not new in our country, for example, registries for patients with rare, rheumatological, and endocrinological diseases are available. Nowadays, the University Clinic of Neurology is in process to establish (MS) registry. We believe that including the NMOSD patients in the upcoming MS patient registry in the future will be beneficial and serve as point for planning, delivery, and review of health care in our country. This will potentially provide us valuable data and insights in exact incidence, prevalence, disease trends and will support us in more efficient usage of health-care resources and will facilitate development of base for clinical investigations.

The importance of accurate and early diagnosis of NMO is emphasized by Mutch *et al.* They concluded that the difficulty and delay in obtaining a diagnosis can lead to an accrual of disability if relapses are not treated quickly [36]. Prior establishing specific diagnostic criteria for NMOSD, patients were often misdiagnosed or diagnosis was delayed which led to inappropriate treatment and further disability progression. Now, AQP4-IgG testing is a core element of confirming the NMOSD diagnosis. However, in our center, AQP4-IgG testing is not available which resulted with significant proportion (70%) of suspected NMOSD

patients not being AQP4-IgG tested. This diagnosis gap influences on early and accurate diagnosis and physician treatment decision-making process. We are convinced that establishment of central laboratory for AQP4-IgG testing in public sector will minimize the risk of misdiagnosis and will shorten the diagnosis period which will ultimately impact on the patients' clinical outcomes. In addition, an action needs to be taken from the Macedonian neurology association to adopt and adapt locally the Revised Diagnostic Criteria for NMOSD, since without unified diagnostic criteria and adherence to them, a risk for misdiagnosis and inaccurate patient data registry will remain.

Until now, there are no curative treatments for NMOSD patients [31]. In addition, there is still no recommended treatment with satisfactory therapeutic efficacy and safety profile for NMOSD. At present, the foremost disease management priorities and treatment goal are prevention of attacks and reduction of the impact of NMOSD associated symptoms as long-term disease course stabilization [40]. Systemic immunosuppressive and chemotherapeutic agents are used off-label to reduce attack frequency and are the main first-line treatment options in our center. Systemic immunosuppression – corticosteroids and cytostatics are the most commonly used as first-line treatment to reduce attacks frequency. In addition, there are no approved medications for acute or maintenance treatment of NMOSD. In the past decade, significant progress has been made in NMOSD scientific research. At present, there are approximately 20 ongoing clinical trials that attract attention [41]. The ongoing Phase III trials are investigating emerging therapies for NMOSD prevention and include biologic agents targeting IL-6 receptor blockade (satralizumab), B-cell depletion targeting CD19 (inebilizumab), complement C5 cleavage inhibition (eculizumab), and B-cell activating factor inhibitor (RC 18). So far, our center was not included in any clinical trial that investigates the novel treatment options. We believe that participation in NMOSD clinical trial might impact on obtaining a more thorough understanding of the efficacy and safety of the investigational medicine and follow the standard routine diagnostic approach which will result in proper and accurate diagnosis. In addition, conducting a phase III clinical trial has many benefits but the biggest is the opportunity for patients to access new treatment in such rare disease where any current drug has not showed high efficacy and tolerability.

The latest investigations showed that a key driver of NMOSD pathophysiology is IL-6. It impacts on B-cell mediated features of NMOSD pathogenesis including AQP4 autoantibody production, blood-brain barrier permeability and granulocyte infiltration and complement activation [42], [43], [44], [45], [46]. The potential blockade of IL-6 receptor is thought to reduce IL-6 signaling and therefore reduces downstream inflammatory effect [43]. An emerging therapy that

targets IL-6R is satralizumab, which selectively inhibits the inflammatory effects of IL-6. Satralizumab was engineered to maximize suppression of IL-6 signaling, minimize safety risks, and enable convenient dosing for patients with NMOSD. Satralizumab is a humanized monoclonal antibody with a long plasma circulation which is currently investigating in two pivotal clinical trials enrolling patients with NMO or NMOSD. SAKuraSky and SAKuraStar trials are evaluating the efficacy and safety of satralizumab administered by subcutaneous injection compared with placebo [47]. In addition, it is also being studied in pediatric patients as young as 12 years of age (SAKuraSky). Trials showed that satralizumab significantly reduced the risk of protocol-defined relapse and was well tolerated both in combination with immunosuppressants and as monotherapy. In June 2016, European Medicines Agency granted orphan drug designation and in December 2018, U.S. Food and Drug Administration (FDA) has granted breakthrough therapy designation to satralizumab for the treatment of NMO and NMOSD.

Eculizumab is a monoclonal antibody which administered by intravenous infusion binds to and inhibits the terminal complement component five and the membrane attack complex. In addition to NMOSD, it was investigated for the treatment of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, and generalized myasthenia gravis. Eculizumab was investigated among patients with AQP4-IgG-positive NMOSD in PREVENT clinical trial, which showed that those who received eculizumab had a significantly lower risk of relapse than those who received placebo and no significant between-group difference in measures of disability progression. In June 2013, eculizumab received an orphan drug designation by the FDA, which provides incentives to assist and encourage the development of drugs for rare diseases.

The recent published data from clinical trials are encouraging since treatments showed consistently and effectively prevention of relapses, and reduction of other disease-associated symptoms. We endorse development and research of novel treatment options whose might fill the current significant unmet needs in the treatment of NMOSD patients and with the improvements in the diagnosis and care are expected to decrease the NMOSD mortality rates.

## Conclusion

The analysis showed that the current situation in NMOSD setting in our country is challenging with many significant, yet unmet diagnostic and therapeutic needs. The highest priorities that will foster improvement of health care and quality of life of NMOSD patients are introduction of routine APQ4-IgG testing, establishment

of patient registry according to adapted diagnostic and treatment recommendations and availability of novel emerging treatment options.

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