National consensus on the diagnosis and treatment of neuromyelitis optica spectrum disorders

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Bulgarian Society of Neurology

On this day, 13.04.2023, we, the undersigned specialists, reached a consensus on the diagnosis and treatment of neuromyelitis optica spectrum disorders:

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Devic's syndrome (disease) (neuromyelitis optica NMO) is now included in a Neuromyelitis Optica Spectrum Disorders (NMOSD) group that is yet to be determined. As brain syndromes also occur in NMO, the term NMOSD covers the full clinical spectrum and was proposed in 2015 by the International Panel for Neuromyelitis Optica (NMO) Diagnosis (IPND). First described over a century ago, neuromyelitis optica is a severe autoimmune inflammatory demyelinating disease of the central nervous system (CNS). The relationship between NMO and multiple sclerosis (MS) has long been debated, but since the discovery of the NMO-typical aquaporin-4 antibodies, NMO has been found to have clinical, MRI, laboratory, and immunopathological features different from those of MS. The so-called Asian optic-spinal multiple sclerosis belongs to this group and is no longer considered an MS variant.

Prevalence varies from 0.52 to 4.4 per 100,000 people, which is much lower than the prevalence of multiple sclerosis. The overall NMOSD prevalence for the period from 1993 to 2013 was determined to be 1.82 per 100,000 people. It is found in 1-2% of the patients with a misdiagnosed multiple sclerosis. One in 770,000 people worldwide is diagnosed with this disease annually. NMOSD is a rare disease whose worldwide prevalence is not well understood due to the changing diagnostic criteria and the accuracy of serological diagnostic tests.

As of 2020, approximately 16,131 people (0.003%) in all 28 EU Member States have been diagnosed with NMOSD, with 46.2% diagnosed as AQP4-IgG seropositive.

The female-to-male incidence ratio ranges from 3:1 in France and 4.5:1 in Germany (47) to 10:1 in Japan. In NMOSD-AQP4 IgG seropositive patients, the prevalence of the disease among the female patients was associated with an earlier age of onset of symptoms (41 years instead of 48.7 years), more frequent optic neuritis as an initial symptom (in 44% instead of 17%), and greater annual incidence of optic neuritis (0.27 instead of 0.08). Women with NMOSD more often suffer from relapsing-remitting type compared to men, in whom the disease is more often monophasic. The female to male ratio is 40:8 in relapsing NMOSD and 11:12 in monophasic NMOSD, respectively. In minors (<18 years), the female-to-male incidence ratio is 1:1. Caucasians are affected less often than other races.

Currently, there are no epidemiological data on the frequency and prevalence of NMOSD in Bulgaria.

Etiology of NMOSD still remains unknown.

Genetic factors. The risk genes for the development of the disease are HLA-DPBI (in Japanese) and HLA-DRBI. There is no such association among the Europeans. However, 95% of the patients diagnosed with NMOSD have no family history of the disease. About 50% of the NMOSD cases have a family member with a family history of another autoimmune disease other than NMOSD.

There is an association between NMOSD and Sjögren's syndrome, lupus erythematosus (SLE) and thyroiditis.

Previous acute infection is established in 15%-35% of the NMOSD patients. They have more severe NMOSD with a relapsing course and a worse prognosis. On average, 25% of them recover completely. However, this association is unclear and further research is needed.

Pathogenesis is associated with humoral disorders and is different from that of MS, where the immune mechanisms are predominantly cellular. It is accepted as a B-cell (antibody) mediated channelopathy due to NMO-IgG autoantibodies to the water channel antigen aquaporin-4 (AQP4). In 70% of cases, the AQP4 receptor is the target antigen of NMO-IgG, which has a direct role in the NMOSD pathogenesis. Antibodies recognize the extracellular epitopes of the membrane protein AQP4. Complement activation, granulocyte infiltration of CNS, and cell-mediated cytotoxicity occur. Aquaporin-4 is the major water channel associated with fluid homeostasis in the central nervous system and contributes to the integrity of the blood-brain barrier. Antigens are located in the astrocytes, which are positioned near the capillaries, pia and Virchow-Robin spaces in the periventricular regions, around the spinal canal, spinal gray matter, hypothalamus, trunk and optic nerve. The high density of AQP4 antigens around the III and IV ventricles explains the lesions in the area of denser localization of the receptors and the clinical manifestations with unresponsive nausea, vomiting and hiccups (area postrema syndrome), as well as the hypothalamic disorders. NMO-IgG binding to AQP4 induces astrocyte injury via antibody-dependent cell-mediated cytotoxicity and activation of the complement pathway. These signaling pathways attract inflammatory cells, including T- and B-lymphocytes, macrophages, neutrophils, and eosinophils. AQP4 expression is impaired, and the permeability of the endothelial-astrocyte barrier increases. Water homeostasis and glutamate transport are impaired. Oligodendrocytes are damaged, demyelination and axonal degeneration occur. The causes of the demyelination are unclear.

Interleukin 6 (IL6) levels are elevated. It is involved in the differentiation of native T cells to proinflammatory T17 helper cells, which together with IL6 potentiate the B-cell differentiation to AQP4-IgG-producing plasmablasts. NMOSD pathogenesis is associated with the IL6 functions that include B-cell activation, B-cell differentiation to plasmablasts and production of pathological autoantibodies (against AQP4, a water channel protein expressed primarily by astrocytes in the CNS), as well as Th17-cell activation and differentiation, inhibition of regulatory T cells, and changes in the permeability of the blood-brain barrier.

It is suggested that the AQP4-IgG seronegative NMOSD has other underlying pathogenetic mechanisms, including myelin oligodendrocyte glycoprotein immunoglobulin G (MOG-IgG). It was

identified in 42% of the patients with AQP4-IgG-seronegative NMOSD and rarely overlaps with AQP4-IgG-positive expression.

The clinical onset of the disease is 10 years later than MS. It occurs in children and young adults aged 33-46 years, but it can also occur in old age (over 70). In 50% of the patients, it is preceded by prodromes resembling a viral disease, which suggests that it is triggered by a viral infection. The onset of the neurological symptoms may be preceded by radicular pain and paresthesia in the lower limbs.

It occurs with acute (for hours to days) bilateral or unilateral involvement of the optic nerve, papillitis and subsequent complete and bilateral transverse myelitis, with symptoms of spinal shock - acute flaccid paraplegia, areflexia and disorders of the pelvic ileal reservoir due to bladder atony. The spinal symptoms may be milder, asymmetric, and not associated with complete disruption of the transverse section of the spinal cord. Optic neuritis and transverse myelitis are also observed in other neurodegenerative diseases.

Myelitis can ascend to the medulla oblongata and lead to hiccups, respiratory disorders and death, but these symptoms subside after the acute phase has passed. Bulbar symptoms, facial nerve involvement, trigeminal neuralgia, ophthalmoplegia, diplopia, vertigo, dysarthria, nausea, vomiting, narcolepsy, hearing loss, hemiparesis, encephalopathy, tremor, and ataxia may occur.

In some cases, more often in women, myelitis may occur some time (weeks to months) after optic neuritis. This development suggests a relapsing-remitting course of the disease.

Optic neuritis is severe and may affect one or both eyes (simultaneously or gradually). During the attack, severity of the damage varies from blurred vision to severe total blindness, but afterwards vision recovers in 80% of the patients. With repeated attacks, however, visual deficits accumulate. After 8 years, more than 50% of the patients with NMOSD are completely blind in one eye and 15% are blind in both eyes. Optic neuritis affects the back of the optic nerve, often involving the chiasm.

Symptoms outside the spinal cord and optic nerve occur in 10-15% of the patients. Lhermitte's symptom and paroxysmal tonic spasms occur.

The disease has a typical relapsing course. NMOSD relapses are more severe than MS and often lead to permanent disability and vision loss. The secondary-progressive course is extremely rare, in contrast to MS. In some patients, the disease progresses with frequent relapses followed by remissions, and in 2% of the patients, the symptoms between the relapses progressively worsen.

Laboratory tests. Patients must be tested for serum AQP4-IgG antibodies. Ideally, testing must be performed during relapses and prior to initiation of immunotherapy, as immunotherapy may change the seropositive status to seronegative. Patients who are initially AQP4 antibody seronegative

must be retested, if NMOSD is suspected. Serum tests for the presence of AQP4-IgG are more accurate than CSF tests and are sufficient to make an accurate diagnosis of NMOSD.

The serum autoantibody AQP4-IgG, also known as NMO-IgG, is a specific biomarker for NMOSD. About 70% of the patients are AQP4 positive.

In the absence of serological tests for AQP4-IgG or in AQP4-IgG-seronegative patients, the diagnosis must be clarified. Testing of differential blood count, coagulation, serum biochemistry, erythrocyte sedimentation rate, blood sugar, vitamin B12, folic acid, antibodies associated with other neurological and autoimmune demyelinating diseases, urine and sediment tests, hemagglutination, and analysis of paraneoplastic antibodies (especially anti-CV2/CRMP5) are required. Based on the clinical presentation and CSF results, an analysis for acquired copper deficiency, which may result from gastrointestinal surgery, excessive zinc intake (e.g., excessive use of denture cream) and other causes, must be performed.

Seronegative NMOSD differs from seropositive NMOSD in certain characteristics, including an equal male-to-female ratio and a greater possibility of concurrent optic neuritis and transverse myelitis at the onset of the disease.

A small number of AQP4-seronegative patients, mainly children, have serum antibodies against MOG (myelin oligodendrocyte glycoprotein). MOG autoantibodies define an overlapping clinical syndrome known as myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), which often meets the clinical criteria for NMOSD but has some differences in the characteristics compared to AQP4 antibody-associated NMOSD, including:

- Concomitant bilateral optic neuritis with papilledema established by fundoscopic examination is more likely to occur.
- It is more likely to be monophasic or have fewer relapses.
- It is less likely to be associated with other autoimmune diseases.
- Proportionally more brainstem and cerebellar lesions and fewer supratentorial lesions.
- Spinal cord lesions occur mainly in the lower part of the spinal cord.
- The spectrum of the disease includes acute disseminated encephalomyelitis (ADEM), particularly in children.
- The male-to-female ratio is close to 1:1, in contrast to the female predominance in NMOSD with AQP4-IgG antibodies.

Cell-based serum assays are not yet widely available. The consensus on the diagnosis of NMOSD recommends cell-based serum assays (microscopy or flow cytometry-based detection) to detect auto-AQP4-IgG antibodies considering the high sensitivity of the methods (76.7% with a 0.1% false positive rate in the MS cohort).

Indirect immunofluorescence assays and enzyme-linked immunosorbent assay (ELISA) are more accessible methods for auto-AQP4-IgG antibody assay but have a lower sensitivity (63%-64%) and a higher index of false positive results (0.5%-1.3% for ELISA).

Cerebrospinal fluid (CSF) analysis is useful to distinguish NMOSD from multiple sclerosis when the diagnosis is uncertain. Patients with a typical presentation of NMOSD often do not need a lumbar puncture for CSF examination. Cerebrospinal fluid abnormalities are found in the majority of the NMOSD patients. They affect the number of the immune cells associated with the inflammatory process, the amount of the pro-inflammatory proteins and oligoclonal bands (OCB). Pleocytosis, characterized by the presence of abnormally high numbers of monocytes and lymphocytes in CSF, occurs in 14–79% of patients. In 13-35% of them, the number of immune cells exceeds the normal 50 cells x 109L and in some cases reaches 1000 cells x 109L. LETM patients more frequently have pleocytosis than ON patients. Pleocytosis with more than 50 cells x 10^9L is rare in MS. Elevated levels of proinflammatory proteins are present in 46–75% of the cases. Rarely (in 20-30%) in contrast to MS (over 90%) oligoclonal fractions, which may be transient in contrast to MS, are detected.

The presence of neurofilaments is also indicative of NMOSD. Neurofilaments are released into the cerebrospinal fluid after axonal damage, including as a result of optic neuritis. Heavy chain (NfH) levels are significantly higher in CSF of patients with NMOSD compared to those with MS. Also, the amount of glial fibrillary acidic protein (GFAP) is significantly higher in CSF of patients with NMOSD compared to those with MS, spinal cord infarction, and acute disseminated encephalomyelitis (ADEM).

CSF analysis provides supportive data that is not very sensitive or specific for the diagnosis of NMOSD and must be performed during or shortly after an acute relapse. Data of lymphomononuclear pleocytosis with more than 50 x10^9L cells, presence of neutrophils/eosinophils, and absence of OCB in CSF may be indicative but not specific for NMOSD.

Neuroimaging studies magnetic resonance imaging (mandatory) and optical coherence tomography (recommended) are diagnostic methods for NMOSD, especially in AQP4-IgG-seronegative patients and in cases where serological AQP4-IgG tests are not available.

Magnetic resonance imaging (MRI) shows the most specific NMOSD characteristic that is not found in MS patients - the presence of a LETM lesion (longitudinal extensive transverse myelitis) of the spinal cord. Lesions are usually in the central gray matter of the spinal cord and often reach and damage the brainstem. The upper thoracic and cervical (60%) segments are mainly affected. The length of the lesion is directly proportional to the occurrence of relapses and the severity of the attacks of transverse myelitis. Acute T_2 spinal cord lesions involve most of the cross-sectional area of the affected segment and are edematous and Gd+ (detected days to months after the relapse). The owl's

eye sign is due to hyperintensity of anterior horn cells in the spinal gray matter, suggesting vertebral artery ischemia, and may be seen in acute inflammation. In severe cases there is cavitation. Sometimes the inflammation and swelling of the spinal cord is so severe that the lesion can mimic a tumor. Gadolinium enhancement of the lesions disappears with treatment, and the lesions are reduced during remission. Over time, significant spinal cord atrophy may occur.

Spinal cord lesions longer than 3 spinal segments occur more frequently in AQP4-IgG-seropositive patients. For lesions shorter than 3 vertebral segments, prognosis and response to corticosteroid treatment are better. Medullary lesions are associated with higher annual relapse rate (ARR) and EDSS scores. They, as well as LETM relapses, are indicators of a severe course of the disease and a poor prognosis. In comparison, spinal lesions in MS are one or less than one spinal segment long and predominantly involve white matter. Although LETM is characteristic of NMOSD, 7%–14% of the initial and 8% of the subsequent episodes of transverse myelitis in AQP4-IgG-seropositive patients do not meet the definition of LETM. In early phases or in remission of the disease, the lesions may not cover 3 spinal segments. In addition, an MRI LETM pattern may also occur in patients with infectious, granulomatous, neoplastic, and paraneoplastic diseases, acute disseminated encephalomyelitis (ADEM), spinal cord infarction, or dural arteriovenous fistula. Therefore, the presence of LETM alone is not sufficient evidence of NMOSD.

Brain MRI is normal in 55 to 84% of NMOSD patients or shows 2-3 atypical lesions in the cerebral white matter that do not meet the criteria for multiple sclerosis. A typical sign of acute ON (94%) is optic nerve gadolinium enhancement or lesions along the optic nerve that cover half its length. The MRI lesion reaches up to chiasma opticum. However, in 60% of the patients with white matter lesions, NMOSD is not a definite diagnosis.

Over time, MRI evidence of brain involvement is found in up to 85% of the patients with NMOSD. Lesions are found in the trunk, central medulla, hypothalamus, thalamus, diencephalon, and around the III and IV ventricles, corresponding to areas of high AQP4 expression. There may be large lesions in the cerebral hemispheres and subcortical white matter. These lesions sometimes meet the diagnostic criteria for spatial dissemination of MS. Corticospinal tract lesions also suggest NMO.

Short-tau inversion recovery (STIR) sequences provide fat suppression that is favorable for evaluation of the optic nerve. Using STIR sequences, increased signal intensity on T2 optic nerve scans was reported in 84% of the cases of acute ON and in 20% during remission. Blood-brain barrier disruption leads to gadolinium enhancement on T1 spin-echo sequences.

Optical coherence tomography (OCT) is a rapid and non-invasive technique for imaging unmyelinated CNS axons in the retina (the retinal nerve fibers, RNFL). Retinal damage is common in NMOSD and is mainly characterized by a reduction in the thickness of the retinal nerve fiber layer.

There is significant RNFL loss in patients with NMOSD, particularly in the active stage of the disease. It is not clear whether these pathological changes can be associated with a risk of recurrence. The utility of optical coherence tomography as a diagnostic tool is not well established.

Electrophysiological studies (visual, somatosensory, motor and brainstem auditory evoked potentials) are useful in NMOSD.

Visual evoked potentials often change in NMOSD. Prolonged P100 latencies are found in about 40% of the cases and reduced amplitudes or missing potentials - in about 25%. *Somatosensory evoked potentials* are reported as atypical in 86% of the cases, visual evoked potentials - in 83%, and *motor evoked potentials* - in 37%. Anomalies of the *auditory evoked potentials* of the brain stem are more common in people of African origin compared to patients of other ethnic groups (78% vs. 29%).

Diagnosis is based on diagnostic criteria. In 2015, an international panel revised the existing diagnostic criteria (IPND) and officially designated NMOSD - a unifying term for the entire clinical spectrum of the disease expression. A distinctive marker for the diagnosis of NMOSD, not found in other autoimmune diseases with a similar clinical picture, is the presence of AQP4 autoantibodies. Despite the diagnostic criteria, patients are still often initially diagnosed with MS. Delay in accurate diagnosis carries the risk of severe relapses. In addition, the administration of some immunomodulatory therapies for MS may lead to deterioration in AQP4-IgG seropositive NMOSD patients.

The International NMOSD Diagnostic Panel adapted the clinical diagnostic criteria by stratifying NMOSD by serological status, i.e. with or without the presence of AQP4-IgG. Diagnostic criteria in AQP4-IgG seronegative patients include more stringent clinical and imaging tests. In both patient populations, regardless of the presence or absence of autoantibodies, clinical evaluation remains the key.

Diagnostic criteria for NMOSD in adult patient with or without AQP4-IgG

Diagnostic criteria for NMOSD with AQP4-IgG
1. At least one basic clinical characteristic 2. A positive AQP4-IgG test for using the best available detection method (cell-based assay is strongly recommended due to high sensitivity (~75%) and specificity (95%-100%) over enzyme-linked immunosorbent assays)
Diagnostic criteria for NMOSD AQP4-IgG seronegative or with unknown AQP4-IgG status

1. At least two basic clinical characteristics resulting from one or more clinical attacks and the presence of all of the following requirements: a. At least one of the clinical characteristics must be optic neuritis, transverse myelitis with LETM, or area postrema syndrome b. Dissemination in space (presence of two or more different basic clinical characteristics) c. Characteristic MRI finding (fulfilment of the MRI requirements, if applicable) 2. Negative AQP4-IgG tests using the best available method, or no testing performed 3. Exclusion of alternative diagnoses
Basic clinical characteristics
1. Optic neuritis 2. Acute transverse myelitis 3. Area postrema syndrome manifested by otherwise unexplained hiccups, nausea, or vomiting 4. Acute brainstem involvement 5. Symptomatic narcolepsy or an acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions 6. Symptomatic brain syndrome with brain lesions typical of NMOSD
Additional MRI requirements in NMOSD AQP4-IgG seronegative or with unknown AQP4-IgG status (determined by clinical presentation)
1. **Optic neuritis:** brain MRI showing **a.** normal results or non-specific white matter lesions only, or **b.** MRI of the optic nerve with a T2-hyperintense lesion or a Gd+ T1- lesion covering more than half the length of the optic nerve or involving the chiasma opticum 2. **Acute myelitis**: MRI - intramedullary lesion involving three or more adjacent segments (LETM) or three or more adjacent segments of focal spinal cord atrophy in patients with a proven history of relapse consistent with acute transverse myelitis 3. **Area postrema syndrome**: presence of lesions in medulla oblongata or in the typical area 4. **Brainstem affected**: periependymal lesions present in the brainstem

AQP4-IgG - aquaporin-4 immunoglobulin G; LETM - longitudinal extensive transverse myelitis; MRT - magnetic resonance tomography; NMOSD - neuromyelitis optica spectrum disease; ON - optic neuritis.

Certain clinical manifestations are particularly characteristic of NMOSD. For example, bilateral optic neuritis, with chiasma opticum involvement. This results in defects in the visual field or severe residual vision loss. Complete and not partial involvement of the spinal cord, especially

accompanied by neurological paroxysmal symptoms, as well as manifestation of area postrema syndrome (with a frequency of 16%-43% of cases), are also indicative of the disease.

Pediatric diagnostic criteria for NMOSD

IPND also confirmed the applicability of the 2015 diagnostic criteria to pediatric cases but noted that a greater part of children had cerebral syndromes and that LETM-associated myelitis was less frequently associated with NMOSD in children than in adults.

The Pediatric Task Force noted that most of the clinical, neuroimaging, and laboratory characteristics of pediatric NMOSD are similar to those of the disease in adults. The differences are characterized by a lower frequency of the disease in girls and a more frequent manifestation of the disease as monophasic.

The task force warns that caution must be exercised when applying adult NMOSD criteria to children, noting that the detection of a LETM lesion associated with acute myelitis on MRI may be less specific for NMOSD. Approximately 15% of the children with MS may have LETM during a relapse. LETM can also accompany monophasic ADEM, and AQP4-IgG is rarely detected in children with monophasic LETM.

In children diagnosed with acute disseminated encephalomyelitis (ADEM), the presence of AQP4-IgG favors the diagnosis of NMOSD.

Excluding the warnings listed, the currently proposed diagnostic criteria for NMOSD in adults (≥ 18 years) are also suitable for both pediatric and adolescent patients. The accurate diagnosis of NMOSD may require continuous monitoring of the clinical course and retesting of AQP4-IgG status in some children, especially AQP4-IgG-seronegative individuals with an ADEM-like event that includes optic neuritis and LETM.

Differential diagnosis with multiple sclerosis is difficult as NMOSD has similar clinical manifestations. Both diseases have the typical manifestations of optic neuritis and transverse myelitis. The most common considerations in the differential diagnosis of aquaporin-4 (AQP4)-immunoglobulin G (IgG) antibody-positive NMOSD are multiple sclerosis and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD).

In early 2023, an international expert panel proposed diagnostic criteria for the differentiation of MOG-IgG-related diseases (MOGAD). Correct MOGAD diagnosis is important as the pathology, treatment and prognosis of this disease are different from those of multiple sclerosis or neuromyelitis optica and its spectrum disorders.

Acute disseminated encephalomyelitis and other autoimmune diseases such as systemic lupus erythematosus and Behçet's disease may rarely have similar manifestations as NMOSD.

In cases of recurrent optic neuritis, which is not due to neuromyelitis optica, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), or multiple sclerosis, other causes of recurrent optic neuritis, such as sarcoidosis, lupus erythematosus, chronic relapsing inflammatory optic neuropathy (CRION), or paraneoplastic optic neuropathy must be investigated (serum CRMP5/CV2 antibody).

Longitudinal extensive transverse spinal cord lesion is not specific to NMOSD. It has been described in patients with other autoimmune or inflammatory diseases, including systemic lupus erythematosus, Sjögren's syndrome, neuro-Behçet's disease, sarcoidosis, MS, MOGAD, parainfectious diseases (e.g., acute disseminated encephalomyelitis) and anti-N-methyl-D-aspartate receptor encephalitis.

Acute myelopathies occur with intrathecal tumors, vascular abnormalities (eg, spinal dural arteriovenous fistula and infarcts due to anterior spinal artery occlusion), metabolic conditions (eg, vitamin B12 deficiency causing subacute combined degeneration of the spinal cord), radiation therapy, and viral infections (e.g., HIV-1, HTLV-1).

Treatment with disease-specific therapy to prevent relapse is of primary importance and must be started early. Many patients have permanent and severe disability after the first clinical presentation and may deteriorate with each subsequent relapse.

The therapeutic approach includes:

a. Treatment of acute attacks.

b. Attack prevention.

c. Relief of residual symptoms.

Treatment of an attack does not differ in seronegative and seropositive NMOSD.

An NMOSD attack is defined as objective neurologic deterioration due to focal or multifocal inflammation of the central nervous system that develops acutely or subacutely in the absence of fever or infection, lasting at least 24 hours and occurring more than 30 days after the previous attack. This definition is similar to the definition of multiple sclerosis relapse.

The initial treatment of an attack is with high doses of intravenous methylprednisolone - 1 g. daily for 3 to 5 consecutive days. This is followed by a slow withdrawal of corticosteroid therapy and administration of a maintenance dose (10-20 mg) for 2 to 6 months to achieve effective steroid-sparing immunosuppression.

The response to the initial treatment is often suboptimal, and most patients need a repeat course of high-dose corticosteroids (CS). Additional courses, especially the second one, are associated with an increased remission rate.

Escalation therapy with plasma exchange is more often used as a next course of treatment in the absence of an effect. Exchanges take place every other day to a total of seven. For patients with severe symptoms or vision loss who are poorly responsive to CS, therapeutic plasma exchange is the working "adjuvant" or "rescue" treatment.

Limited data suggest (retrospective and uncontrolled studies) that patients with severe NMOSD attacks do better if plasma exchange is started early as adjunctive therapy to CS. Initial treatment with intravenous CS plus early therapeutic plasma exchange is associated with improved outcomes compared to delayed initiation of plasma exchange after CS treatment. Intravenous immunoglobulin has not been specifically evaluated for acute NMOSD attacks and is rarely used.

Immunomodulatory treatment with intravenous immunoglobulins (IVIG) as immunomodulatory therapy may be effective given the potential humoral immunopathogenesis. However, the supporting data in the literature is very insufficient.

Many patients with unproven NMOSD are initially diagnosed with MS and treated with immunomodulatory therapies such as interferon-β and glatiramer acetate. Some disease-modifying therapies used to treat MS may worsen NMOSD. Exacerbations of severe ON and transverse myelitis may occur in NMOSD patients treated with interferon-β 1b.

Immunosuppressive treatment with drugs not registered for prophylaxis, such as prednisolone, azathioprine, mycophenolate mofetil, mitoxantrone, rituximab, tocilizumab, cyclophosphamide, and methotrexate is administered to prevent NMOSD relapse. Their use is based on small, open-label and/or uncontrolled clinical trials.

Prednisolone in low doses (5–20 mg daily) reduces the frequency of attacks. Relapses occurred significantly more frequently when the dose was reduced to 10 mg/day.

Azathioprine must be initially combined with corticosteroids. The treatment will be effective in 3-6 months. Prednisolone (1 mg/kg/day) in combination with azathioprine (75–100 mg daily) are effective for a treatment period of 19 months (improvement in EDSS and no relapses). Clinical deterioration was observed when prednisolone was reduced below 5–15 mg/day.

Cyclophosphamide is partially effective in NMOSD and similar autoimmune diseases. Immunosuppression is transient when cyclophosphamide is given in standard pulse doses and the immune system returns to baseline within several months to a year after treatment is discontinued. Treatment regimens with intravenous cyclophosphamide ranged from 7 to 25 mg/kg every month for a period of 6 months. However, to prevent hemorrhagic cystitis, uromitexan must be infused with each dose. In addition, there is an increased risk of amenorrhea and sepsis.

Methotrexate (intravenously 50 mg weekly) in combination with prednisolone (1 mg/kg/day) results in clinical stabilization.

Mitoxantrone is an anthracenedione antineoplastic agent that interacts with DNA and inhibits DNA and RNA synthesis, thereby suppressing T-cell and B-cell immunity. A prospective study (12 mg/m2 monthly for 6 months followed by three more treatments every 3 months) established that four out of five patients with relapsing NMOSD stabilized and reported improvements on MRI.

Mycophenolate mofetil at an oral dose of 1-3 g/day is recommended in cases requiring immunosuppression and is used mostly when a rapid therapeutic effect is needed and when there is no response to the azathioprine therapy. The mean annual attack rate after mycophenolate mofetil treatment was lower than before the treatment.

Rituximab is an anti-CD20 monoclonal antibody that is able to deplete mature and precursor B cells, reduce disease activity and prevent the accumulation of neurological deficit. Most of the evidence supporting the effectiveness of rituximab, which is also an off-label drug for NMOSD treatment, comes from small uncontrolled clinical trials. Rituximab has controversial effects in NMOSD with exacerbation of the disease symptoms. The reasons for this may be due to the fact that CD20 is not expressed on plasmablasts that produce anti-AQP4-IgG and has no effect on the increased production of B-cell activating factor (BAFF) or genetic polymorphisms in the Fc receptor gene FCGR3A.

Combination therapy is a potential option for patients with a relapsing course of the disease. Oral corticosteroids combined with azathioprine lead to a reduction in the annual attack rate. Methotrexate in combination with oral corticosteroids leads to disease stabilization. Cyclosporine A, on the other hand, in combination with low-dose oral steroids is also an effective therapy in NMOSD patients. Periodic plasmapheresis combined with immunosuppressive treatment reduces the clinical manifestations of the disease.

Treatment with drugs registered for prophylaxis that have proven their effectiveness in controlled multicenter studies. Eculizumab, inebilizumab and satralizumab are approved by the US Food and Drug Administration (FDA).

Eculizumab (Soliris) received approval by the European Medicines Agency (EMA) in 2019 as the first preventive treatment in adult NMOSD patients who are positive for AQP4-IgG with a relapsing course of the disease. Eculizumab is a humanized monoclonal antibody directed against the complement component C5. It inhibits the cleavage of C5 c/ C5a and C5b, which leads to blocking the deployment of the terminal complement pathway, including the formation of the membrane attack complex. Eculizumab cannot be prescribed for an initial attack and its widespread use is hindered by its too high costs now.

Satralizumab (Enspryng) was approved by EMA in 2021 as monotherapy or in combination with immunosuppressive therapy (IST) for the treatment of Neuromyelitis optica spectrum disorders

(NMOSD) in adult patients and adolescents over the age of 12 who are anti-aquaporin 4 IgG (AQP4-IgG) seropositive. It is a recombinant humanized immunoglobulin G2 (IgG2) monoclonal antibody (mAb) that binds to soluble and membrane-bound human IL-6 receptors (IL-6R) thus preventing the downstream IL-6 signaling mediated by these receptors. IL-6 levels are elevated in CSF and the serum of NMOSD patients during the disease activity periods.

Satralizumab 120 mg is administered by subcutaneous injection, in a pre-filled single-dose syringe. Initially, a loading dose of 120 mg every two weeks is administered for the first three administrations (first dose at week 0, second dose at week 2 and third dose at week 4) followed by a maintenance dose of 120 mg every four weeks. The dosage in adolescents ≥ 12 years of age with a body weight ≥ 40 kg and adult patients is the same. The first injection must be administered under the supervision of a medical professional. After training on how to administer the injection, an elderly patient/caregiver can administer the other doses at home.

Satralizumab has been investigated in two international, randomized, multicenter, double-blind, placebo-controlled, phase III clinical trials for the treatment of NMOSD. Treatment with satralizumab with or without immunosuppressive therapy has led to an overall 75% reduction in the risk of a confirmed relapse in AQP4-IgG seropositive patients. The annual rate of confirmed relapse has decreased by 90% and the risk of severe relapse, defined as an increase in EDSS ≥ 2 points from the previous EDSS score, has decreased by 85%. Efficacy in AQP4-IgG-seronegative patients was not significant.

Anti-drug antibodies (ADA) were observed in up to 71% of the patients receiving satralizumab, but their ability to neutralize satralizumab binding is unknown.

The most commonly reported adverse reactions were headache (19.2%), arthralgia (13.5%), decreased white blood cell count (13.5%), hyperlipidemia (13.5%), and injection-related reactions (12.5%). The most common injection site reactions were skin redness, erythema, pruritus, rash, and pain. Most of them occur within 24 hours. The most commonly reported systemic symptoms were diarrhea and headache.

Most cases (9.6%) of decreased neutrophil count below 1 x 109/l were transient or intermittent. A decrease in platelet count (below 150 x 109/l) occurred in 24.0% of the patients. It was not associated with bleeding (did not fall below 75 x 109/l) and was transient. Elevations of ALT or AST occurred in 27.9% of the patients. Most cases were below 3 x ULN. They were transient and resolved without treatment interruption. Elevations of ALT or AST > 3 x ULN occurred in 2.9% of the patients, respectively, and were not associated with an increase in total bilirubin. Values returned to normal after treatment was discontinued.

An increase in total cholesterol above 7.75 mmol/l occurred in 10.6% of the patients. An increase in triglycerides above 3.42 mmol/l occurred in 20.2% of the patients.

It is contraindicated in case of hypersensitivity to the active ingredient or to any of the excipients, pregnancy and breastfeeding. The administration of satralizumab must be withheld in patients with active infection until the infection is controlled.

All patients with a positive AQP4-IgG test must receive early long-term immunosuppression with steroid-sparing therapy. The choice must take into account the price, access, comorbidity, pregnancy planning, and logistics.

Additional low-dose maintenance prednisone (5-20 mg/day) may be used in certain situations to increase efficacy.

NMOSD Treatment Criteria	**Treatment is not administered or, if started, is discontinued in case of:**
I. Including 1. Diagnosis of NMO according to the International Panel for NMOSD Diagnosis (IPND) criteria revised by Wingerchuk 2. Age 12 and over. 3. A positive AQP4-IgG test using the best detection method available 4. Disability of up to 6.5 on Kurtzke scale II. Excluding 1. Hypersensitivity to the active ingredient or to any of the excipients 2. Pregnancy and breastfeeding 3. Severe co-morbidities	1. Patient pregnancy. 2. Serious treatment adverse reactions - ALT or AST > 5 x ULN, total platelet count below 75 x 109/l confirmed by retest, total neutrophil count below 1.0 x 109/l and serious hypersensitivity reactions confirmed by retest. 3. Regular failure to comply with the dosage regimen. 4. Absence of clinical effectiveness of the treatment.

Tests and follow-up tests required during the treatment with satralizumab

I. Prior the initiation of treatment:

1. Complete blood count differential count.

2. Serum transaminases, bilirubin.

4. Live and live attenuated vaccines must not be co-administered with satralizumab as their clinical safety has not been established. The interval between the vaccinations with

live vaccines and initiation of satralizumab treatment must be in accordance with the current vaccination guidelines for treatment with immunomodulatory or immunosuppressive agents.

II. Follow-up:

1. In patients receiving treatment with satralizumab, careful monitoring is recommended for timely detection and diagnosis of infections. Treatment must be delayed if the patient develops any serious or opportunistic infection.

2. Serum transaminases must be monitored every four weeks for the first three months of treatment, then every three months for a year and as clinically indicated thereafter.

3. Neutrophil counts must be monitored for 4 to 8 weeks after the initiation of treatment and as clinically indicated thereafter.

Duration of therapy is at least five years for patients who are seropositive for AQP4-IgG antibodies, including those with a single attack, as they are at high risk of relapse. Many experts believe that the treatment should be lifelong, given the nature of the disease, which is often "devastating". However, the optimal treatment regimen and duration of treatment remain to be determined.

The principle of treating seronegative cases is similar if the alternative diagnoses are excluded. Tocilizumab and satralizumab have been shown to be ineffective in AQP4-IgG negative. Seronegative patients were not included in the eculizumab study; therefore, efficacy is unknown.

Prognosis is poor with early vision loss and muscle weakness due to incomplete recovery from the attacks. Spasticity, tonic spasms, dysesthesias, and pelvic-reservoir disorders are common. Over 33% of the NMOSD patients, who initially develop transverse myelitis, have significant disability at 2-year follow-up. 34% of the patients develop permanent motor impairment, and 23% become dependent on wheelchairs. In another study, 50% of the NMOSD patients required assistance walking short distances (EDSS 6) 5 years after the disease onset, and up to 62% of the patients were totally blind within 5–6 years of the disease onset. Each relapse within the first 2 years of the disease onset was associated with a 21% greater risk of mortality in NMOSD patients.

The natural course of NMOSD is progressive deterioration (recurrent attacks) due to accumulation of visual, motor, sensory and pelvic disorders. In most acute attacks, deterioration takes days and recovery takes several weeks to months with significant residual disability. Unlike multiple sclerosis, there is no clear progressive phase.

Death rate is high (up to 32%). It is most often due to neurogenic respiratory failure that occurs with extension of the cervical lesions into the brainstem or from primary brainstem lesions.

Prognostic markers - predictors of worse prognosis include the number of relapses in the first two years, severity of the first attack, older age at disease onset, and association with other autoimmune diseases, including autoantibody status. Currently, available data are conflicting as to whether the AQP4 (NMO-immunoglobulin G) autoantibody can be a marker of disease course and prognosis.

NMOSD during pregnancy - Data on the association of NMOSD and pregnancy are only limited and retrospective. They suggest that NMOSD is associated with a higher risk of miscarriage and that the annual recurrence rate of NMOSD increases during the first three to six months of the postpartum period.

Drugs to be avoided - NMOSD treatment with interferon-β, natalizumab, or fingolimod is not effective and may even be "harmful." There is no published evidence regarding the treatment of NMOSD with ocrelizumab.

Symptomatic treatment is necessary because the disease is associated with chronic symptoms, sometimes the residual neurological deficit is severe, and this deteriorates the quality of life. To assess whether a patient's symptom should be treated, the symptoms must be categorized by degree of severity as mild, moderate, and severe. The symptoms are mild, if they do not interfere with the patient's daily activities and do not require treatment. Moderate symptoms interfere with the patient's daily activities, disturb their social life, and create discomfort. These symptoms need medical treatment. Severe symptoms disable patients and severely limit their daily activities. These symptoms usually do not respond to medical treatment but require more special measures and care.

Fatigue is a common symptom. It may be physical, mental, sleepiness, low mood. It is influenced by several non-drug methods such as aerobics, physical therapy, behavioral therapy etc. Administration of amantadine 200 mg daily, fluoxetine 10 to 40 mg daily, and modafinil 100-400 mg in the morning affects fatigue.

Acquired *narcolepsy* and *hypersomnia* may occur in a diencephalic attack, but often resolve after anti-inflammatory treatment. Permanent hypothalamic dysfunctions are possible and result in reduced orexin levels and subsequent excessive daytime sleepiness and chronic narcolepsy.

Cognitive disorders respond to donepezil 10 mg daily, although the effectiveness of the treatment is poor.

Depression responds to tricyclic and SNRI (serotonin-norepinephrine reuptake inhibitors) antidepressants or serotonin reuptake inhibitors. Bipolar disorders are treated with lithium preparations and anticonvulsants, and pathological laughter and crying are treated with tricyclic antidepressants (amitriptyline 25 mg daily).

Pain in some NMOSD patients is significant. It is often dermatomal and may correspond to a spinal cord lesion, but severity is not associated with the duration of the disease, age, serologic status, or number of attacks. Neuropathic pruritus has also been observed. It responds to tricyclic and SNRI antidepressants (amitriptyline, venlafaxine, mirtazapine, duloxetine, milnacipran), anticonvulsants (carbamazepine, gabapentin, phenytoin, topiramate, gabapentin and pregabalin) and muscle relaxers.

Tonic spasms and other involuntary movements such as paroxysmal or permanent focal dystonia, spinal myoclonus, spontaneous or induced clonus, spinal tremor, and secondary restless legs syndrome are caused by focal lesions of the myelin. They respond to anticonvulsants, especially carbamazepine and oxcarbamazepine.

Muscle weakness is best affected by physical therapy and exercise. Patients should be advised to exercise more. Measures are needed to limit muscle contractures and preserve the range of passive movements in the joints of the affected limbs. Impaired gait may respond to the potassium channel blocker Fampridine (Fampyra). By blocking potassium channels, Fampyra reduces the ionic current, thus prolonging repolarization and enhancing formation of the action potential in the demyelinated axons. One tablet of 10 mg is administered twice a day. Initially, the medication is administered for a period of 2 weeks, after which the clinical effectiveness is evaluated. A test that measures the time it takes to walk 25 feet is used (762 cm). It is called Timed 25-foot Walk, T25FW. If there is no improvement or there is worsening, Fampyra must be stopped.

Spastically increased muscle tone responds well to physiotherapy and muscle relaxers. Tizanidine (Sirdalud) up to 24 mg daily and baclofen up to 70 mg daily are used.

Vertigo, when a residual symptom, is treated with dimenhydrinat 75-150 mg daily, betahistine 48 mg daily, and combined drugs cinnarizine/dimenhydrinat (Arlevert) - 3x1 t. daily.

Tremor is difficult to treat, but in some cases clonazepam 2-4 mg daily, propranolol 50-100 mg daily, isoniazid 1200 mg daily, glutethimide 1000-4000 mg daily or primidone 250 mg daily are effective.

Paroxysmal symptoms respond to anticonvulsants, tricyclic antidepressants and benzodiazepines. Carbamazepine (up to 1200 mg daily) is the drug of first choice.

Epileptic seizures respond well to the standard anticonvulsants carbamazepine, phenytoin and valproate.

Pelvic-reservoir disorders extremely deteriorate the patients' quality of life. The overactive bladder responds to anticholinergic medications (oxybutynin 10 mg daily or tolterodine (detrusitol) 4 mg daily Solifenacin), β3- the adrenergic receptor agonist mirabegron (betmiga) 25-50 mg and tricyclic antidepressants, whereas in flaccid bladder intermittent catheterization is the method of choice. In milder cases, a vibrator is placed to the abdominal wall above the bladder to help urination.

The patient must be monitored for residual urine, occurrence of urinary infection and, accordingly, administration of antibiotic therapy, if required. For nocturia, an intranasal spray of the antidiuretic hormone desmopressin (10-40 μg per night), which reduces urination for 6-8 hours, but may cause hyponatremia, is administered. For detrusor dyssynergy, muscle relaxants and alpha-2 agonists are used.

Sexual disorders are managed by antidepressants, and erectile dysfunction responds to the use of phosphodiesterase type 5 inhibitor - sildenafil (Viagra) 50 up to 100 mg, vardenafil (Levitra) 5-10 mg orally, 1 hour before intercourse, tadalafil (Cialis) 20 mg.

Gastrointestinal disorders, such as nausea, vomiting, or hiccups associated with medullary lesions (area postrema) are sometimes refractory to symptomatic treatment but respond to corticosteroid treatment.

Constipation should be given comprehensive treatment. First, it is necessary to clarify whether some of the medications taken do not contribute to constipation and reduce their dose, accordingly. Patients are then recommended to increase their physical activity, change their diet to include foods containing more cellulose fibers, avoid chocolate products, stay hydrated and use warm drinks to stimulate the gastro-intestinal reflexes. If these measures are not effective enough, mild laxative medications are recommended.

Dysphagia responds to a change in food and feeding style, with insertion of a nasogastric feeding tube as a last resort.

Visual impairments (diplopia) are corrected by wearing prism glasses. Nystagmus responds to baclofen, clonazepam, scopolamine, gabapentin and other drugs.

Respiratory disorders are managed by treatment of respiratory infections, body temperature regulation, which improves axonal conduction, and prophylactic influenza vaccines.

Rehabilitation is very important to the patients. They should be referred to physiotherapy and rehabilitation when their daily activities are already limited, and symptomatic treatment is not effective enough. At some point in their life, patients will need crutches, a walker or a wheelchair, The best option will be determined by a physiotherapist.

General patient care has some specific features.

Temperature and infections must be prevented and treated promptly. Demyelinated fibres are extremely sensitive to the slightest change in body temperature and to mild acidosis. Exposure to heat on beaches, saunas, baths, pools, and the increase in body temperature even by 1-2 degrees during infections deteriorate the disease. For this reason, attacks often occur even after mild respiratory infections. It is extremely important to treat fever in infections, which may significantly improve the neurological symptoms.

Surgical interventions and anaesthesia minimally worsen the patients' condition and can be used in the presence of serious indications, accordingly. Intrathecal and spinal anesthesia should be avoided, the epidural one is well tolerated by patients.

Nutrition and physical activity have been the subject of numerous studies. Normal physical activity, aerobics, and sports that are enjoyable for the patient are recommended, but overheating, dehydration, overexertion, and activities associated with potential injury must be avoided. Swimming is not contraindicated if the water is not warm. Patients with weakness in the lower extremities can participate in sports activity related to the upper extremities (yoga). There is no evidence that any of the proposed diets have a positive effect on the course of the disease. The value of the popular low-fat diet has not been proven. Patients are still offered a diet rich in polyunsaturated fatty acids and vitamin D and low in animal fat, as well as quitting smoking.

Social and psychological aspects of the disease are extremely important. At the beginning of the disease, patients need emotional support after they learn about their gloomy prognosis and uncertain future. As disability progresses, patients can no longer perform their work duties and eventually stop working. Later, they become dependent on other people who care for them in their daily lives. During the different stages of the disease, patients face different problems and should be prepared for them through timely education. Patient education must begin with diagnosis. The nature of the disease and the possibility of a favorable prognosis should be explained to the patient. The hygiene and dietary regimen that must be followed should be explained and advice against "alternative" methods of treatment should be given. In the later stages of the disease, the support that the patient can receive from various associations and communities is extremely important.

I, Darina Georgieva Deneva, Personal No. 6912077050, holder of Confirmation No.16PR-622/07.02.2018, issued by the Consular Relations Directorate at the Ministry of Foreign Affairs of the Republic of Bulgaria, herein certify the authenticity of the translation made by me from Bulgarian into English of the attached document – Article.

The translation consists of 21 pages.

Translator: Darina Georgieva Deneva