NMO Spectrum Disorders

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ABSTRACT

Neuromyelitis optica spectrum disorders (NMOSD) represent a rare subset of chronic-inflammatory diseases of the central nervous system. Despite heterogeneities in disease activity, there is a higher degree of disability accumulation in NMOSD patients compared to MS patients. According to the revised diagnostic criteria, a recommendation was made to abandon the term NMO and to summarize these conditions as NMOSD. Clinical presentation of NMOSD patients in most cases is optic neuritis and transverse myelitis but nevertheless, NMOSD can affect most parts of the central nervous system (e. g. brainstem and hypothalamus). Originally characterized as AQP4-antibody-dependent disease, it has recently been discussed whether conditions with presence of antibodies against myelin oligodendrocyte glycoprotein (MOG) belong to the family of NMOSD. Due to the severity of the disease with often devastating relapses, systematic therapy is necessary. Usually, immunosuppressants or monoclonal antibodies with anti-inflammatory properties are used. Recently, four substances entered clinical testing for treatment of NMOSD.

History and Nomenclature

As early as 1894, the French physician, Eugène Devic, described patients with concomitant symptoms of optic neuritis and transverse myelitis, and designated it as "neuromyelitis optica" (NMO) [1]. For a long time, the NMO was not defined as a separate entity under chronic inflammatory CNS diseases, but as a sub-form of multiple sclerosis. This assessment was abandoned by the turn of the millennium, when Wingerchuk and colleagues first published independent diagnostic criteria for the disease [2]. A major contribution to this new understanding has been the discovery of antibodies in the serum of patients; these were initially referred to as NMO immunoglobulin G (IgG). The membrane protein aquaporin-4 (AQP4) was identified as the target structure of these antibodies [3, 4]. This discovery led to a revision of the diagnostic criteria with the implementation of antibody diagnostics as a biomarker of the disease in 2006. Since in about one-third of the patients with the clinical presentation of an NMO, such antibodies were not detectable, a distinction was made between "seropositive" and "seronegative" NMO [5].

Conversely, antibodies to AQP4 were detectable in patients who did not have the typical symptoms of NMO (optic neuritis and myelitis, also referred to as "classic Devic's syndrome"). Primarily for this reason, the concept of NMO-spectrum diseases (NMOSD) was established and gradually expanded. With the last revision of the diagnostic criteria in 2015, this term was rendered uniform. Its use is now recommended for the description of all seropositive and seronegative CNS disorders with a typical distribution pattern and clinical course [6].

Epidemiology

Basically, the NMOSD is a much rarer entity of chronic inflammatory CNS disorders compared to multiple sclerosis (MS). The geographical distribution of prevalence and incidence is markedly different with a significantly higher incidence in Asian, African and South American patients compared to Caucasians.

In a relatively recent epidemiological study, a prevalence of 3.9/100 000 persons and an incidence of 0.7/1 000 000 person-years were determined in a Caucasian population in North America (Olmsted City, Minnesota). On the Antilles island of Martinique, the prevalence was 10/100 000 persons and the incidence of 7.3/1 000 000 person-years.

This is consistent with a Danish survey that reported a prevalence of 4.4/100 000 inhabitants [7, 8] in the predominantly Caucasian cohorts. Retrospective studies of (Caucasian) patients with chronic inflammatory, demyelinating CNS disorders support these

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numbers, NMOSD cases comprising approximately 1.5 % of all cases in the widest sense [9]. The findings from the Caribbean population underline the fact that, as in the whole of South America, NMOSD is much more common in the Caribbean than in Europe.

Surprisingly, in individual cohorts in Japan, the prevalence of NMOSD at 0.9/100 000 was unusually low [7]. However, it must be taken into account that in Japan often the diagnosis of "opticospinal MS" (OSMS) is made. Although OSMS is not conclusively assigned to the NMOSD spectrum, patients with OSMS share numerous other similarities in addition to the typical distribution of the lesions with only occasional intracerebral demyelinating lesions. These include a comparable course with rapid accumulation of disability; however, oligonoclonal bands [10] are only detected in exceptional cases. However, the strongest argument for such an association is the prevalence of AQP4 antibodies in 50 % of OSMS patients [11, 12].

Including OSMS patients, NMOSD represents approximately half of all cases of chronic inflammatory, demyelinating CNS disorders in Asian patients [13].

For these reasons, the current consensus criteria recommend that the term OSMS be used no longer, but that in these patients the diagnosis of an NMOSD (seronegative or seropositive) should be made.

The age at the initial manifestation of NMOSD is on average 37.8 years, which is approximately 10 years above the mean manifestation age in MS patients. However, initial manifestations were also observed in significantly older patients.

With a ratio of approximately 9: 1 (f: m (female to male sex ratio)), NMOSD occurs significantly more frequently in females, especially in its seropositive forms, than multiple sclerosis (ratio f: m = 2–3: 1 [9, 14]. The preferential occurrence of NMSOD in women decreases in AQP4-seronegative patients and especially with those with detectable antibodies against myelin oligodendrocyte glycoprotein (MOG); MOG antibody-associated NMOSD forms occur even more frequently in men (0.6: 1 (m: f)) [15].

NMOSD patients also tend to develop other antibody-mediated (or at least antibody-associated) autoimmune diseases. Thyroid disorders (~14 % of patients), Sjögren's syndrome (~20 % of patients) and myasthenia gravis (2 %) [16, 17] are the most common diseases in these patients. Overall, approximately one-third of NMOSD patients suffer from at least one further manifest autoimmune phenomenon with marked preference for seropositive patients (58.5 % for AQP4 + patients vs. 8.6 % for AQP4-patients) [14]. The tendency to form autoantibodies is illustrated by the fact that positive antinuclear antibodies without documented clinical manifestation are present in approximately half of all NMOSD patients [17]. There are case reports of manifest systemic lupus erythematosus [18].

Due to the high clinical relevance and the necessity for vigilance, it must be borne in mind that a bi-directional association exists between Myasthenia gravis and NMOSD. Since NMOSD is most common in myasthenia patients after thymus resection, this differential diagnosis should be considered in the presence of the relevant clinical symptoms. It is unclear, however, whether presence of AQP4 antibodies without corresponding clinical symptoms in individual cases of myasthenia patients is a meaningful indication for screening (if necessary, prior to indicated thymus resection) [19].

Pathogenesis

The pathogenesis of NMOSD has not been conclusively clarified. By identifying the target structure Aquaporin-4, however, there has been a gain in the understanding of immunopathogenesis. In this article, only selected aspects, which can explain directly clinical findings, are recapitulated.

A key role in disease development is the autoimmune-mediated destruction of astrocytes by the immune system [20]. The formation of autoantibodies against the water channel protein Aquaporin-4 (AQP4) represents the first step of the immunopathogenesis. This protein is expressed at astrocyte processes involved in the construction of the blood-brain barrier. Furthermore, AQP4 occurs more frequently in the gray matter of the spinal cord and the periaqueductal and periventricular zones [21].

The binding of AQP4 antibodies to the astrocyte processes of the hemophilia barrier leads to cell death of astrocytes, for which, among others, antibody-mediated complement activation and cytotoxic T cells are responsible.

After disruption of the blood-brain barrier, inflammatory cells, in addition to lymphocytes, typically also neutrophils and eosinophilic granulocytes, migrate into the CNS [14]. The inflammatory response leads to secondary damage of neurons and oligodendrocytes with corresponding atrophy and demyelination, possibly by glutamate overstimulation after increased release of this transmitter from dead astrocytes [22–24].

The death of astrocytes and neurons could be visualized in MRI of NMOSD patients. The results differed markedly from MS patients with detectable, primary damage to the oligodendrocytes [25].

In the case of NMOSD patients, the changes in the central nervous system that have been detected so far are strictly limited to those of inflammatory origin. In the case of MS patients, however, structural abnormalities of the white substance not detected by MRI have also been described.

Possibly due to this, there is no generalized or localized (e. g., the thalamus) cerebral atrophy in NMOSD patients. This can explain the absence of a chronic-progressive course of the disease [26].

For the recruitment of the inflammatory cells in NMOSD, interleukin-6 (IL6) more frequently found in the CSF appears to be responsible. IL6 is released, among others, by special subgroups of T lymphocytes (Th17 cells) [27, 28].

The involvement of Th17 cells is a possible explanation for the ineffectiveness of different MS therapeutics in NMOSD patients, as these cells use alternative strategies to invade the CNS compared to "conventional" T cells [29, 30].

However, typical markers of intrathecal antibody synthesis are absent in NMOSD, up to 90 % of the patients lack oligoclonal bands. An MRZ reaction can only be detected in isolated cases [31].

It is worth mentioning that AQP4 is also expressed in other organs, such as the placenta. This could be an explanation for the increased rate of miscarriages and pregnancy complications in NMOSD patients [32].

Manifestations of NMOSD

A major improvement of the revised diagnosis criteria of 2015 is the recognition that although the optic nerve, the spinal cord and area postrema are the preferred sites of NMOSDs manifestation, in

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▶ **Table 1** Characteristics of optic neuritis (ON) in NMOSD and MS.

	NMOSD	MS
Common manifestation	Uni- or bilateral	Unilateral
Extent of loss of vision	High grade, blindness possible	Blindness not common
MRI findings	Extensive lesion (>50%), extending into the optic chiasm	Short lesion, no involvement of the chiasm
Visual evoked potentials	Prolonged latency, Amplitude reduction	Prolonged latency
Convalescence	Frequently high-grade, persisting deficit	As a rule, good recovery

principle they can affect all parts of the central nervous system. Accordingly, three further manifestations were defined in addition to the three "classical" regions. These six categories are presented briefly below.

Nervus Opticus

Optic nerve (neuritis nervi optici, ON) is one of the most frequent manifestations of NMOSD and is therefore also listed as a "core criterion" in the new diagnostic criteria. Even if an optic neuritis can in principle be the expression of numerous isolated or disseminated CNS disorders, the NMOSD-ON has certain characteristic features. The presence of bilateral manifestation is highly suspicious, but unilateral inflammation occurs in about 80 % of the cases at initial manifestation [33]. Clinically, NMOSD-ON impresses with a high degree of loss of visual acuity to blindness and very limited recovery. Radiologically, it is often associated with long-term affection of the corresponding optic nerve, extending into the optic chiasm. Electrophysiologically, the visual evoked potentials often show a significant amplitude reduction. The combination of persisting deficit and electrophysiological findings can suggest a vascular genesis [34]. The differential diagnosis can be made more difficult by the fact that no oligoclonal bands are detectable in a majority of NMOSD patients (see chapter "CSF Diagnostics") (▶ Table 1).

Relapsing, but monotopic manifestations in AQP4-negative patients, such as the chronic-relapsing inflammatory optic neuropathy (CRION), are not as yet included in NMOSD. CRION is characterized by severe clinical symptoms that can lead to blindness in untreated patients and quickly responds to therapy with corticosteroids. Uni- and often bilateral manifestations occur, and orbital pain is often very pronounced, especially in the initial phase. Further differential diagnosis including MRI imaging is inconspicuous with regard to disseminated inflammatory activity. The relapsing course requires in long-term immunosuppression, the majority of the drugs listed the chapter "Therapy" is effective [35].

Spinal Cord

Myelitic manifestations of NMOSD have a prominent position in the manifestation sites due to the fact that they contribute significantly to the accumulation of disability and also to the mortality.

In NMOSD, most impressive variant of transverse myelitis extends over more than three segments. This is designated as "longitudinally extensive transverse myelitis" (LETM) [36]. During acute inflammation, the affected spinal cord segment usually shows marked swelling. In addition to pronounced T2 hyperintensity in spinal MRI, lesions often show strong contrast-enhancement after application of gadolinium.

MRI images acquired very early in the course of the disease demonstrate either multiple short lesions that become confluent with time, or even isolated lesions that expand correspondingly [37]. Cervical lesions often extend into the medulla oblongata. In a small longitudinal cohort with 63 patients, one-fifth of the patients also showed cystic lesions [38]. Clinically, severe sensorimotor deficits as well as bladder and bowel dysfunction are in the foreground. Even a single episode can lead to being permanently chained to a wheelchair due to severe paraplegia or tetraplegia [39]. As a correlate of the severe defect with spastic paresis, MRI reveals a high degree of atrophy of the areas the previously swollen areas ("hourglass-shaped atrophy of the spinal cord") after the inflammatory activity has subsided. This impressively illustrates the functional discontinuity of the spinal cord [40] (▶ **Fig. 1**).

Area Postrema and Brainstem

In addition to the caudal medulla oblongata that is affected in the context of LETM originating from the cervical spine, NMOSD can also primarily affect the brainstem. The classical localization is the area postrema (due to the strong expression of aquaporin-4). There is clinical manifestation of area postrema syndrome (APS) with persistent hiccups, nausea and vomiting [41]. If inflammation spreads from the area postrema into the adjacent brainstem, cranial nerve failure, vegetative dysfunction and sensorimotor deficits of the whole body can occur. Since such severe, potentially life-threatening relapses can be induced by an area postrema syndrome, MRI should be performed generously in NMOSD patients with suspicious symptoms [42].

However, brainstem lesions can also primarily occur apart from the area postrema and lead to corresponding symptoms (including oculomotor dysfunction, facial palsy, trigeminal neuralgia) [43]. These rare lesions are summarized in the revised diagnostic criteria under the term "acute brainstem syndrome" and distinguished from the classical area postrema syndrome.

Diencephalon

Lesions in the area of the diencephalon, which can occur in the context of NMOSD, are most frequently associated with disorders of sleep-wake rhythm in the sense of symptomatic narcolepsy. Likewise, disturbances of thermoregulation may appear as an expres-
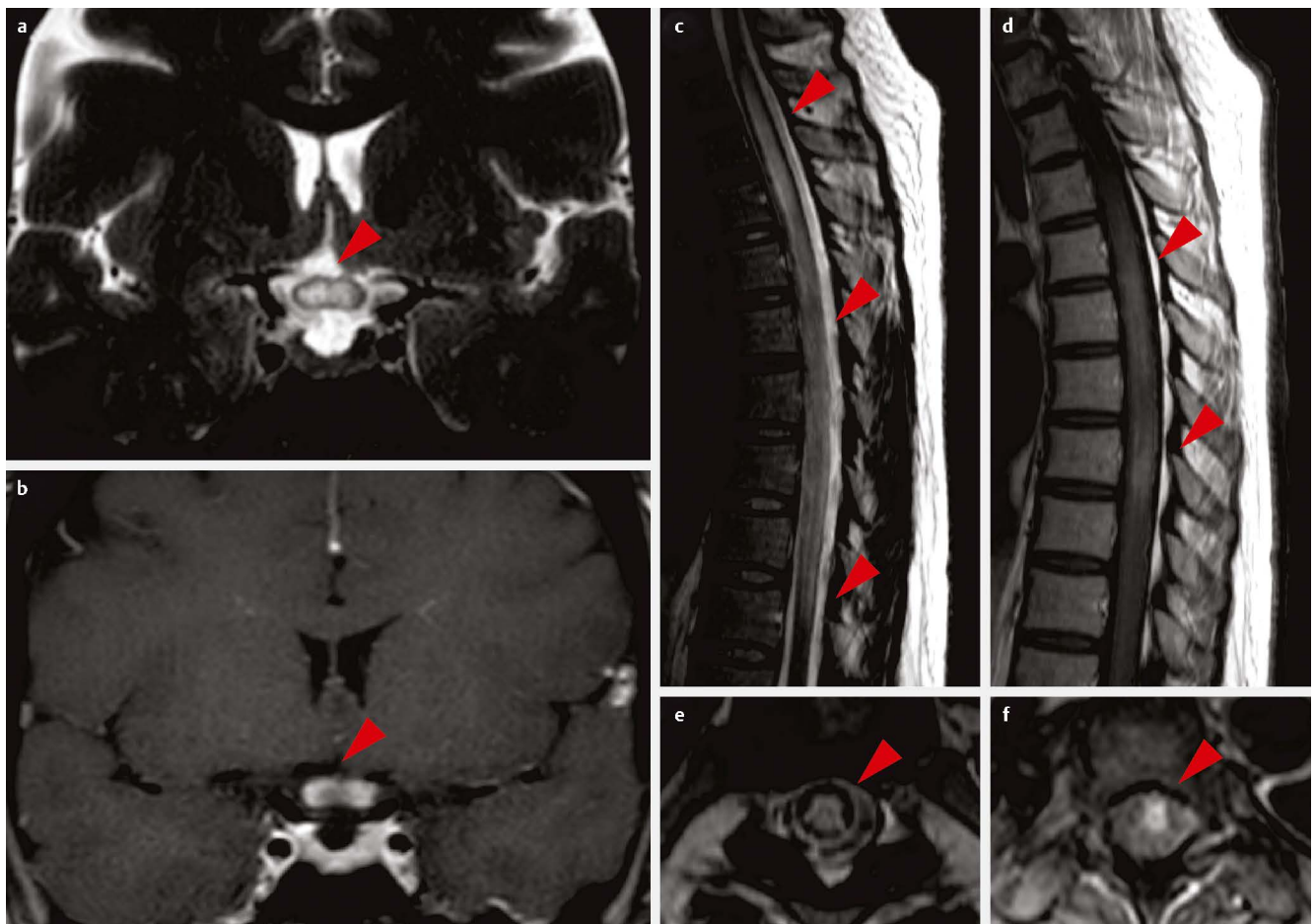
▶ **Fig. 1** MRI findings in NMOSD-associated ON and LETM of a single patient. **a, b**: Coronary T2 and T1Gd visualization of the optic nerve at the level of the optic chiasm with signs of blood brain barrier disruption and edematous swelling due to bilateral ON. **c/d**: Sagittal representation of the spinal cord in T2 **b** and T1Gd **c**. LETM extending over at least 9 segments with edematous swelling and barrier disorder. **e/f**: Axial representation correlated to **c/d**: at segment Th1. Typical is the concentric affection of the spinal cord, which also leads to the gray matter being affected. Clinically, the patient presented with high-grade tetraplegia.

sion of hypothalamic dysfunction or endocrinological syndromes with underlying pituitary insufficiency. MRI correlates of these disorders are signal alterations in the region of the hypophysis, hypothalamus or adjacent to the third ventricle [44, 45]. These symptoms are summed up in the revised diagnosis criteria under the term "diencephalic syndrome".

Cerebral Hemispheres

One of the clearest changes in the diagnostic criteria of NMOSD is in relation to the occurrence of cerebral white matter lesions. In the previous revision of the NMO diagnostic criteria, such lesions were listed as "red flags", if not as an exclusion criterion for diagnosis. The only exception was leukoencephalopathy of alternative origin, for instance, as a result of cerebral microangiopathy. Meanwhile, however, longitudinal studies have shown that up to two-thirds of NMOSD patients also develop inflammatory white matter lesions. There are some morphological differences compared to MS-typical lesions. Thus, NMOSD-associated lesions are usually larger and in the acute phase more markedly edematous [46]. These lesions are often localized subcortical and periventricular, but the latter

are not oriented perpendicularly to the lateral ventricles (like the "Dawson's fingers" in the MS), but align themselves parallel to this, affecting over 50 % of the roof of the ventricle. Subcortical lesions usually follow the course of corticospinal tracts. In contrast, NMOSD is unlikely if disseminated, juxtacortical lesions are present or the inferior temporal lobes are involved; these lesions should suggest a diagnosis of MS [47]. Isolated cases running a fulminant course with cerebral demyelination, cerebral edema with herniation and death have been described [48] (▶ **Fig. 2**).

Diagnosis Based on the Revised Diagnostic Criteria

Seropositive NMOSD

In presence of AQP4 antibodies, a diagnosis of NMO-spectrum disorder can and should be made if one of the six sites is affected. For example, in the case of optic neuritis and detection of AQP4 antibodies, a diagnosis of seropositive NMOSD should be strived with all its therapeutic consequences.

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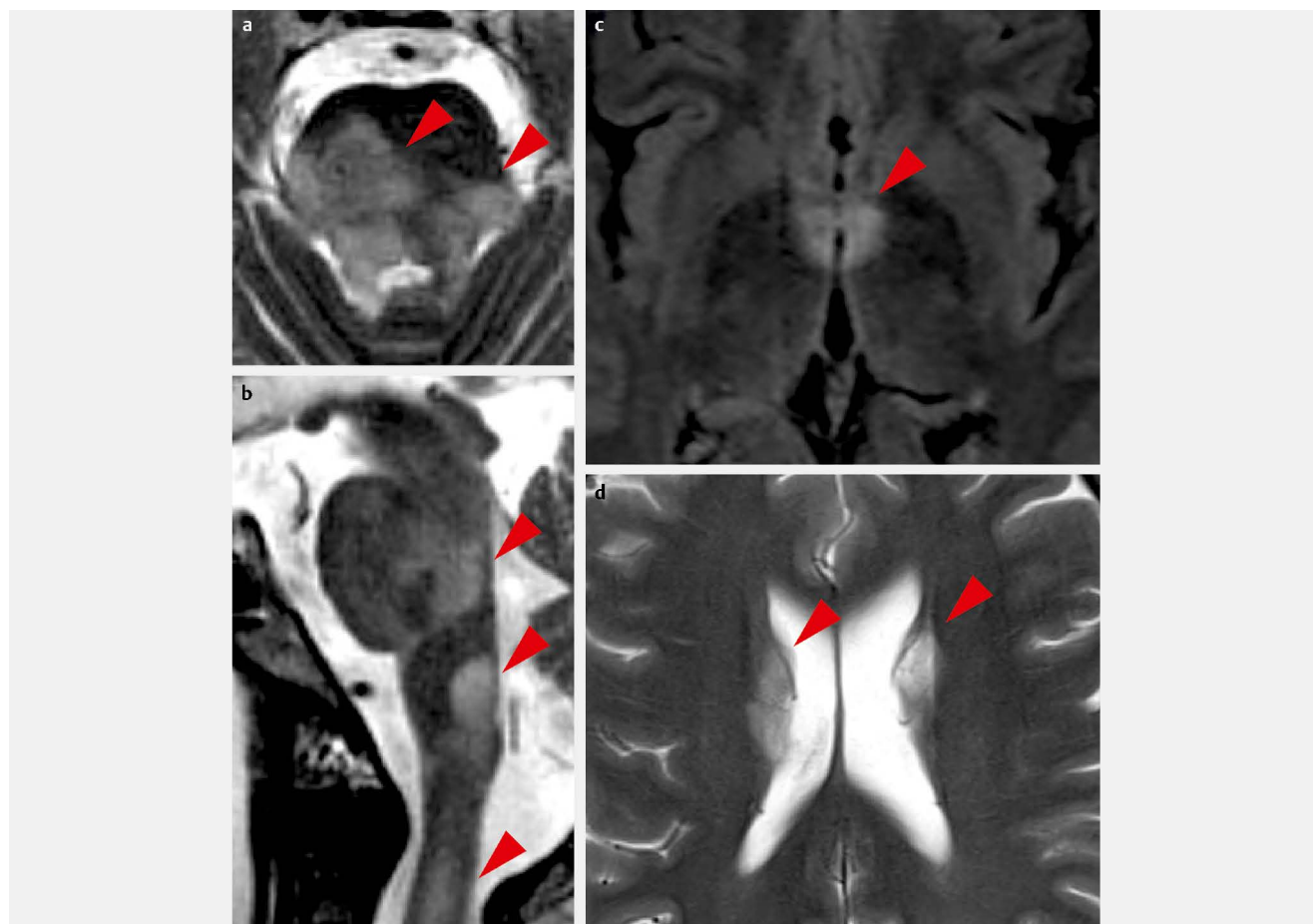
▶ **Fig. 2** MRI findings of intracerebral manifestations in NMOSD. **a/b**: axial and sagittal T2 imaging of the brain stem in patients with area postrema syndrome and multiple intracranial nerve deficits (including oculomotor dysfunction and dysphagia). The cervical spinal cord also shows a section of an LETM: section of the upper cervical region. **c**: Axial FLAIR representation of the dicephalon of a patient with newly diagnosed narcolepsy and evidence of AQP4 antibodies. **d**: Evidence of periventricular white matter lesions in patients with known NMOSD. In contrast to MS-typical lesions, here they run a parallel course along the ventricle.

The criterion of temporal dissemination in time the diagnosis of NMOSD does not exist because of the existence of monophasic disease coureses. This appears to be meaningful in the face of accumulation of severe disabilities during disease exacerbation and the associated necessity to start a disease-modifying therapy quickly.

It is important to note that cell-based detection methods should be used because they are superior to the ELISA-based method in specificity and sensitivity. False-positive antibody detection in cohorts with definitive diagnosis of MS was found in 1.3 % of cases in ELISA tests, whereas in similar cohorts, there were only 0.1 % false-positive results in studies using cell-based detection methods [49].
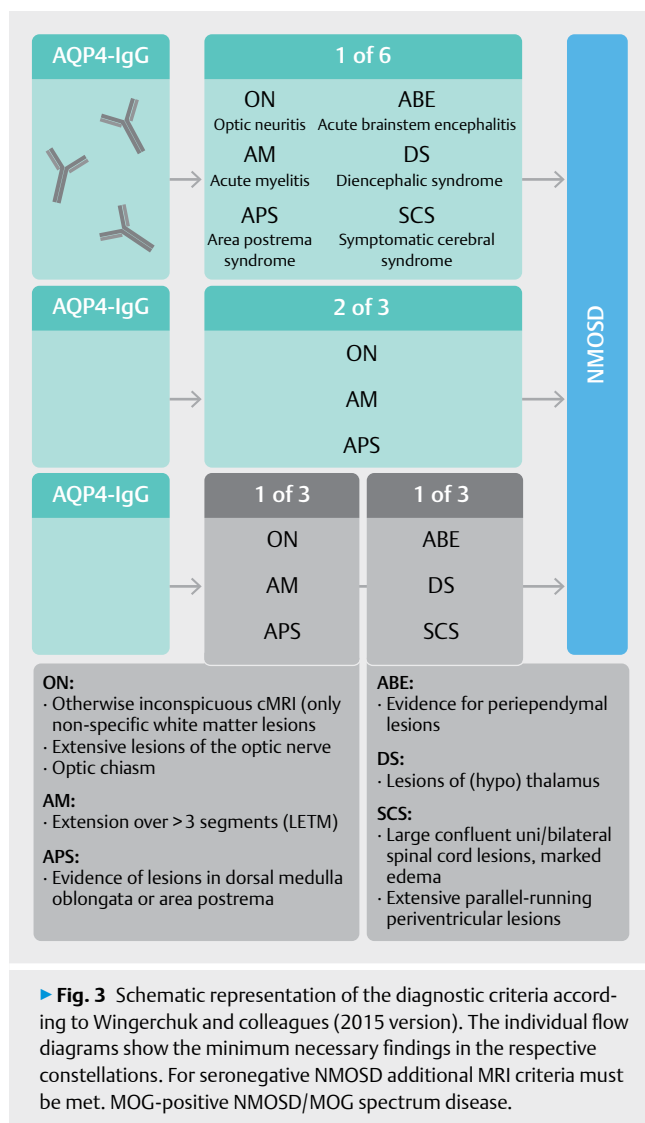
Seronegative NMOSD

In absence of antibodies against AQP4, more stringent criteria apply for classifying an inflammatory syndrome of the CNS as NMOSD. In contrast to the seropositive variant, there is dissemination to at least two sites necessary. At least one of which must correspond to a "classical" site (spinal cord, optic nerve or area postrema). Furthermore, the additional requirements for MRI findings listed in ▶ **Fig. 3** apply. Special care is required to differentiate suspected NMOSD with optic neuritis and cerebral demyelination areas. The diagnosis of NMOSD can only be made in this situation if the optic neuritis shows clear signs of NMOSD-ON. Due to therapeutic consequences of the assignment of a case to either MS or NMOSD, diagnosis should be done in consultation with specialists or by a specialized center. As already mentioned, the diagnostic criteria do not include a criterion of dissemination in time. Accordingly, NMOSD can not be diagnosed in seronegative patients with a monotopic manifestation but with a relapsing course (in ~10% of patients) [14].

MOG-positive NMOSD/MOG spectrum disorder

In recent years, autoantibodies to the myelin oligodendrocyte glycoprotein (MOG) have been detected in about a quarter of the AQP antibody-negative patients with clinical suspicion of NMOSD [6]. In seropositive patients, however, they are virtually never demonstrable. In contrast to AQP4, MOG is not an astrocytic protein, but is expressed on the surface of oligodendrocytes and has been considered as a possible autoantigen in multiple sclerosis. Antibodies against MOG have so far been reported mainly in children with acute demyelinating encephalomyelitis (ADEM), where they are more frequently detectable [50]. Due to the clinical course, com-

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AQP4-IgG	1 of 6		NMOSD
	ON Optic neuritis	ABE Acute brainstem encephalitis	
	AM Acute myelitis	DS Diencephalic syndrome	
	APS Area postrema syndrome	SCS Symptomatic cerebral syndrome	

AQP4-IgG	2 of 3
	ON
	AM
	APS

AQP4-IgG	1 of 3	1 of 3
	ON	ABE
	AM	DS
	APS	SCS

ON:
· Otherwise inconspicuous cMRI (only non-specific white matter lesions
· Extensive lesions of the optic nerve
· Optic chiasm

AM:
· Extension over >3 segments (LETM)

APS:
· Evidence of lesions in dorsal medulla oblongata or area postrema

ABE:
· Evidence for periependymal lesions

DS:
· Lesions of (hypo) thalamus

SCS:
· Large confluent uni/bilateral spinal cord lesions, marked edema
· Extensive parallel-running periventricular lesions

▶ **Fig. 3** Schematic representation of the diagnostic criteria according to Wingerchuk and colleagues (2015 version). The individual flow diagrams show the minimum necessary findings in the respective constellations. For seronegative NMOSD additional MRI criteria must be met. MOG-positive NMOSD/MOG spectrum disease.

parable laboratory findings and results of CSF examination and partially comparable pathomechanisms, patients with appropriate symptoms and with demonstrable MOG antibodies are occasionally included in the "seronegative NMOSD spectrum". This assignment is certainly not final at the present time; schematically, the "MOG antibody spectrum" is often located between "classical" NMOSD, ADEM and MS.

MOG-positive patients are significantly more frequently male, mostly younger and more frequently show positive oligoclonal bands in the CSF [6]. Spinal manifestations are less frequent, but optic neuritis occurs more frequently. In particular, bilateral optic neuritis or involvement of the conus medullaris in myelitis is suggestive for the presence of MOG antibodies [51]. The latter can be the trigger for significant bowel and bladder dysfunction. MOG-positive patients were generally thought to have more favorable clinical course with better recovery of deficits and slower accumulation of disabilities [15]. Recent retrospective data clearly indicate the opposite. Thus, the lower disability accumulation per relapse appears to be cancelled by a higher relapse frequency. The interval between the first and the second relapse also appears to be short-

er [52]. There are also no differences in impairment of visual acuity [53]. Furthermore, approximately one-third of the patients develop brainstem involvement, some with dramatic consequences [54]. Overall, the MOG-positive NMOSD also appears to need unrestricted and long-term treatment.

Clinical Course

In approximately 90% of the cases, NMOSD runs a relapsing course, and in only about 10%, the disease is monophasic [6]. A second relapse occurs in 60% of patients in the first year, and in 90% of patients within 3 years after diagnosis [2]. Often the course of NMOSD runs in "clusters" with phases of frequent exacerbation, alternating with low activity phases.

Monophasic disease course is more common in seronegative, younger patients, but there are no reliable predictive markers. Remarkably, the relapses in monophasic patients are often more severe than those in patients with a relapsing form of the disease.

In view of the high relapse-associated morbidity, monophasic disease should be assumed at the earliest after 5 years of relapse-free course [14]. With increasing effective long-term therapy, the question will arise more frequently as to whether the degree of disease-freedom is the consequence of per se decreasing disease activity or, whether it results from adequate immunosuppressive therapy.

Accumulation of disability is strictly relapse-dependent in NMOSD patients; a chronic-progressive form exists, if at all, only in exceptional cases [6].

Due to the severity of the disease, half of the patients get blind after 5 years and are no longer independently mobile. In addition, 20% of patients die after 5 years. The most frequent cause of death is respiratory failure and associated complications, mostly as a result of cervical transverse myelitis [55]. These values have probably improved with the availability of monoclonal antibodies; however, recent data are not available besides individual therapy test reports.

Diagnostics

As with all inflammatory syndromes of the CNS diseases, diagnosis is based primarily on imaging and laboratory values, together with clinical findings.

MRI

In patients with suspicion of NMOSD based on history and clinical presentation, MRI scan of the head and entire spinal cord is indicated including application of gadolinium. Even if clinically silent manifestations are rare, MRI has a central role in differential diagnosis. Follow-up examinations, especially in unclear cases or an with atypical clinical course (especially in chronic progression) are useful. In contrast to MS, regular MRI examinations to detect paraclinical disease activity are of minor importance [6]. In line with the guideline of the German Society of Neurology (DGN) for the diagnosis of multiple sclerosis, the imaging of the head should include native axial T2 sequences as well as axial T1 sequences, without and with gadolinium administration. In particular, to distinguish NMOSD from MS, a T2 sequence in sagittal plane is recommended. Imaging of the spinal cord should include sagittal T1 sequences before and

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after gadolinium application as well as a sagittal T2 sequence. Axial sequences in axial T1 and T2 sequences weighting complete the basic program. In the case of clinical suspicion of an affection of certain specific structures (optic nerve, brain stem, etc.), appropriate thin-sliced imaging of these structures is recommended [6].

CSF diagnosis

Lumbar puncture should be performed for the purpose of differential diagnosis. Typically, NMOSD patients exhibit lymphogranulocytic pleocytosis with the presence of neutro- and eosinophilic granulocytes. The cell count can increase significantly in acute attack, values of more than 50 cells/µL have been regularly observed. Oligoclonal bands are only detectable in 10–20 % of the patients and should give rise to a more thorough diagnostic process. A polyspecific antiviral immune response ("MRZ reaction") is detectable only in isolated cases [56]. This is in contrast to MS, where oligoclonal bands are detectable in over 90 % of cases [23]. Numerous other observations have been published which have a high specificity for NMOSD, but are still of no relevance in clinical practice.

These include, among others, an increase in the levels of interleukin-6 and detection of glial fibrillary acidic protein as a correlate of astrocytic damage [57]. Extensive measurements of the cytokine levels in the CSF or the determination of AQP4 or MOG antibodies in the CSF have no confirmed value [58].

Diagnosis of AQP4 and MOG Antibodies in Serum

Due to the impressive specificity of a positive AQP4 antibody finding, a test should always be carried out in case of suspicion. Three important findings are to be taken into account in the test: firstly, the strength of a finding depends to a considerable extent on the related diagnostic process. Secondly, AQP4 titers may drop after therapy or in phases of low disease activity or seroconversion may even occur in a patient. Thirdly, in patients initially seronegative, AQP4 antibodies may be detected over time [59].

The first available tests detected AQP4 antibodies using ELISA technology. Since no native but denatured AQP4 was used in this test method, the sensitivity was only 60 %. Cell-based methods, in which serum is incubated with AQP4-expressing cells and subsequently evaluated by means of flow cytometry or microscopy, reach values of up to 77 %. Accordingly, only the latter methods should be applied [49].

In seronegative patients with suspicion of NMOSD, a diagnosis should be based on the presence of MOG antibodies. Here too, cell-based test methods should be used [50].

In the case of seronegative patients with suspicion of NMOSD, the test should be repeated with regard to AQP4 and MOG antibodies, and blood should be drawn before the start of therapy. In individual cases, the corresponding antibodies were detectable in the CSF in patients with inconspicuous serum findings. Accordingly, in seronegative patients with high clinical suspicion, such CSF diagnosis may be useful [60].

Differential diagnosis

The most important differential diagnosis of NMO-spectrum disorders is multiple sclerosis. A confirmed diagnostic classification is essential due to major differences in therapy. It is therefore not surprising that most of the "red flags" explicitly named in the diagnostic criteria for NMOSD of 2015 are simultaneously reliable characteristics of MS.

MRI findings of periventricular lesions, lesions in the inferior temporal lobe, "Dawson fingers" and juxtacortical lesions, especially involving the U fibers, more likely suggest multiple sclerosis.

The cranial MRI of NMOSD patients is usually inconspicuous, especially when patients with symptomatic cerebral syndrome are excluded [47]. Even if due to the localization there is no suspicion of MS, cases with relevant lesions in the cerebral cranial MRI require particularly critical evaluation.

The detection of oligoclonal bands in the CSF is more likely suggestive of multiple sclerosis, whereas the demonstration of granulocytes in CSF suggests NMOSD. ▶ Table 2 lists "red flags" in the differential diagnosis of the NMOSD.

In addition to multiple sclerosis, other systemic and CNS autoimmune diseases, vasculitides, malignomas as well as hereditary and infectious CNS diseases should be taken into account in differential diagnosis. Attention is specially drawn to neurosarcoidosis since it can manifest itself with NMOSD-typical symptoms such as optic neuritis and LETM, and presents great difficulties in differential diagnosis [61].

In general, LETM as a common manifestation cannot be classified solely on the basis of MRI findings. Corresponding cases have been documented by Trebst and colleagues [36].

The diagnosis is sometimes made more difficult by the detection of antinuclear antibodies in NMOSD patients [62]. Furthermore, several autoimmune diseases can also be present concomitantly. For instance, there are reports of patients with concomitant systemic lupus erythematosus and NMOSD [63]. ▶ Table 3 gives a selected overview of differential diagnoses.

▶ **Table 2** "Red flags" in NMOSD, modified according to [6].

Course of the disease
– Chronic-progressive course, relapse-independent deterioration
– Progressive worsening of suspicious symptoms over several weeks
– Spontaneous remission of neurological deficits after a short time

Clinical and laboratory findings
– Detection of oligoclonal bands in the CSF
– Serologic testing of serum/CSF (e. g., HIV, syphilis, borreliosis)
– Detection of solid or hematological tumor diseases
– Proof of generalized or hilar lymphadenopathy

MRI findings
– relevant lesion burden in cranial MRI, in particular with
– Detection of MS-typical lesions ("Dawson's fingers")
– Detection of cortical lesions
– Detection of lesions of the inferior temporal lobes
– Proof of persistent gadolinium-enhancement
– Detection of persistent short-range lesions in the spinal cord

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Therapy

Treatment of acute relapses

As with multiple sclerosis, there are essentially four procedures available for the treatment of acute relapses of NMOSD: corticosteroids, plasmapheresis, immunoadsorption and intravenous immunoglobulins.

High-dose administration of intravenous corticosteroids (1 g/d methylprednisolone over 5 days) is currently the most frequently used therapy for acute attacks [64, 65]. In the absence of improvement after therapy with 1 g/d methylprednisolone, a further cycle of 2 g/d can be added on for a further 5 days. Ulcer and thrombosis prophylaxis are essential.

▶ **Table 3** Overview of selected differential diagnoses of the NMOSD.

Multiple Sclerosis
Autoimmune diseases – Systemic lupus erythematosus – Sjögren's syndrome – Sarcoidosis – Behçet's disease
Vascular diseases – Systemic vasculitides – Primary angiitis of the central nervous system (PACNS) – Spinal dural arteriovenous fistulas
Infections – Neuroborreliosis – Neurosyphilis – Whipple's disease – Listeriosis – HIV-associated myelopathy/encephalopathy – Infectious spastic paraparesis (HTLV 1) – Cerebral abscesses
Hereditary diseases – Hereditary spastic paraparesis – Leber hereditary optic neuropathy – Arnold-Chiari malformation
Neoplastic diseases – Primary tumors of CNS – Metastases – CNS lymphomas – Paraneoplastic syndromes – Angiomas
Metabolic diseases – Vitamin-B12 deficiency – Adrenoleukodystrophy/-myelopathy

Alternatively, plasmapheresis or immunoadsorption can be carried out. Both methods have shown comparable efficacy. The selection can accordingly be oriented, besides availability, to the side effects/to the side effects profile profile (necessity of having to substitute foreign blood components after plasmapheresis, stronger affection of the coagulation function after plasmapheresis). The effect of plasmapheresis or immunoadsorption is not categorically different in seropositive or seronegative patients [66].

In a recent retrospective study of the NEMOS study group, it was found that there was complete remission in only 21.6 % of the patients and partial remission in 72.4 % of the patients after all therapeutic procedures had been exhausted. It is astonishing that already 19.1 % of the patients achieved complete remission after the first of up to five therapy courses. Plasma exchange methods have led to improved symptom control especially in patients with acute myelitis. The positive effect of plasma exchange decreased with the increase in previously undergone therapy procedures. These data were not significant when comparing all kinds of relapses but other studies support the estimation that plasma exchange is superior [65, 67]. Individual studies also showed a cumulative effect of combined steroid pulse and apheresis treatment (for example plasma exchange and infusion of corticosteroids on alternating days) [68].

Intravenous immunoglobulins (IVIG) are currently only used in exceptional cases for the treatment of relapses, as for instance in children. Currently there are no larger studies, but patients are being recruited for a study on the treatment of acute transverse myelitis with IVIG [69]. Different case series have documented the positive effects of IVIG so that its use as second-line therapy can be justified (0.4 g/kg for five consecutive days) [70]. On the one hand, the therapy should be carried out only after plasma exchange has been completed because efficacy is not clearly established and there is the risk of leaching. Individual studies in pediatric patients showed a positive effect of IVIG in maintenance therapy (dose: 0.4 g/kg bw every 4 weeks) [71] (▶ **Table 4**).

Disease-modifying therapy

Contrasting the 15 approved medications for the treatment of MS, there is no approved drug for the treatment of NMOSD. This is mainly due to the absence of relevant randomized, placebo-controlled trials. In addition to the rarity of the disease, other factors contribute to this situation. On the one hand, approval authorities usually do not recognize comparative studies between several unauthorized medications. On the other hand, there are significant ethical concerns about placebo-controlled studies in the face of threat of severe impairment after a single relapse. For the first time, different drugs are tested in controlled clinical trials. Different

▶ **Table 4** Overview of available acute therapies for relapses in NMOSD.

Medication	Dosage and interval
Corticosteroids [63]	1 g Methylprednisolone/d over 5 days, if needed escalation with 2 g Methylprednisolone/d (latter over a maximum of 5 days)
Plasmapheresis [64]	5–7 cycles every other day (exchange of 1.1 to 1.5 plasma volumes per session)
Immunadsorption [64]	5–6 cycles on consecutive days; tryptophan or protein A-columns (adsorption of 2 to 2.5 plasma volumes per session)
Intravenous immunoglobulins [69, 70]	0.4 g/kg/d over 3–5 days, maintenance dose: 0.4 g/kg once a month

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▶ **Table 5** Overview of available long-term therapeutics for NMOSD.

Substance (Study reference)	Mechanism of action	Dosage and interval
Azathioprine (+ low dose prednisolone 1 mg/kg/d) [74, 76]	Inhibition of nucleic acid synthesis	2–3 mg/kg divided over 3 single doses depending on lymphocyte number ca. 75–175 mg/d
Mycophenolate mofetil [77]	Inhibition of nucleic acid synthesis	1 g twice daily
Rituximab [79]	Depletion of CD20+ B cells	A) Induction with two infusions of 1000 mg each within a two-week interval. Re-administration upon increase of peripheral B cell count, but at least every six months B) Induction with 4 infusions of 375 mg/m² each once a week, afterwards depending on peripheral B cell count, e.g. 1000 mg/m² within a two-week interval.
Tocilizumab [81, 82]	Blockade of IL6 receptor	8 mg/kg once every 4 weeks
Eculizumab [83]	Inhibition of complement activation by binding to C5	600 mg/week over 4 weeks, once 900 mg in week 5 and thereafter 900 mg once every two weeks (Duration of therapy investigated: 48 weeks)

methods, for instance, asymmetric randomization in favor of the study medication, definition of the first relapse as clinical end point or narrow time limitation of the study medication, were used for risk minimization [72].

With the exception of mitoxantrone, rituximab and azathioprine, most drugs known from MS therapy are either ineffective (e. g., glatiramer acetate) or even counterproductive (e. g., interferon-beta, fingolimod, natalizumab, alemtuzumab). Under no circumstances should they be used in the therapy of NMOSD. Instead, classical immunosuppressants and various monoclonal antibodies are prefered in treatment of NMOSD [73].

As a rule, according to how well a drug is clinically established, three categories of drugs can be defined: (1) "established" drugs with longer experience in off-label use, (2) medication successfully used in individual cases, (3) drugs currently being tested in studies.

Even though a wide range of drugs has already been used in the therapy of NMOSD, the greatest amount of experience is available in relation to azathioprine, mycophenolate mofetil and rituximab. Accordingly, these drugs are regarded as first choice drugs. In some cases, the recommendation is made to use azathioprine and mycophenolate mofetil for "mild" forms and rituximab for "highly active" forms of the disease. However, in view of the risk of mortality, such considerations should be left to a specialized center.

For azathioprine, several studies with approximately 100 patients each showed significant reduction in the relapse rate and disability accumulation [74, 75]. The high dropout rate of around 60 % after two years, usually due to side effects, as for example elevated liver enzymes, appears to limit its use. Due to the delayed onset of drug effect, overlapping therapy with oral prednisone appears to be useful after steroid pulse [76].

Mycophenolate mofetil (MMF) was effective in several smaller studies with up to 59 patients [77]. Randomized prospective studies, which allow a definite statement compared to azathioprine, are not available. However, the fact that therapy dropouts were rarer during the observation period than in the case of azathioprine speaks in its favor.

There are also positive data in support of the use of anti-CD20 antibody rituximab in NMOSD patients. Numerous studies showed a sig-

nificant reduction in the rate of relapses and accumulation of disability. Long-term data of up to 67 months are available for this drug [78, 79]. Overall, its efficacy is superior to azathioprine and MMF, which is why its use in "severe disease course" is recommended [80]. Because a priori the risk of rapid disability accumulation is already high after a single relapse event in NMOSD, we tend to use primarily rituximab, particularly in seropositive patients. We believe that this approach is supported by the lack of reliable prognostic markers.

In particular, with regard to rituximab, there are two treatment schemes both of which are equally effective: Scheme (1) was originally designed for the treatment of lymphoma. Despite the higher amount of drug used, it lacks superiority compared to scheme (2). As costs of this off-label use have to be negotiated with the health insurance, scheme (1) has largely been abandoned in Germany.

Maintenance therapies should be performed when there is a renewed increase of CD19+ B cells or CD27+ memory B cells in the peripheral blood, but at the latest after 6 months in each case. Various biomarkers, such as the FCGR3A polymorphism, associated with a poorer response to therapy, are not currently established in the clinical routine [79].

Tocilizumab is the second successfully used monoclonal antibody. Tocilizumab binds to the IL6 receptor, without activating it and thus blocks the proinflammatory effect of the cytokine IL6. In 2013, first positive data were published [81] and in 2015, the drug was found to be effective in a small study of 8 rituximab-refractory 8 patients [82]. Usually 8 mg/kg body weight is infused every 4 weeks (▶ **Table 5**).

Eculizumab, which intervenes in the complement cascade by binding to the protein C5, is an option as well; data, however, are sparse but positive. In 2013, an open-label study with 14 patients observed over a period of 48 weeks reported disease stabilization [83]. Under treatment with eculizumab, there was a significantly increased susceptibility to meningococcal meningitis. Accordingly, in addition to high clinical vigilance, the administration of a protective vaccination and/or an antibiotic prophylaxis according to summary of product characteristics (SMPC) is indicated.

▶ **Table 6** Overview of active phase III therapy studies on NMOSD, with study data registered up to 09/2016.

Study	Drug studied	Mechanism of action	Benchmark data	Identification number (Clinicaltrials.gov)
"PREVENT"	Eculizumab/Placebo	Inhibition of complement activation by binding to C5	Completion planned 12/2016 (132 Patients), only AQP4$^+$	NCT01892345
„N-MOmentum"	MEDI-551/Placebo	Depletion of CD19+ B cells	Completion planned 04/2020 (212 Patients), AQP4$^{+/-}$	NCT02200770
SA-237 (Monotherapy)	SA-237/Placebo	Blockade of IL6 receptor	Completion planned 03/2019 (90 Patients), AQP4$^{+/-}$	NCT02073279
"Sakura-SKY" (Add-on-Therapy)	SA-237/Placebo	Blockade of IL6 receptor	Completion planned 06/2020 (70 Patients), AQP4$^{+/-}$	NCT02028884

Current therapies of NMOSD and Perspectives

Although, as stated at the beginning of the previous section, clinical studies on the implementation of therapies in NMOSD remain difficult, several large-scale Phase III trials are recruiting patients.

As a consequence of the positive but highly preliminary results of an open-label study of eculizumab, the manufacturer initiated a phase III study, which is expected to deliver first data by the end of 2016. However, only AQP4-seropositive patients were included. Eculizumab was added to an existing immunosuppression – with the exception of rituximab.

In the N-MOMENTUM study, patients are randomized 3: 1 to MEDI-551, a B cell-depleting antibody directed against CD19. The therapy duration is limited to 197 days, followed by the option to participate in an extension study [72].

Two studies were started to evaluate the IL6 receptor antibody SA-237, which is a derivative of tocilizumab and has an approximately fourfold longer half-life. In the first phase III trial, 70 patients are scheduled to receive either SA-237 as monotherapy or placebo. The parallel-running Sakura-SKY study randomizes 90 patients to SA-237 or placebo under continuation of the existing immunosuppressive therapy. The results of the studies on MEDI-551 and SA-237 are not expected to be available until 2019 at the earliest.

Other therapeutics are in early stages of development, such as the monoclonal antibody aquaporumab, which binds to AQP4 and prevents the interaction of the protein with endogenous AQP4 antibodies and the resulting cell damage [84]. However, no clinical trials have yet been registered with this antibody. Ublituximab is another B-cell depleting antibody in Phase I trial (NCT02276963) (▶ **Table 6**).

Conclusion for Practice

By revising the diagnostic criteria, the term neuromyelitis optica (NMO) is being increasingly replaced by NMO-spectrum diseases (NMOSD). In the future, the new term will cover a broader range of clinical presentations with presumably comparable immunopathogenesis. The "MOG Antibody Spectrum", a new entity crystallized out of diseases, has its own biomarker and partly already included in the NMO spectrum. However, monotopic presentations such as isolated, relapsing transverse myelitis or chronic recurrent inflammatory optic neuritis are not (yet) included in this spectrum. For the first time, controlled therapies have been initiated for NMOSD patients, but results are still pending.

The initial diagnosis should include spinal and cranial MRI images as well as CSF and laboratory diagnostics. Special attention should be paid to cell-based antibody diagnosis. Following acute therapy where necessary, NMOSD patients should be referred to a specialized center for further diagnosis and implementation of long-term immune therapy concepts. Taking up contact to national or international study groups (e.g., german NMO study group (www.nemos-net.de)) is recommended.

Conflict of interest

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