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Pathogenic antibodies to AQP4: Neuromyelitis optica spectrum disorder (NMOSD)

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Abstract

NMOSD is a rare but severe relapsing remitting demyelinating disease that affects both adults and children. Most patients have pathogenic antibodies that target the central nervous system AQP4 protein. This review provides an update on our current understanding of the disease pathophysiology and describes the clinical, paraclinical features and therapeutic management of the disease.

Keywords

AQP4, NMOSD, neuroinflammation, neuronal antibodies, immunotherapy, MOGAD

Abbreviations

AQP4 = Aquaporin-4; NMOSD = neuromyelitis optica spectrum disorder; CNS central nervous system; LETM = longitudinally extensive transverse myelitis; CSF = cerebrospinal fluid; MOGAD = Myelin oligodendrocyte protein antibody associated disease

Introduction

Neuromyelitis spectrum disorder (NMOSD) is a rare neurological condition characterised by inflammation of the spinal cord (myelitis) and optic nerve (optic neuritis). Our understanding of this central nervous system (CNS) inflammatory disease was transformed by the discovery of autoantibodies to the aquaporin 4 protein (AQP4) in a subset of patients suffering with these symptoms[1, 2]. This review will aim to discuss our current understanding of the clinical features and treatment options in NMOSD, as well as the underlying proposed pathogenic mechanisms of AQP4 antibodies.

Disease pathogenesis

As well described in other articles within this issue, AQP4 is a water-channel protein widely expressed in the brain, spinal cord and optic nerve, particularly in the foot processes of astrocytes at the blood brain barrier. It is also expressed outside the CNS and found in the epithelial cells of the kidney, parietal cells of the stomach, airways and exocrine glands [3, 4]. The function of AQP4s in the CNS is to facilitate water movement across the blood brain barrier (and blood spinal cord barrier), modulate neuronal excitability, enhance astrocytic migration, as well as being involved in neuroinflammation [5].

As mentioned above, antibodies to the AQP4 protein (predominantly IgG subclass 1) are found in the majority of patients with NMOSD. These antibodies bind to extracellular epitopes of the supramolecular aggregates of AQP4 tetramers predominantly of the M23 and M1 isoform. The arrays are composed primarily of M23 (as demonstrated in the graphical abstract) as the M1 isoform alone cannot form supramolecular arrays. This then activates the complement system (initiated with binding of C1q) leading to lytic damage from the ensuing inflammatory response [6, 7]. Using AQP4-IgG has been a starting point for most of the animal models of NMOSD. Trying to capture the relapsing/remitting nature of NMOSD and characteristic features including co-occurrence of spinal, optic nerve and brain lesions is challenging. In studies of pathological specimens from patients with active NMOSD, different lesion types have been identified, including complement activation and immune cell infiltration, demyelination, and others display astrocyte loss without complement activation and granulocyte infiltration [3, 8]. In the early mouse models, it was discovered that cerebral injection of AQP4-IgG alone was not sufficient to produce

symptoms of NMOSD and addition of human complement was required to demonstrate histological inflammatory changes similar to that seen in the human CNS [9, 10]. The use of rats in cerebral and intrathecal passive transfer models has since shown further success with NMOSD-like lesions in brain, spinal cord and optic nerve [11, 12] as well as functional impairment; the classical complement pathway in rats can be activated by human AQP4-IgG. However, animal models have so far failed to recapitulate all the clinical and pathological features of the human disease. Table 1 compares some more of the experimental models recently published, and this subject is further reviewed in detail in [13].

Disease classification

NMOSD defines a group of CNS diseases characterised by inflammation and demyelination, distinct from multiple sclerosis, that can be associated with antibodies to the water channel protein AQP4. The core *clinical* characteristics of NMOSD as defined by an International Consensus Panel in 2015 [14] include;

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episodes of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic syndrome with NMOSD-typical diencephalic MRI lesions
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions

If AQP4 antibodies are detected then only one of these core clinical criteria are required for diagnosis. If the antibody testing is negative or unavailable, two core characteristics with dissemination in space and additional MRI brain and spine requirements are needed to meet the diagnostic criteria [14].

Epidemiology and demographics

NMOSD is rare, the average yearly incidence rate recently calculated in the Swedish population was 0.79 per 1,000,000 individuals [15]. The disease is more common in women and the average adult age of onset in a recent U.S. study was found to be 41.1 years [16].

Interestingly, epidemiological studies in adults have found that prevalence of NMOSD is higher in non-white than white populations [17, 18]. Paediatric NMOSD may account for 3-5 % of all NMOSD cases with most studies also showing a female preponderance, with average age of onset around 10 years [19, 20]. In both adults and children, there is often a family or personal history of other systemic autoimmune diseases [21].

Clinical and paraclinical features

The 2015 diagnostic criteria, listed above, summarise the classical clinical presentations of both adults and children with NMOSD. The characteristic presentation of acute myelitis in NMOSD is longitudinally extensive transverse myelitis (LETM), defined as an MRI spinal cord lesion spanning ≥ 3 contiguous vertebral segments [14]. Patients will present with rapidly progressive weakness initially in the lower limbs, urinary retention and a sensory level will be discernible on clinical examination. With optic neuritis, there will be acute painful visual loss, unilateral or bilateral. Optic neuritis +/- transverse myelitis is the most common presentation of NMOSD in children [19]. Area postrema syndrome (APS) is frequently misdiagnosed as a gastrointestinal disorder such as cyclical vomiting or even anorexia nervosa [22] . APS attacks can occur at disease onset or during the course of the disease but presentation at disease onset often leads to a diagnostic delay while gastrointestinal investigations are performed [22]. Features of acute brainstem syndromes include diplopia, facial nerve palsy, loss of hearing, trigeminal neuralgia and other cranial nerve signs and are all seen in adults and children at similar frequencies (~ 30%) [23, 24], usually in the early stages of disease. Narcolepsy has also been described in NMOSD as AQP4 is highly expressed in the hypothalamic periventricular lesions thus bilateral lesions will affect hypothalamic hypocretin neuronal function [25]. Finally, cerebral lesions can present with hemiparesis, visual field deficits, as well as encephalopathy and seizures [26].

Detection of serum autoantibodies to the AQP4 protein (AQP4-IgG) is best achieved through testing with cell-based assays that have the highest sensitivity and specificity [27]. CSF testing for AQP4-IgG is not essential. Unlike multiple sclerosis (MS), oligoclonal bands in CSF are also rarely found [28]. The presence of serum AQP4-IgG is associated with a relapsing disease course [29].

In some patients with symptoms of NMOSD, antibodies against myelin-oligodendrocyte-glycoprotein (MOG) are detectable. Although there is overlap in clinical presentation and imaging findings with NMOSD with and without AQP4-Ab, MOG-Ab-associated disease (MOGAD) can be differentiated as it has specific clinical and radiological features [30].MOGAD can present with optic neuritis, autoimmune encephalitis with or without demyelinating lesions, and/or myelitis [30, 31]. MOG-Abs are more commonly detected in children, typically in acute disseminated encephalomyelitis (ADEM) (which can be relapsing) in the younger age group, and optic neuritis and/or transverse myelitis in older children [32, 33]. Expert consensus guidelines for the classification, radiological features, treatment and outcomes of paediatric MOGAD have recently been published in view of the increased identification of these antibodies [34-37]. With progress in diagnostic tests, advanced neuroimaging and increased understanding of the underlying pathophysiology, the distinction between the neuroimmune conditions MOGAD, NMOSD and multiple sclerosis are becoming clearer and more well-defined in paediatric and adult patients [38].

Brain and spine abnormalities are frequently seen on MRI in seropositive AQP4-IgG patients in the corresponding anatomical areas of the clinical symptoms described. The main differential diagnosis is MS and MS-like lesions may appear in around 10% of NMOSD cases; an expert neuroradiology opinion is therefore essential [39]. Examples of the radiological findings in NMOSD are shown in Figure 1, the Case Vignette.

Treatment and outcomes

Approximately 85% of patients with NMOSD relapse. Recovery from attacks is often incomplete and neurologic deficits accumulate during the disease course[40]. NMOSD attacks are often severe and carry high risk of significant disability, therefore, patients need early diagnosis, aggressive treatment of acute attacks and preventative therapy to reduce the relapse risk.

In terms of the acute attack the treatment goals are to reduce inflammation and remove circulating levels of AQP4-IgG if present. Treatment with intravenous methylprednisolone (1g over 5 days in adults, followed by a course of tapering oral steroids) is often first-line, although patients may also need plasma exchange (usually 5 cycles) in the acute phase if very severe. Retrospective studies have confirmed improved clinical benefit of early

initiation of plasma exchange during severe attacks, with probability to regain complete improvement reducing from 50% when given at day 0 to 1-5% after day 20 [41, 42].

It is recommended that all patients with AQP4-Ab NMOSD start preventative therapy after their first acute attack as the time to first relapse is typically short (~4 months in children) [20]. There are no published randomised controlled trials regarding optimal preventative therapies, treatment decisions are therefore mainly based on observational studies, and clinician experience. Importantly, disease modifying drugs used for multiple sclerosis must be avoided as these have been shown not be effective at preventing relapses and may even aggravate NMOSD [43-45].

The most commonly used first line immunosuppressants are azathioprine and mycophenolate mofetil (MMF), both are taken orally. In children, treatment with rituximab, a B-cell depleting therapy, resulted in the lowest annualised relapse rate (ARR) [20]; and has shown similar impressive results in some adult studies [46, 47]. In adults, use of disease modifying therapies such as azathioprine, rituximab and MMF were also found to be associated with reduction in relapse risk and disability progression [48]. Newer monoclonal therapies with specific immunological targets have recently been developed and evaluated in clinical trials [49-51]. The FDA recently approved three of these monoclonal antibodies for the treatment of AQP4-NMOSD in the US, including eculizimab (inhibits C5 protein in terminal part of the complement cascade), inebilizumab (targets and depletes CD19 positive B-cells) and satralizumab (inhibits interleukin-6 mediated signalling). Eculizimab, satralizumab and inebilizumab have all also been approved for use in Europe and Japan. The most commonly used first- and second-line treatment drugs are summarised in Table 2.

The management of relapsing NMOSD is challenging, particularly in paediatrics when treatments have to be extrapolated from consensus statements made for adults where more evidence is available. These challenges are illustrated in the paediatric Case Vignette. Despite treatment, at a median follow-up of 4 years nearly 60% of paediatric patients were found to have a permanent disability in one study [20]; cognitive impairment was detected in 25%, with risk higher at younger age of disease onset. In adults, increasing age and disease duration were more likely to be associated with a higher rate of disability as measured by the expanded disability status score (EDSS)[48]. These disabilities and disease

sequelae include painful tonic spasms which can follow an acute transverse myelitis; symptomatic treatment with low-dose carbamazepine can be beneficial here [52]. Other symptoms that will require multi-disciplinary assessment and management include neuropathic pain, fatigue, and depression.

Summary

NMOSD is a rare but severe relapsing remitting demyelinating disease that affects both adults and children. Most patients have pathogenic antibodies that target the CNS AQP4 protein, these antibodies are now readily detectable in highly sensitive specific and sensitive cell-base assays. From retrospective studies, the evidence is clear that early diagnosis and prompt initiation of preventative immunotherapy is the key to improving prognosis and slowing the accruement of permanent disability. Recruitment of sufficient patient numbers for clinical trials is difficult due to low numbers, but nevertheless newer therapies are being developed and becoming more readily available particularly with our improved understanding of the underlying disease patho-mechanisms.

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Competing interests

A.V. and the University of Oxford hold patents and receive royalties for antibody tests.

Table 1 Rodent models of NMOSD

Type of model	Experimental methods	Main pathological effects	Inferences and limitations
AQP4-IgG passive transfer to the brain[9-11]	Direct intracerebral injection – single or continuous infusion +/- complement	Loss of astrocytes and GFAP immunoreactivity. Right turning behaviour in mice injected with AQP4-IgG and complement into right hemisphere. Changes not seen in AQP4 knockouts.	Established crucial role of complement mediated tissue destruction and pathogenicity of AQP4-IgG. Limited behavioural phenotype of relapsing/remitting nature of disease.
AQP4-IgG passive transfer to the spinal cord [53, 54]	Direct injection or infusion of AQP4-IgG into cerebrospinal space	When CD59 deficient mice used, LETM lesions seen with loss of AQP4 and GFAP, inflammation, deposition of complement and demyelination. Additionally, hindlimb motor function was impaired. In a repetitively intrathecal injected model, the rats developed progressive motor deficit and showed recovery after discontinuation of injections. MRI resembled human spinal lesions in NMOSD.	NMOSD spinal lesions can be recapitulated *in vivo* with passive transfer models. Implicated CD59 as an important modulator of immune response in NMOSD.

Optic neuritis[55]	Continuous intracranial infusion of AQP4-IgG near optic chiasm	Developed characteristic NMOSD pathology in optic nerves. More severe effects in CD59 deficient mice as previously.	Similar pathogenesis to the spinal cord and brain lesions.
Passive transfer of AQP4-IgG by intraperitoneal delivery [56, 57]	Intravenous injection of AQP4-IgG • Addition of focussed ultrasound to disrupt the blood-brain barrier • Use of monoclonal antibodies	Initial attempts to deliver AQP4-IgG peripherally led to deposition in peripheral organs but not the brain. Focussed ultrasound causing temporary disruption of BBB produced localised NMOSD-type brain pathological changes in rats with positive AQP4-IgG serum. IP injections with a monoclonal antibody derived from an affected patient produced robust NMOSD type lesions without the need for BBB disruption	Early results promising with both focussed USS and monoclonal antibodies. These require validation and replication; monoclonal antibodies are usually of high concentration so direct comparison to the human disease is made with caution.

Table 2 Drugs used for preventative therapy in NMOSD (* most commonly used in the UK [58])

Drug/dose/route	Proposed mechanism of action	Adverse effects	Additional info
*Azathioprine 2.5-3.0mg/kg/day PO	Purine analogue that converts to active metabolites by the action of enzyme TPMT. Inhibits purine synthesis and disrupts DNA and RNA synthesis.	GI symptoms, rash, hypersensitivity, bone marrow suppression, liver toxicity, increased risk of infection	Need to test TMPT levels pre-treatment Regular blood monitoring required Oral steroid cover (~30mg/day) may be required at start of treatment for AZA to take full effect
*Mycophenolate mofetil 2-3g/day PO	Inhibitor of enzyme IMPDH, inhibits proliferation of T and B lymphocytes	GI symptoms, bone marrow suppression, contraindicated in pregnancy due to teratogenic effects	Regular blood monitoring required Oral steroid cover (~30mg/day) may be required at start of treatment for MMF to take full effect
*Rituximab 1g, then further 1g after 2 weeks IV	Depletes CD20-expressing B cells	Infusion related hypersensitivity, haemolytic anaemia, infections, Hepatitis B reactivation	Further doses given every 6 months or based on re-emergence of CD19+ B cells
Tocilizumab 8mg/kg every 4 weeks IV (off-label use for	Anti Interleukin-6 (IL-6) receptor, suppresses IL-6	Severe liver injury, infection, reactivation of latent TB	Must monitor neutrophils and platelet counts

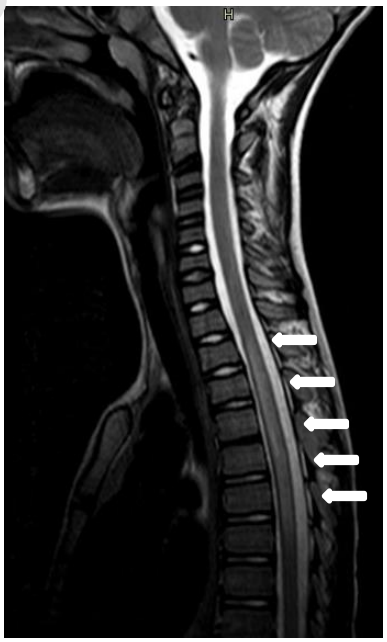
NMOSD in the UK)			
Eculizimab 900mg weekly for 4 weeks initial treatment, then increased to 1.2g weekly for 2 weekly maintenance dose IV	Inhibits terminal complement activation at the C5 protein	Upper respiratory tract infections, headache, increased risk of meningococcal and encapsulated bacterial infection	Manufacturer advises vaccinate against *Neisseria meningitidis* at least 2 weeks before treatment.

GI Gastointestinal IV intravenous PO oral route of administration

TPMT thiopurine methyltransferase

Figure 1. Case vignette

This 9 year old white Caucasian male presented with blurred vision in the left eye and headache with distortion to his affected visual field seeing glittery black and white spots. Following urgent assessment this was diagnosed as left optic neuritis, treated with intravenous methylprednisolone with good recovery of vision. MRI Brain was consistent with optic neuritis and serum AQP4 antibodies were strongly positive; spine MRI was normal at this time, and CSF oligoclonal bands were negative. In view of the NMOSD diagnosis, the patient was commenced on MMF treatment. At 4 months, the patient experienced a recurrence of left optic neuritis and despite acute treatment with steroids, was left with markedly reduced vision in the left eye, and optic atrophy. Eight months later, he presented with numbness in both legs but minimal weakness, spinal MRI confirmed longitudinally extensive transverse myelitis which was responsive to steroids. This abnormality is shown in the sagittal spinal MRI scan pictured here (white arrows show lesion extending over more than 3 vertebral segments). In view of the continuing relapses, the patient was changed to rituximab treatment and has remained stable with only one further mild episode optic neuritis which responded positively to steroid treatment.

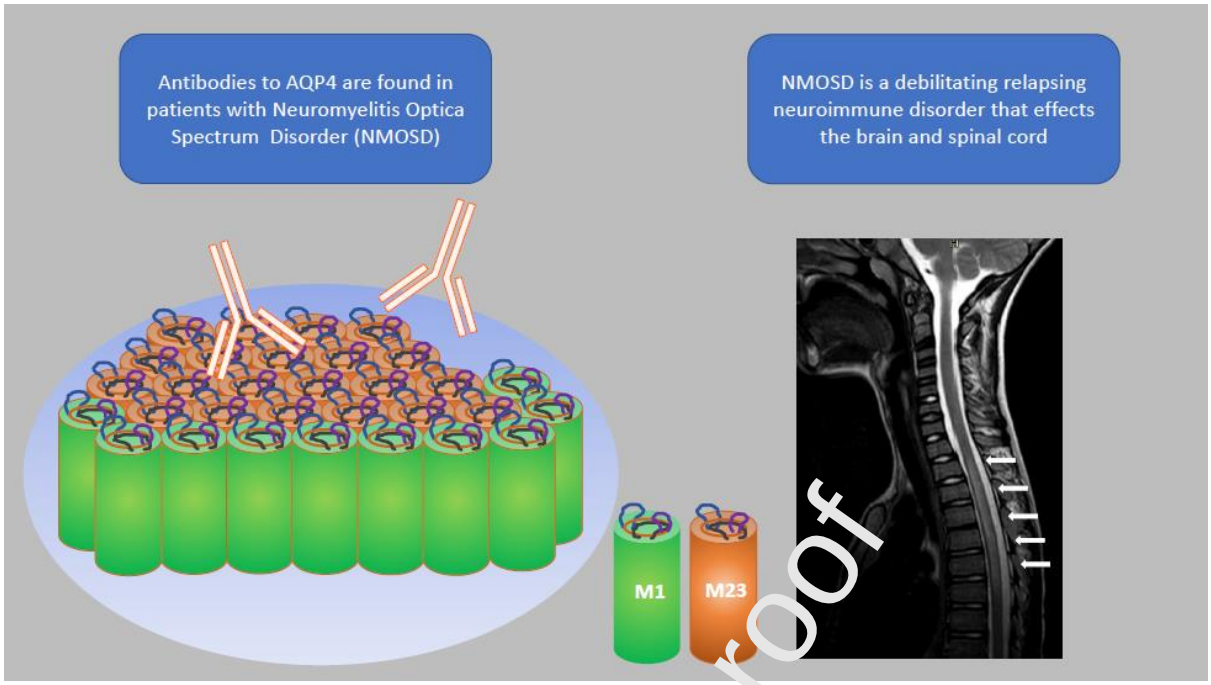


Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Angela VIncent has patent with royalties paid to Angela Vincent for Euroimmun.



Graphical abstract

Highlights

- Antibodies to Aquaporin-4 are found in Neuromyelitis spectrum disorder (NMOSD)
- Patients suffer from recurrent attacks of neuroinflammation affecting the spinal cord and optic nerves
- There is no cure for NMOSD at present; treatment is aimed at treating acute attacks and preventing future relapses