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REVIEW

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Magnetic resonance imaging in neuromyelitis optica spectrum disorder

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Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disease of the central nervous system (CNS) associated with antibodies to aquaporin-4 (AQP4), which has distinct clinical, radiological and pathological features, but also has some overlap with multiple sclerosis and myelin oligodendrocyte glycoprotein (MOG) antibody associated disease. Early recognition of NMOSD is important because of differing responses to both acute and preventive therapy. Magnetic resonance (MR) imaging has proved essential in this process. Key MR imaging clues to the diagnosis of NMOSD are longitudinally extensive lesions of the optic nerve (more than half the length) and spinal cord (three or more vertebral segments), bilateral optic nerve lesions and lesions of the optic chiasm, area postrema, floor of the IV ventricle, periaqueductal grey matter, hypothalamus and walls of the III ventricle. Other NMOSD-specific lesions are denoted by their unique morphology: heterogeneous lesions of the corpus callosum, 'cloud-like' gadolinium (Gd)-enhancing white matter lesions and 'bright spotty' lesions of the spinal cord. Other lesions described in NMOSD, including linear periventricular peri-ependymal lesions and patch subcortical white matter lesions, may be less specific. The use of advanced MR imaging techniques is yielding further useful information regarding focal degeneration of the thalamus and optic radiation in NMOSD and suggests that paramagnetic rim patterns and changes in normal appearing white matter are specific to MS. MR imaging is crucial in the early recognition of NMOSD and in directing testing for AQP4 antibodies and guiding immediate acute treatment decisions. Increasingly, MR imaging is playing a role in diagnosing seronegative cases of NMOSD.

KEYWORDS

diagnosis, magnetic resonance imaging, multiple sclerosis, neuromyelitis optica

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INTRODUCTION

Historical perspective

A distinct clinical pattern of demyelination affecting optic nerves and spinal cord associated with a characteristically destructive pathological picture was first described more than 150 years ago [1–3]. What became known as Devic's disease or neuromyelitis optica (NMO) remained ambiguous, regarded by some as an extreme variant of multiple sclerosis (MS) and by others as a separate disease state, until 2004 when Lennon and colleagues highlighted an association between cases of longitudinally extensive transverse myelitis with optic neuritis and antibodies with a specific staining pattern on suitably prepared samples of mouse brain and kidney [4]. These 'NMO immunoglobulin (Ig)G' antibodies were subsequently demonstrated to bind to the aquaporin-4 (AQP4) water channel and have become *sine qua non* for NMO spectrum disorder (NMOSD) [5]. Interestingly, some of the cases described by Devic, particularly those with simultaneous or sequential transverse myelitis in younger adults, may have had antibodies to myelin oligodendrocyte glycoprotein (MOG) and what is now referred to as MOG antibody-associated disease (MOGAD) [6]. The spectrum of disease associated with AQP4 antibodies has spread to encompass area postrema, hypothalamic and diencephalic syndromes, as well as encephalitic presentations [7]. In contrast, MOGAD includes acute disseminated encephalomyelitis (ADEM) presentations (particularly in paediatric populations), focal encephalitic presentations and frequent optic neuritis in a clinical picture that previously would have been difficult to distinguish from MS, as well as longitudinally extensive transverse myelitis [8]. It will be apparent that these two antibody-mediated central nervous system (CNS) inflammatory diseases share clinical overlap with MS and other disorders that can affect the optic nerves and spinal cord, such as neurosarcoidosis [9] and chronic relapsing idiopathic optic neuritis (CRION) [10]. Isolating antibodies has become essential in diagnosing antibody-mediated CNS inflammatory diseases. However, false-positive and -negative results remain a problem. For example, if used as a screening test in all cases of CNS inflammatory disease, where in populations of European ancestry MS outnumbers antibody-mediated disease by at least 50:1 [11], false-positive tests may lead to inappropriate management and skew epidemiological data. Consequently, clinical features and other ancillary tests, magnetic resonance imaging (MRI) in particular, remain extremely important in raising suspicion for these diagnoses. For the purposes of this narrative review, we will concern ourselves only with MRI features of AQP4 antibody-positive NMOSD and will refer to this as NMOSD throughout.

Clinical features

The clinical hallmarks of NMOSD are attacks of optic neuritis (severe, painless, bilateral or sequential with poor recovery), transverse myelitis (severe, bilateral and involving motor, sensory and sphincteric control pathways, sometimes with pain and pruritus), area postrema syndrome (persistent nausea, vomiting and hiccoughs), acute brain stem syndromes (cranial nerve palsies, ataxia and limb weakness), diencephalic syndromes (narcolepsy, hypothermia, daytime somnolence and obesity) and cerebral syndromes (encephalopathy and seizures) [12]. Attacks of optic neuritis tend to occur earlier in the disease course [13]. Acute myelitis (partial or complete) and optic neuritis predominate with other types of attack being less common [13]. The attacks occur more frequently and brain stem/cerebellar presentations are relatively less common compared to MS [14]. Without treatment to prevent further attacks the prognosis in NMOSD is generally worse than it is in MS [14,15].

Serological markers

The discovery of antibodies to AQP4 in NMOSD has been integral to developing a greater understanding of the pathophysiology of NMOSD and have helped to identify distinct patterns in MR [16] and ocular computed tomographic [17] imaging that are specific to NMOSD. AQP4 antibodies in NMOSD are predominantly IgG and bind to the AQP4 protein, a water channel found abundantly in foot processes of astrocytes forming part of the blood–brain barrier in the CNS [18]. The AQP4 protein forms a tetramer of two isoforms (M1 and M23, with M1 being 22 amino acids longer) [19]. AQP4 tetramers are arranged in orthogonal arrays of multiple channels and the extent to which this occurs depends upon the proportion of the M23 isoform, which is the predominant form in the CNS [20–22]. AQP4 antibodies in NMOSD have greater avidity for orthogonal arrays of the M23 isoform than they do of the M1 or isolated tetramers, presumably due to conformational differences [23]. This led to difficulties with earlier assays being less sensitive because they used the M1 isoform, but these issues have now been resolved. The gold standard for AQP4 detection is a live-cell based assay [24], but dried cell-based assays are now almost as sensitive and specific [25]. Immunofluorescence methods (Figure 1a) using rat or mouse brain and kidney are less sensitive, but have good specificity in most centres [24,25]. Enzyme-linked immunosorbent assays (ELISA) are the least sensitive and specific, but permit ready estimation of an antibody titre when positive [24,25]. Neurofilament light and glial fibrillary acidic protein (GFAP) are emerging as

potentially useful serological biomarkers of disease activity in NMOSD [26].

Diagnostic criteria

The 2015 IPND diagnostic criteria for NMOSD[12] are widely accepted and have good clinical utility. In patients presenting with one of the above-listed clinical syndromes, positive AQP4 antibodies in serum is confirmatory of the diagnosis provided no better explanation exists. In situations where AQP4 antibodies are not found or testing is not available the diagnosis of NMOSD requires at least one attack of optic neuritis, transverse myelitis or area postrema syndrome and a second clinical attack of one other syndrome, including acute brain stem, diencephalic and cerebral syndromes. In addition, to fulfil seronegative criteria episodes of optic neuritis, acute myelitis, area postrema

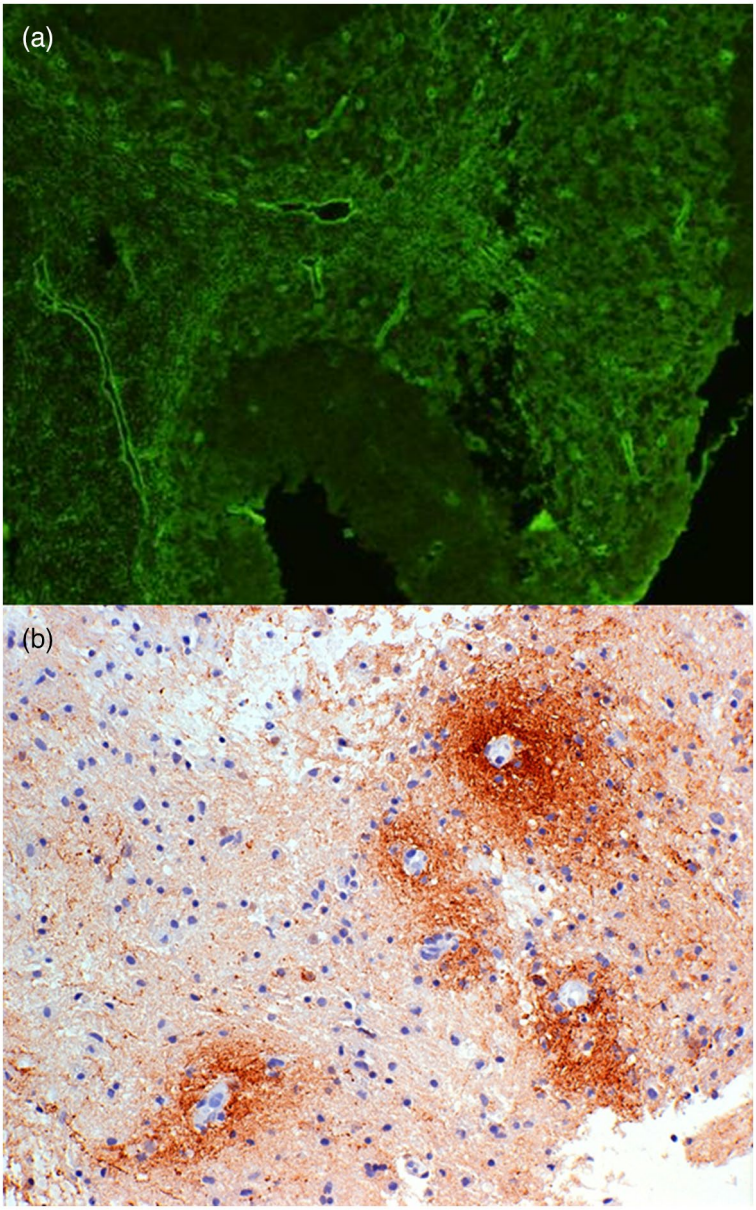

FIGURE 1 Perivascular distribution of aquaporin-4 (AQP4) antibodies and complement in neuromyelitis optica spectrum disorder (NMOSD). AQP4 antibody positive immunofluorescence (green) in mouse cerebellum [serum dilution 1:40, goat anti-human immunoglobulin (Ig)G F(ab)2 fluorescein isothiocyanate, ×200 magnification], showing microvessel staining of the granular layer, molecular layer and white matter (a). Section of early white matter lesion in NMOSD immunostained (brown) for Cd3 showing typical perivascular complement deposition around small blood vessels (b)

TABLE 1 2015 IPND MR imaging criteria for diagnosing seronegative NMOSD

Clinical attack	Additional MR imaging criteria for a seronegative diagnosis of NMOSD
Optic neuritis	(1) Normal MR imaging of the brain or non-specific white matter changes only or (2) T2 ot T1 Gd enhancement of the optic chiasm or extending over half the length of the optic nerve on MR imaging of the orbits
Acute myelitis	Longitudinally extensive spinal cord lesion (or atrophy) ≥ 3 vertebral segments on MR imaging of spine
Area postrema syndrome	Area postrema lesion on MR imaging of brain
Acute brain stem syndrome	Peri-ependymal brain stem lesion on MR imaging of brain

IPND = International Panel for NMO diagnosis; MR = magnetic resonance; NMOSD = neuromyelitis optica spectrum disorder; Gd = gadolinium (Gd).

syndrome and acute brain stem syndrome must be associated with typical changes on MRI, as listed in Table 1.

Epidemiology

In populations with predominantly European ancestry the prevalence of NMOSD is approximately one in 100 000, and the incidence is approximately 0.6/million [11]. Comparative studies to assess prevalence have suggested higher rates of NMOSD in East Asian [27] and black populations [28,29]. Age of onset can range from 10 to 80 years, with a peak of approximately 30–39 years [30].

Concomitant autoimmune disease

Co-occurrence of autoimmune disease, most notably systemic lupus erythematosus (SLE) and Sjögren's disease, has been noted in NMOSD [31]. This complicates interpretation of MR imaging in NMOSD. In SLE, neurological features and MRI abnormalities may be a consequence of concomitant NMOSD (optic neuritis, transverse myelitis), anti-phospholipid syndrome (stroke-like syndromes, hemichorea, neuropsychiatric presentations) [32] and vasculitis [33]. Similarly, cases of longitudinally extensive spinal cord lesions in Sjögren's disease may reflect co-existent NMSOD [34]. Concomitant type I diabetes mellitus [35] and autoimmune thyroid disease [36] will increase the likelihood of CNS vascular disease, further compounding findings on MRI.

Pathophysiology

Current evidence indicates that AQP4 antibodies are pathogenic and lead to a severe astrocytopathy through complement-mediated cell lysis (Figure 1b) [37]. Demyelination and neuronal loss are a secondary consequence of the acute inflammatory response associated with complement activation [38,39]. This involves neutrophils, natural killer cells, macrophages, tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β and interferon (IFN)-γ [40]. This process is summarized in Figure 2. Much has been made of the distribution of the pathology in NMOSD being located at peri-ependymal regions, particularly in relation to the lateral, third and fourth ventricles, cerebral aqueduct and central canal of the spinal cord [41,42]. This may be because these regions correspond to locations of greatest AQP4 density on astrocytes; they are rich in draining venules or have increased susceptibility of the blood–brain barrier [43]. Pathologically, NMOSD leads to destructive lesions with prominent loss of astrocytes, in addition to loss of myelin and neurones [38]. Areas of necrosis, with cavitation, hyalinization of small vessels and perivascular inflammatory infiltrates, are commonly seen. Collectively, these features help to distinguish NMOSD from MS. In the majority of NMOSD cases the condition arises as a primary autoimmune disease, but a small proportion of paraneoplastic cases has been noted [44].

Treatment of NMOSD

The early and accurate recognition of NMOSD is important because optimal acute and preventive treatment is different to MS. Plasma exchange is particularly helpful, as acute treatment in addition to early intravenous high-dose corticosteroids for NMOSD [45–47]. Treatment with IFN-β [48], fingolimod [49] and natalizumab [50] appear to make NMOSD worse. Standard immunosuppression (azathioprine, methotrexate and mycophenolate mofetil) and B cell depletion with rituximab have been recommended to prevent future attacks of NMOSD [51]. Phases II/III clinical trials of inebilizumab (anti-CD19 B-cell depletory) [52], satralizumab (anti-IL-6) [53] and eculizumab (anti-complement 5) [54] monoclonal antibodies have all shown positive results in NMOSD.

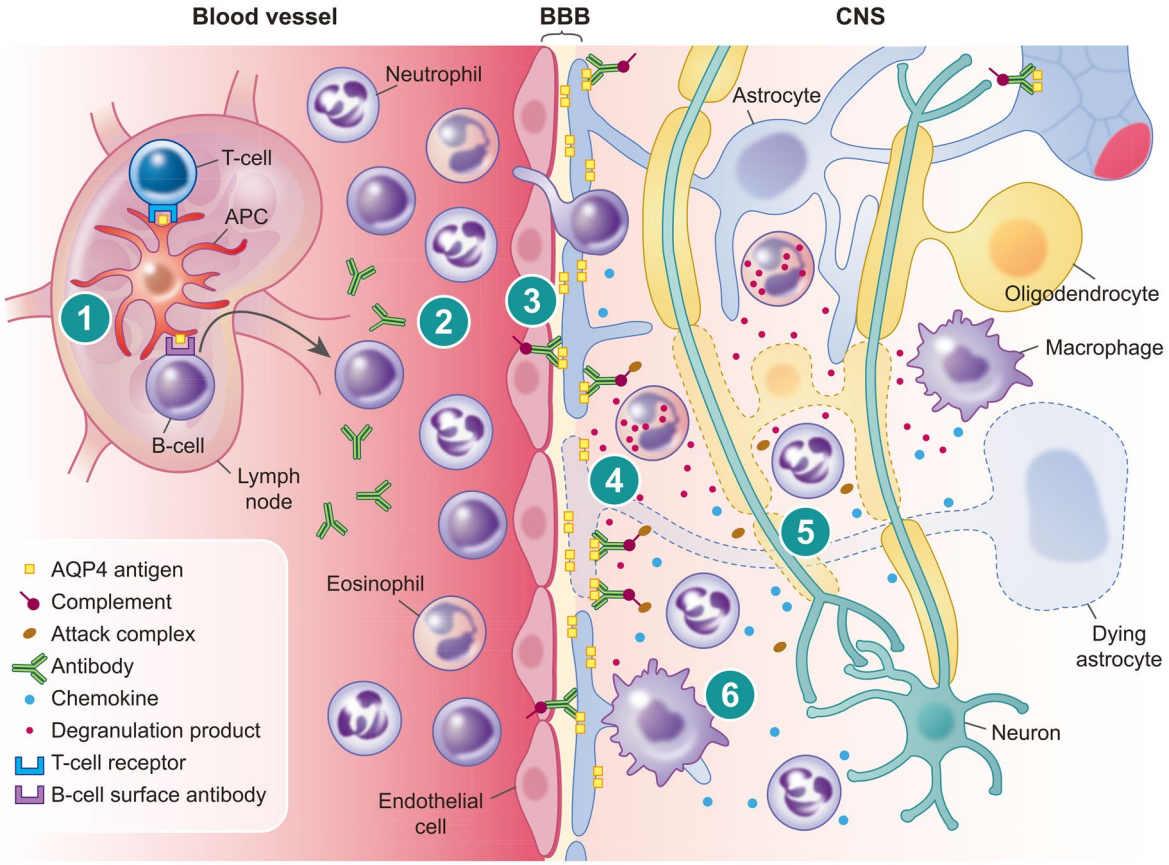

FIGURE 2 Schematic representation of the pathogenesis of neuromyelitis optica spectrum disorder (NMOSD). (1) Presentation of aquaporin-4 (AQP4) antigen via an antigen-presenting cell (APC) in a peripheral lymph node with promotion from T helper cell leads to activation of autoreactive B cells. (2) Maturation of antibody producing plasma cells results in free circulating autoreactive antibodies to AQP4. (3) Break-down of the blood–brain barrier (BBB) leads to escape of autoreactive antibodies and extravasation of immune cells in response to chemokines. (4) Opsonization of autoreactive antibodies on AQP4 rafts situated on the astrocyte foot process leads to activation of complement and cell-mediated lysis of astrocytes. (5) Indiscriminatory inflammation mediated via chemokines, activated complement and degranulation products, as well as loss of trophic support from astrocytes, leads to lysis of oligodendrocytes and neurons. (6) Macrophages attracted by chemokines released by leukocytes and astrocytes produce further proinflammatory products and phagocytose cellular debris and myelin

CONVENTIONAL MR IMAGING LESIONS

Optic nerve

Simultaneous or sequential involvement of both optic nerves on MR imaging of the orbits is highly suggestive of NMOSD (Figure 3a), with lesions sometimes being asymptomatic [55]. A recent study found bilateral optic nerve involvement in almost 50% of cases with optic nerve lesions [56]. A lesion of the optic nerve on MR imaging of the orbits that extends over at least half of the length of the optic nerve (Figure 3b) is suggestive of NMSOD [55,57,58]. Lesions involving the optic chiasm on MR imaging of the orbits (Figure 3c,d) seems to be quite specific for NMOSD and may be seen in a quarter of cases [42,55,56,59,60]. Any lesion of the optic nerves may be more common in NMOSD than in MS [55]. Optic perineuritis may be of particular value in distinguishing NMOSD and MS from other autoimmune causes of optic neuritis [61], including MOGAD [62].

Spinal cord

Longitudinally extensive spinal cord lesions spanning three or more vertebral segments (Figure 3e) are seen in two-thirds to three-quarters of patients with NMOSD at some point in their disease course [63–77]. The most common sites are in the cervical region and upper to mid-thoracic region [78]. Long lesions in the cervical region that extend up into the medulla are helpful in distinguishing NMSOD from MS [66,79–81], but are of less value in distinguishing NMOSD from other causes of longitudinally extensive

spinal cord lesions [82]. Longitudinally extensive spinal cord lesions are also seen in MOGAD [83] and monophasic (or relapsing) transverse myelitis without associated antibodies [84]. Lesions extending the whole length of the spinal cord to the conus can be seen in MOGAD, and this is uncommon in NMOSD [85,86]. In antibody-negative longitudinally extensive transverse myelitis the occurrence of another form of NMOSD-associated clinical attack would suggest seronegative NMOSD. There are reports of longitudinally extensive spinal cord lesions in MS [78,87], where the clinical picture and MR imaging is highly consistent with that disease and AQP4 antibodies are negative. However, such cases appear to be extremely rare [88]. As has been indicated previously, the possibility of NMOSD or MOGAD co-existing with MS as another autoimmune disease needs to be considered, as does the possibility of

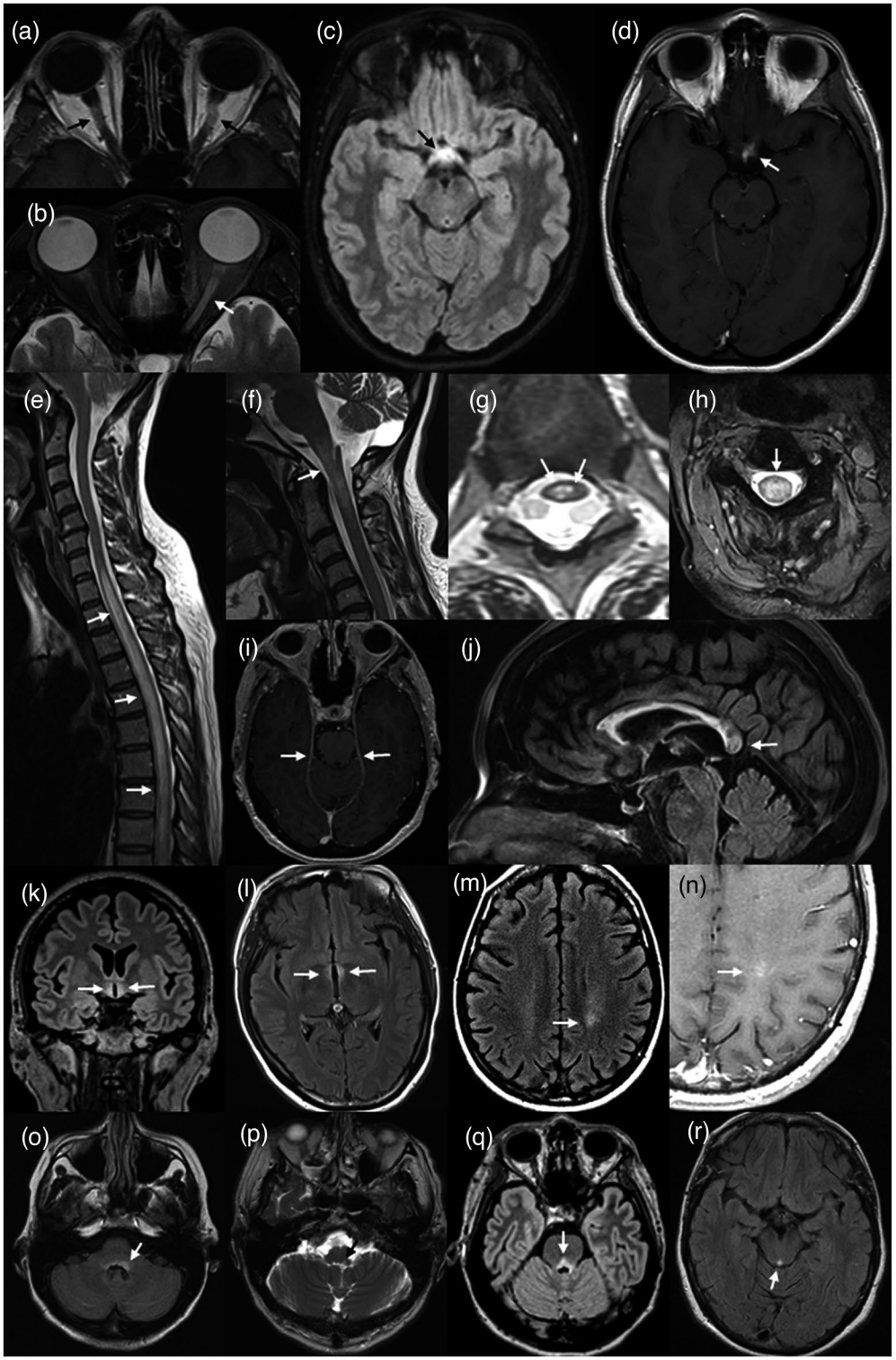

FIGURE 3 Magnetic resonance (MR) imaging of lesions (arrows) associated with aquaporin-4 (AQP4)-positive neuromyelitis optica spectrum disorder (NMOSD). Bilateral Gd-enhancing retro-orbital lesions of the optic nerves on axial T1 weighted image of the orbits (a). Longitudinally extensive (more than half the length of the optic nerve) high signal lesion of the left optic nerve on axial T2 image of the orbits (b). High signal lesion of the optic chiasm on volumetric, axial FLAIR image of the brain (c). Asymmetric gadolinium (Gd)-enhancement of the same lesion (d). Longitudinally extensive high signal lesion of the thoracic spinal cord, associated with cord swelling, on sagittal T2 imaging of the spine (e). High cervical cord high signal lesion extending into the medulla on sagittal T2 image of the cervical cord (f). 'Bright spotty lesions' of the thoracic spinal cord on axial T2 imaging of the spine (g). Central, whole cord high signal lesion on axial T2 image of the cervical cord (h). Leptomeningeal Gd-enhancement on axial T1 weighted imaging of the brain at the level of the upper pons (i). Heterogeneous rounded lesion of the corpus callosum on sagittal fluid-attenuated inversion recovery (FLAIR) imaging of the brain (j). Hypothalamic high signal lesion on volumetric coronal FLAIR imaging of the brain (k). High signal change in the wall and adjacent parenchyma of the III ventricle on axial FLAIR imaging of the brain (l). High signal lesion of the left posterior frontal white matter on axial FLAIR imaging (m) showing 'cloud-like' enhancement on axial T1 imaging of the same region (n). Bilateral area postrema lesions (more prominent on the left) on axial FLAIR image at the level of the medulla (o). Left nucleus solitarius lesion on axial T2 image at the level of the medulla (p). High signal FLAIR lesion of the pons, involving the floor of the IV ventricle (q). High signal lesion of the peri-aqueductal grey matter on axial FLAIR image through the mid-brain (r)

epitope spreading in MS leading to the generation of autoreactive AQP4 antibodies over time in some cases. Superior extension of high cervical cord lesions, referred to as central medullary lesions, can be seen in NMOSD (Figure 3f) [42,73,79,89–92]. Short segment spinal cord lesions are also seen in approximately 15% of NMOSD cases [76].

Small areas of high signal predominantly seen on axial T2 imaging of the spinal cord in NMOSD have been described as 'bright spotty' lesions (Figure 3g) [93–97]. This picture seems to correlate with acute active inflammation, the resulting heterogeneous lesion giving rise to alternate areas of high and relatively low signals on T2 images. These bright areas do not usually show gadolinium (Gd)-enhancement. In contrast to MS, where spinal cord lesions are usually partial and relatively peripherally situated, in NMOSD the most common axial distribution of lesions is a central location with radiation to the outer ependymal surface [95,98]. All four quadrants are affected equally and may be associated with significant cord swelling (Figure 3h) [65]. We have noted that any form of Gd-enhancement on T1 imaging of the spinal cord is more commonly seen in NMOSD than in MS. Others have noted that axial 'ring' enhancement is quite specific for NMOSD [65,99,100]. Heterogeneity of Gd-enhancement in the spinal cord may be specific to NMOSD, reflecting the variable degree of destruction across lesions. Past episodes of longitudinally extensive transverse myelitis due NMOSD can sometimes be surmised due to regions of significant spinal cord atrophy spanning at least three vertebral segments [80,101]. This appears to be extremely uncommon in MS and MOGAD.

Normal brain MRI

One of the most common findings of MR brain findings in NMOSD is no abnormality or minimal non-specific changes. This finding is seen in approximately 20–40% of cases at presentation [102–104].

Cerebrum

Diffuse leptomeningeal enhancement on T1 MR brain imaging (Figure 3i) has been noted in NMOSD [105,106]. This is a feature seldom seen in MS, but can be seen in neurosarcoidosis and other forms of aseptic meningitis [107]. Rounded lesions with a 'ground glass'-like heterogeneous appearance within the body of the corpus callosum appear to be quite specific to NMOSD (Figure 3j) [108,109]. Corpus callosum lesions of various types are common in both NMOSD and MS. They can also be seen in vascular disease [110] and other CNS disorders [111]. Heterogeneous lesions are the only ones that appear to be specific for NMOSD, while triangulated lesions arising from the inferior margin of the corpus callosum are typically seen in MS [112].

A relative increase in signal of the ependymal lining of the hypothalamus is common on fluid-attenuated inversion recovery (FLAIR) sequences of the brain in normal healthy brains. In NMOSD a high T2 signal, particularly on FLAIR images, can be seen to extend into the adjacent parenchyma (Figure 3k), and it is this that represents a lesion of the hypothalamus [42,69,80,113,114]. High signal lesions on T2 and FLAIR sequences in the ependymal lining and adjacent parenchyma of the walls of the III ventricle can be seen as an extension of a hypothalamic lesion or as a lesion on its own in NMOSD (Figure 3l) [42,79,92]. In contrast to the situation encountered in spinal cord imaging of CNS inflammatory disorders, we have found that Gd-enhancing lesions of the brain are rare in NMOSD and less common than in MS. However, one pattern of hemispheric Gd-enhancement has been found to be specific for NMOSD. Diffuse and heterogeneous T2/FLAIR lesions of the white matter with patchy, faint Gd-enhancement and a wispy quality are seen in NMOSD. This pattern of enhancement has been termed as 'cloud-like' (Figure 3m,n) [90,115]. It has been noted that cerebral T2 lesions in NMOSD almost universally decrease in size over time, but

that the majority persist as a residual high T2 signal [116]. This contrasts with MS, where many lesions persist, and MOGAD, where lesions are more likely to resolve.

Other brain lesions, including linear periventricular peri-ependymal [91,92,109,117–120], bridging lesions of the splenium [121,122], small subcortical lesions (punctate and patch lesions) [89,92,118,119] have been seen in NMOSD, but we have noted that these lesion types are seen just as commonly in MS. The latter are very non-specific and have been described in migraine [123]. Tumefactive [79,121,124] and ADEM-like lesions [125] have also been noted in NMOSD, but these lesions are also recognized to occur in MS and MOGAD [90–92,116,126,127]. It is interesting to consider the extent to which these lesions represent a common pathogenesis, whereby breakdown of the blood–brain barrier occurs in particular regions in response to some environmental factor that is ubiquitous, leading to the differing forms of immunological attack seen in MS, NMOSD and MOGAD in similar anatomical distributions. There have been several case reports of posterior reversible encephalopathy syndrome (PRES)-like lesions in NMOSD [128–130] and it has been speculated that this could reflect dysregulation of osmotic homeostasis due to blocking of AQP4, but a similar picture was also recently reported in MOGAD [131], suggesting that a different mechanism may be responsible for this picture.

Brain stem and cerebellum

The third most common clinical presentation in NMOSD is the area postrema syndrome (persistent nausea, vomiting and hiccoughs) [13]. A high signal lesion in the posterior segment of the medulla on T2/FLAIR MR imaging (Figure 3o) is a distinctive and seemingly specific lesion for NMOSD [79,80,132,133]. This area of the medulla is an intrinsic component of the autonomic nervous system that controls vomiting and hiccoughs through the vagus nerve [134]. Lesions of the adjacent nucleus tractus solitarius which extend into the pons have also been noted in NMOSD (Figure 3p) [135], as have lesions of the floor of the fourth ventricle in the pons (Figure 3q) [42,90,92,105,109,118,127].

Peripherally situated, crescent-shaped, subependymal lesions of the brain stem have been noted in NMOSD [79,119]. A particularly striking lesion of NMOSD is a T2/FLAIR high signal involving the peri-aqueductal grey matter (Figure 3r). Sometimes these lesions of the posterior mid-brain can be large [42,79,136]. Lesions of the anterior mid-brain, both linear peri-ependymal [42] and extensions of longitudinal corticospinal tract lesions through the cerebral peduncles, have been described [91,92,109,137]. Lesions of the cerebellum are less common in NMOSD than in MS, but lesions of the dentate nuclei and cerebellar peduncles adjacent to the fourth ventricle can be seen [138].

Imaging of the peripheral nervous system

A recent case report had shown the presence of high signal lesions within lumbar nerve roots in a patient with NMOSD [139].

ADVANCED MRI TECHNIQUES IN NMOSD

High-field MRI

Several studies have looked at the use of 7T MR imaging in NMOSD. These studies have shown that the rim-like and nodular pattern of paramagnetic phase changes, suggestive of iron deposition which are seen in some MS brain lesions, are not seen in NMOSD [140–142]. No difference in T1 relaxation time between NMOSD and healthy controls has been observed [143]. High-field MR imaging in NMOSD has suggested a lower rate of lesion accrual (approximately 1% per year) than is seen in MS [141].

Multi-modal MRI

Multi-modal MRI has shown fewer changes in the normal appearing white matter of NMOSD patients than is seen in MS [144–146]. One consistent pattern has been the finding of reduced fractional anisotropy on diffusion tensor imaging of the optic radiation [144,147] and reduced functional connectivity strength in the occipital cortex [145]. An association with retinal nerve fibre layer thinning on optical coherence tomography [145] suggests that this reflects degeneration secondary to optic nerve lesions. A recent study using probability maps has indicated that lesion distribution is of little value in distinguishing NMOSD from MS [145]. However, a combination of diffusion parameters and functional connectivity strength on 3T MR imaging may have high sensitivity and specificity to distinguish NMOSD from MS. Similar differences in normal-appearing white matter between NMOSD and MOGAD are also emerging as a useful way to distinguish these two conditions [148].

Other advanced MRI techniques

Studies have shown less marked reductions in overall brain volumes between NMOSD and MOGAD or healthy

controls when compared to MS, although reduced white matter volume [149] and a trend towards reduced total brain volume [148] have been noted. The cortex seems to be relatively spared in NMOSD [150]. Pain in NMOSD is a common feature and correlates with spinal cord disease. An interesting observation was that reduced volume of the ventral posterior nucleus of the thalamus is associated with pain intensity in NMOSD [151]. Other studies have shown correlations in thalamic volume and clinical disease activity [152]. Decreased volumes of the nucleus accumbens and caudate nucleus were associated with clinical measures of disability [153]. The cross-sectional area of the optic chiasm was found to be associated with clinical measures of visual acuity [154]. Functional MRI (fMRI) has been used to show increased recruitment of the sensorimotor network during motor tasks [155] and reduced resting state activity in the precuneus and cingulate cortex [156] in NMOSD. Increased resting fMRI activity in the inferior temporal lobes of patients with normal brain imaging may also correlate with disability [157]. Deep learning approaches have been applied to distinguish NMOSD from MS and show high accuracy [158].

DIFFERENTIAL DIAGNOSIS OF MRI APPEARANCES SUSPICIOUS FOR NMOSD

In cases presenting with typical clinical presentations of NMOSD, MRI changes consistent with NMOSD and positive AQP4 antibodies, the diagnosis of NMOSD is straightforward. However, when MRI changes are atypical or AQP4 antibodies are negative the situation is more complicated. The co-appearance of clinical and MRI features suggestive of both NMOSD and MS within the same individual has been reported [159]. The value of NMOSD-specific MRI features has been questioned in some non-European ancestry populations where MS is less common [103]. In this study from Malaysia, the majority of seronegative cases had at least some features suggestive of NMOSD on MRI without necessarily meeting 2015 IPND diagnostic criteria for seronegative NMOSD.

PROGNOSTIC VALUE OF MRI IN NMOSD

Combinations of various NMOSD-specific lesions have been shown to have high specificity and reasonable sensitivity in predicting AQP4 seropositivity and distinguishing from MS in cohorts of CNS inflammatory disease. However, it is notable that the specific features identified have varied from study to study and validation in an independent data set is lacking. The length [160,161], degree of cord swelling [161], persistent Gd-enhancement [162] and presence of T1 hypodensity [161] in spinal cord lesions have been found to predict both the acute nadir of disability and ultimate extent of recovery in acute myelitis associated with NMSOD.

ROLE OF ROUTINE MRI FOLLOW-UP EXAMINATIONS IN NMOSD

As noted above, the frequency of clinically silent MR brain lesions in NMOSD is much lower than in MS, and it has therefore been argued that there is less of a role for routinely repeating MR imaging in NMOSD [163]. However, recent work has suggested that new lesions are predictive of future clinical events and may therefore play a role in monitoring disease progress and treatment response [141]. Asymptomatic Gd-enhancing brain lesions are particularly uncommon with no enhancing lesions being identified from 708 person-years of follow-up in one study [164]. There is therefore little value in requesting contrast imaging of the brain in routine follow-up of NMOSD.

CONCLUSIONS

MR imaging in cases of suspected CNS inflammatory disease is crucial in raising the possibility of NMOSD and prompting testing for AQP4 antibodies. It is also an essential component in confirming seronegative NMOSD [12]. Despite this, a significant number of suspected cases remain without a definite diagnosis and the status and treatment of these cases remains uncertain. This remains a significant dilemma in East Asian populations, where the prevalence of MS is lower and atypical forms of inflammatory CNS disease are the norm. In these cases MR imaging is of considerable potential value in determining the underlying cause [165]. However, continued work to find more precise diagnostic features on MRI is needed. Advanced MR techniques including diffusion tensor imaging may prove useful in this regard. Spinal cord lesion characteristics are of prognostic value and can indicate a need for more aggressive therapy in the setting of acute myelitis.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Not relevant.

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