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SPECIAL FEATURE REVIEW

Pathogenesis of autoimmune demyelination: from multiple sclerosis to neuromyelitis optica spectrum disorders and myelin oligodendrocyte glycoprotein antibody-associated disease

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Abstract

Autoimmunity plays a significant role in the pathogenesis of demyelination. Multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) are now recognised as separate disease entities under the amalgam of human central nervous system demyelinating disorders. While these disorders share inherent similarities, investigations into their distinct clinical presentations and lesion pathologies have aided in differential diagnoses and understanding of disease pathogenesis. An interplay of various genetic and environmental factors contributes to each disease, many of which implicate an autoimmune response. The pivotal role of the adaptive immune system has been highlighted by the diagnostic autoantibodies in NMOSD and MOGAD, and the presence of autoreactive lymphocytes in MS lesions. While a number of autoantigens have been proposed in MS, recent emphasis on the contribution of B cells has shed new light on the well-established understanding of T cell involvement in pathogenesis. This review aims to synthesise the clinical characteristics and pathological findings, discuss existing and emerging hypotheses regarding the aetiology of demyelination and evaluate recent pathogenicity studies involving T cells, B cells, and autoantibodies and their implications in human demyelination.

Keywords: AQP4 antibody, autoimmune demyelination, MOG antibody, multiple sclerosis, neuromyelitis optica spectrum disorders, pathology

INTRODUCTION

Central nervous system (CNS) demyelination occurs when the myelin responsible for the insulation of axons is damaged, resulting in poor conduction of action potentials, impaired neuronal signalling and, in some cases, partial or complete neuronal loss. Adaptive immunity enables a rapid and intensive response against subsequent exposures to previously encountered antigens. B and T lymphocytes are the key mediators of this branch of the immune system and are responsible for the humoral and cell-mediated adaptive immune response, respectively. Antibodies or immunoglobulins (Igs) are specialised proteins produced by B cells with a precise affinity and specificity for their target antigen. Historically, the brain and spinal cord were perceived as immune-privileged sites, lacking the conventional lymphatic system accessible to the remainder of the body.[1] Recent decades have shed light upon the complexity of ongoing immune trafficking across the blood–brain and blood–cerebrospinal fluid (CSF) barriers.[2] This intricate interplay between the CNS and the immune system has highlighted the notion that certain neurological demyelinating disorders are attributable to an inflammatory autoimmune pathophysiology.

In this review, we explore the complex role of autoimmunity in CNS demyelinating disorders, namely multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Firstly, we investigate the similarities and differences in the clinical characteristics and pathologies between the three disease entities. We then consider hypotheses regarding the autoimmune aetiology of these disorders and the mechanisms involved in disease pathogenesis. Lastly, we discuss trends in the diagnosis and therapy of these disorders as well as future directions in the field of autoimmune demyelination.

CLINICAL AND PATHOLOGICAL FEATURES OF AUTOIMMUNE DEMYELINATING DISORDERS

Multiple sclerosis

Multiple sclerosis is a chronic inflammatory neurological disorder characterised by numerous white matter lesions or plaques throughout the CNS. The prevalence of MS is rising globally with an estimated 35.9 people per 100 000 affected by MS which varies significantly depending on geography and ethnicity.[3] Of those diagnosed with MS, there is a clear female preponderance with females 2–4 times as likely to be affected than males.[3] Relapsing–remitting MS (RRMS) is the most common form of the disease and involves the onset of symptoms that are alleviated during periods of recovery until an eventual subsequent attack. While some patients experience recovery from symptoms during remission phases, others persist with residual disability following attacks.[4] Relapse rates can vary, with reported annualised relapse rates of 0.27–1.66 relapses per year in treatment-naïve MS patients.[5] Between 50 and 80% of patients with RRMS develop debilitating symptoms which worsen in a progressive manner.[6] At this stage, relapsing–remitting patients are recognised as having transitioned to secondary progressive MS (SPMS). There are limited clinical and pathological indicators that identify the transition of RRMS to SPMS.[4] Approximately 15% of MS patients are diagnosed with primary progressive MS and experience persistent accumulation of neurological deficits from disease onset.[7] Disease-modifying therapeutics are often inefficacious at alleviating symptoms of the progressive forms of MS.[8]

Diagnosis of MS has been achieved by expert consensus as defined by 2010 McDonald criteria and its subsequent revision in 2017 and particularly emphasises the clinical presentation of demyelinating episodes or attacks that are disseminated in space and time.[9] These episodes are complemented by paraclinical findings of typical white matter lesions observed using magnetic resonance imaging (MRI), abnormalities in visually evoked potentials (VEPs) which evaluate the function of visual pathways, and laboratory CSF testing including the presence of oligoclonal bands (OCBs).[10] There are currently no clinical biomarkers that can predict or distinguish between different MS disease courses.[4,11]

The pathological features of MS lesions strongly support the notion that inflammation-driven mechanisms contribute to the disease. Most demyelinating sites form confluent, perivenous focal lesions observed throughout the CNS in both white and grey matter regions with variable axonal loss and reactive gliosis.[12] Spatial distribution of MS lesions is partial to

periventricular, juxtacortical white matter, infratentorial areas such as the cerebellum and the pons, and short lesions of the cervical and thoracic spinal cord.[13] Lesion pathologies are heterogeneous and vary across MS patients, and are composed of mainly activated macrophages and microglia and $CD8^+$ T lymphocytes, with smaller populations of $CD4^+$ T cells, B lymphocytes and plasma cells[12,14] (Figure 1). Although distinct neuropathological patterns have been classically defined,[14] recent recommendations have been made to classify lesions based on the distribution and contents of activated macrophages and microglia.[15] Active lesions can be temporally divided into early or late demyelinating lesions, with the latter characterised by macrophages and microglia containing the more abundant, and thus less readily cleared myelin proteins such as myelin basic protein and myelin proteolipid protein (PLP), while the former also contains these in addition to less abundant, more readily cleared proteins such as myelin oligodendrocyte glycoprotein (MOG) and myelin-associated glycoprotein.[15] Contrastingly, inactive lesions have significantly reduced numbers of macrophages and microglia, are mostly devoid of oligodendrocytes and predominate in MS patients with extended disease durations and progressive forms of MS.[15,16]

Neuromyelitis optica spectrum disorders

Neuromyelitis optica spectrum disorders, previously known as Devic's disease or neuromyelitis optica (NMO), refer to a class of demyelinating syndromes characterised by the co-occurrence of inflammation in the optic nerves and spinal cord. The prevalence of NMOSD ranges between 0.5 and 4 people affected per 100 000[17] and has a significantly greater female preponderance compared to MS with a female:male ratio of up to 9:1, particularly in Afro-Caribbean populations.[18,19] Although a subtype of MS with optic nerve and spinal cord lesions was historically identified in the Asian population, termed 'opticospinal MS', this has since been included under the diagnosis of NMOSD.[20] The age of onset of NMOSD is higher compared to MS and is rarely seen in paediatric patients.[21] NMOSD patients relapse more frequently compared to MS and accumulate greater disability as measured by median expanded disability status scale (EDSS) scores.[21] Furthermore, longitudinally extensive spinal cord lesions were more frequent in NMOSD than in MS.[21]

The discovery that the large majority of NMOSD patients harboured IgG antibodies targeting the aquaporin-4 (AQP4) water channel on astrocytes has since become pivotal in NMOSD diagnosis.[22,23] Consensus diagnostic criteria for NMOSD have been defined by Wingerchuk and colleagues in 2007[24] and refined in 2015[20] subdividing patients into AQP4 antibody (Ab)-positive or AQP4 antibody-negative NMOSD, with the former making up between 60 and 70% of NMOSD cases.[25] Core clinical characteristics defined for NMOSD include optic neuritis (ON), acute myelitis, area postrema syndrome, acute brainstem syndrome, and observation of NMOSD-typical brain lesions with diencephalic clinical syndrome and symptomatic cerebral syndrome.[20] Diagnosis of NMOSD requires the observation of at least one of the aforementioned clinical characteristics upon discovery of AQP4 Ab while more stringent diagnostic requirements need to be met if AQP4 Ab serostatus is negative or unknown.[20] The co-occurrence of other autoantibody-mediated diseases such as systemic lupus erythematosus, Sjogren's syndrome and myasthenia gravis is observed more frequently in NMOSD compared to MS and can strengthen the diagnosis of NMOSD.[20]

Pathology of NMOSD lesions is driven by the binding of pathogenic AQP4 Ab on astrocytic endfeet surrounding endothelial cells and has been long identified as a demyelinating disease that is secondary to a primary astrocytopathy.[26] In contrast to the $CD8^+$ T cell predominance in MS lesions, activated $CD4^+$ T cells infiltrating the CNS are central mediators in NMOSD lesion formation[27] (Figure 1). Preferential localisation of NMOSD lesions in the spinal cord and optic nerves can be accounted for by the higher expression of AQP4 in these regions relative to the brain.[28] Lesions in NMOSD can be present with relative preservation of myelin or as classically demyelinated lesions. Demyelinated lesions are characterised by infiltration of macrophages containing myelin and astrocyte debris, marked axonal loss, astrocytic damage, decreased AQP4 expression, granulocytic inflammation, immunoglobulin and complement deposition, and vacuolated myelin.[26,29,30]

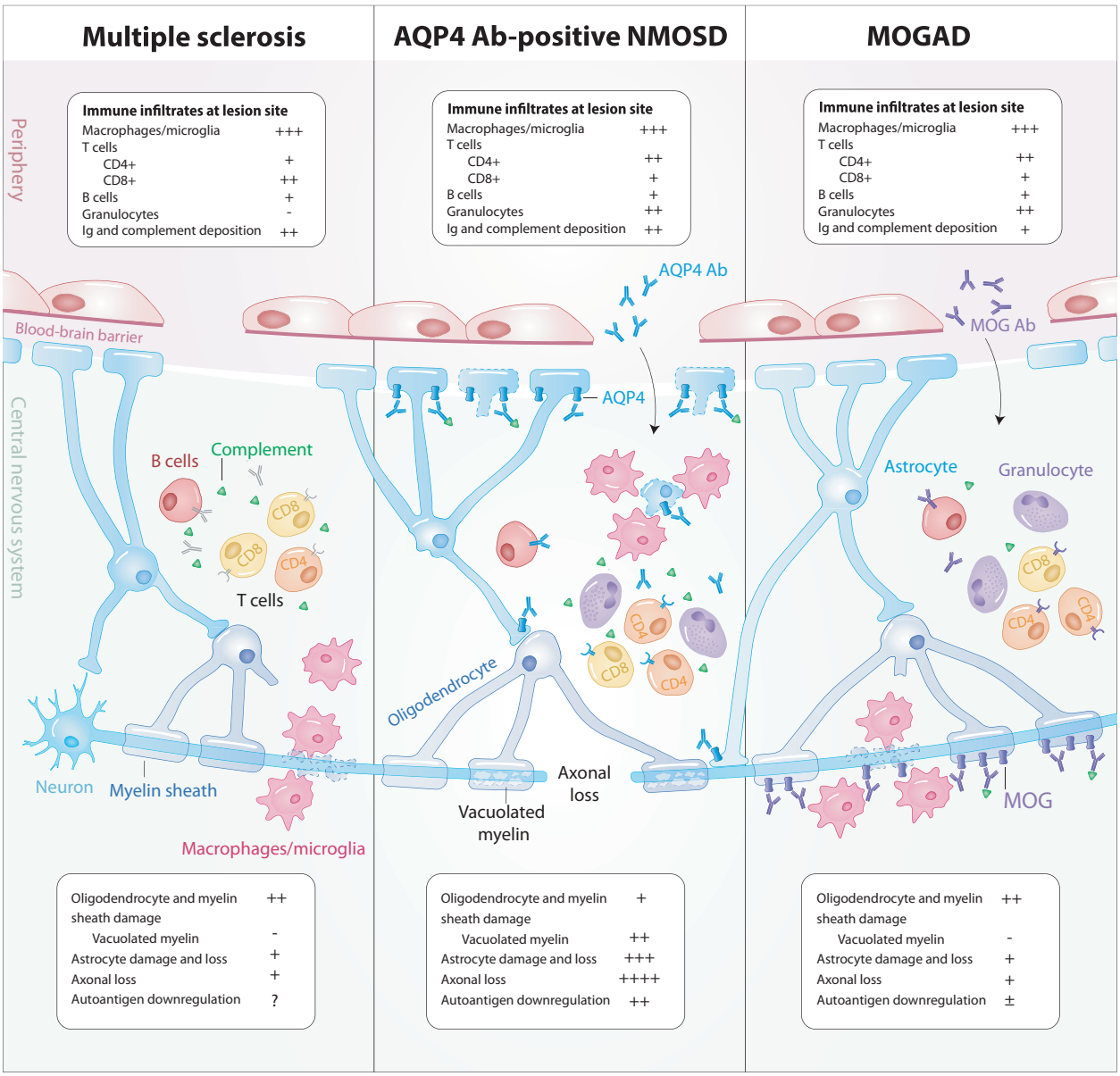

Figure 1. Pathological features of lesions in autoimmune demyelination. Demyelinating lesions commonly consist of immune cell infiltrates predominated by activated macrophages and microglia, lymphocytes, and varying degrees of immunoglobulin and complement deposition. $CD4^+$ T cells outnumber $CD8^+$ T cells in MOGAD and NMOSD while $CD8^+$ T cells predominate in MS. Granulocytic infiltration is seen in MOGAD and NMOSD while not frequently observed in MS lesions. Axon and astrocyte loss is profound in NMOSD while astrocytes and axons are largely preserved in MS and MOGAD. AQP4 downregulation is observed in NMOSD while conflicting reports of MOG internalisation have been seen in MOGAD. Ab, antibody; AQP4, aquaporin-4 water channel; Ig, immunoglobulin; MOG, myelin oligodendrocyte glycoprotein; MOGAD, MOG Ab-associated disease; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders.

MOG antibody-associated disease

Myelin oligodendrocyte glycoprotein (MOG) has been extensively studied as a candidate autoantigen in demyelination initially because of its involvement in animal studies of experimental autoimmune encephalitis (EAE), a leading *in vivo* rodent model of MS. The development of assays which presented MOG in its native conformation was the first to uncover the presence of high titres of MOG Ab in paediatric demyelination cohorts, particularly prominent in children with acute

disseminated encephalomyelitis (ADEM).[31–34] In particular, the live cell-based assay which involves the recombinant expression of conformational MOG on the cell surface of eukaryotic cell lines has become the gold standard detection method for MOG Ab. Further investigations using these methods revealed the presence of MOG Ab in 20–50% of adults with AQP4 Ab-negative NMOSD.[25,35–37] This has sparked the current consensus to distinguish patients with MOG Ab as a separate disease entity from NMOSD, termed MOGAD.

Despite numerous international recommendations, determination of consensus diagnostic criteria for MOGAD is still ongoing. The typical clinical characteristics of MOGAD include ON, myelitis, and encephalitis, and these phenotypes can be monophasic or relapsing in disease course.[38] The clinical spectrum of MOGAD is continually expanding with emerging reports of MOG Ab associated with seizures and cortical encephalitis.[39] Interestingly, despite the lack of MOG expression in the peripheral nervous system (PNS), MOG Ab has been described in patients with co-existing inflammatory PNS syndromes.[40] The co-incidence of these PNS symptoms and their direct association with MOGAD warrants further investigation.

Prevalence studies involving MOGAD cohorts are scarce. In a recent UK study, the prevalence of MOGAD was approximately two per 100 000 with the female:male ratio estimated at 1.8:1, proportionally affecting more men compared to NMOSD and MS.[41] Patients with MOGAD have been reported as having less residual functional impairment compared to AQP4 Ab-positive NMOSD,[25,42,43] although this is not universal with some patients, particularly those with a relapsing disease course, suffering permanent visual loss or paraplegia.[44] The co-existence of MOG Ab and AQP4 Ab in the same individual is seldom reported and occurs in as low as 0.06–8% of patients with demyelination.[45,46] A small subset of MS patients are seropositive for MOG Ab.[47–49] In contrast to MS, CSF findings in adult and paediatric MOGAD cohorts show that OCBs are less commonly observed in MOGAD compared to MS, and are seen in 10–30% of patients.[50,51] Radiological differences highlight that MOGAD and NMOSD patients with ON are more likely to have bilateral and longitudinally extensive optic nerve lesions compared to MS patients with ON.[52] Comparatively, MOGAD patients with ON more frequently experienced lesions in the anterior visual pathway relative to NMOSD patients with ON in which lesions were observed posteriorly including the optic chiasm and optic tract.[52] Area postrema involvement is less common in MOGAD and more predominant in NMOSD.[53] Similar to NMOSD, longitudinally extensive transverse myelitis (TM) is observed in MOGAD and rarely observed in MS.[54] Short lesions of TM similar to those seen in MS also occur in MOGAD.[55] While there is currently no clinical predictor of relapse in MOGAD patients, persistent MOG Ab seropositivity has been associated with a relapsing disease course while those with transient seropositivity were more likely to be monophasic.[56,57]

MOGAD lesions are characterised by perivenous, confluent demyelination, axonal preservation, reactive astrocyte gliosis, prominent intracortical demyelination, with immune cell infiltrates, complement deposition and evidence of oligodendrogliopathy.[58,59] Granulocytes and $CD4^+$ T cell infiltrates are observed in high frequencies in MOGAD lesions with astrocyte populations preserved and AQP4 expression sustained in contrast to NMOSD[58] (Figure 1). Intracortical lesions were more frequent in MOGAD than in MS and NMOSD.[58] Similar to MS, subpial demyelination was also observed in MOGAD.[58,59] Complement and Ig deposition were less frequently observed in MOGAD lesions compared to NMOSD.[59] Although AQP4 internalisation is an established pathogenic mechanism in NMOSD, some reports have observed MOG-dominant myelin loss at MOGAD lesions,[59] while others have shown evidence of complement deposition without selective loss of MOG expression.[58]

AUTOIMMUNE AETIOLOGY AND TRIGGERS OF CNS DEMYELINATION

While clinical presentations are similar between MS, NMOSD and MOGAD, differences in the origin of the autoimmune response in each disease remain to be explored and these have distinct implications to our understanding of each disease entity. Currently, the location of the initiating pathogenic event in demyelination remains contentious. In the 'outside-in' model, disease pathogenesis begins peripherally, in which autoreactive immune cells traffic into the CNS and elicit an autoimmune response. EAE rodent models are a classical demonstration of this, whereby demyelination is initiated through

immunisation of adjuvant-administered myelin proteins resulting in expansion and activation of myelin-reactive $CD4^+$ T cells.[60–64] The likelihood of peripheral immune-mediated pathogenesis is strengthened by large genome-wide association studies which have shown MS susceptibility to be enriched in genes associated with B and T lymphocytes, natural killer cells and microglia.[65,66] Conversely, an 'inside-out' model posits that disease is resultant of pre-existing damage to oligodendrocytes and myelin, prompting immune cell recruitment to sites of injury, following which an inflammatory response proceeds. This is exemplified in cuprizone-induced models of demyelination which directly elicits oligodendrocyte cytotoxicity and subsequent inflammatory demyelination.[67] Furthermore, alterations to myelin-related genes support this 'inside-out' model of disease pathogenesis, as seen in PLP1 missense mutations found in a subset of MS patients and cause oligodendrocyte apoptosis.[68] While continued investigation is warranted into the compartment of disease onset, several genetic and environmental factors have been commonly investigated across these diseases.

HLA genotypes

The presence of HLA-DRB1*15:01 and the absence of HLA-A*02 have been frequently associated with a significantly increased risk of developing MS.[69] In some cases, MS has been postulated to be a neurodegenerative disorder where the inflammatory response is secondary to neurodegeneration.[70,71] However, in a multinational genome-wide association study of 9772 cases of MS, genes relevant to inflammation-independent neurodegenerative pathways lacked an association to MS, while genes for $CD4^+$ T cell differentiation were over-represented and implicated in disease pathogenesis.[66] In a next-generation sequencing study of 31 Japanese NMOSD patients, HLA-DQA1*05:03 was found to be significantly associated with NMOSD.[72] More recently, in a cohort of 165 NMOSD patients, HLA-DRB1*08:02 and HLA-DPB1*05:01 were found to be susceptibility alleles while HLA-DRB1*09:01 was found to be protective.[73] In contrast, HLA-A*01, HLA-B*08 and HLA-DRB1*03 were associated with NMOSD in a recent Dutch study while no association between HLA and MOGAD was observed.[74] This study, however, did not separate adult and paediatric MOGAD cohorts, whereas in a recent Chinese study of 95 MOGAD patients (51 paediatric, 44 adult), HLA-DQB1*05:02–DRB1*16:02 alleles were associated with paediatric onset of MOGAD while no association between adult-onset MOGAD and HLA genotype was observed.[75]

Infectious prodrome

Viral infection is among many environmental factors that have been commonly linked to or seemingly preceding autoimmune disease. Arguably, most renowned is the association between MS and Epstein–Barr virus (EBV) with almost all MS patients having been previously infected with EBV.[76] EBV Ab seropositivity is observed at higher rates in MS patients and is strongly correlated with disease onset.[77,78] Additionally, EBV-induced infectious mononucleosis is found to be associated with a twofold risk of developing MS.[77] Autoreactive B cells latently infected with EBV are proposed to contribute to MS pathogenesis by evading elimination of $CD8^+$ T cells and accumulating within the CNS, producing myelin-reactive antibodies and survival signals for T cells.[78] Induction of MOGAD by a viral infection has also been reported, with the most common occurrence observed in paediatric patients who develop ADEM following viral infection. Postinfectious MOGAD cases include HSV-1 infection followed by ADEM[79] and ON[80] and rubella infection followed by ON.[81] Up to 40% of patients experience a non-specific viral prodrome with or without fever, prior to clinical onset. Most recently emerging, two reported cases of SARS-CoV-2 infection were followed by MOG Ab-associated ON[82] and NMOSD.[83] Despite these cases, the association between viral infection and demyelination remains unclear and leading hypotheses regarding molecular mimicry of myelin proteins because of their structural overlap with viral proteins remain largely unvalidated in humans. Other than viral infection, there is also emerging evidence regarding non-infectious clinical prodromes preceding autoimmune demyelination. Within 5 years of disease onset, patients with MS were reported to have greater fatigue, sleep disorders, anaemia and pain compared to healthy controls.[84] Neuropathic pain has been reported in MOG Ab- and AQP4 Ab-positive patients,[85] with another study identifying prodromal headaches in almost 50% of patients with MOG Ab-positive ON.[86]

Vitamin D and UV exposure

Low vitamin D levels, insufficient UV exposure and higher latitudes have each been linked to an increased risk of developing MS.[87] In a recent study of two independent multicentre cohorts, lower disease severity was seen in MS patients with higher vitamin D levels.[88] Although UV exposure is correlated with the maintenance of sufficient levels of vitamin D, the role of sun exposure in the development of MS may be vitamin D-independent.[89] For instance, while whole-body UV irradiation of mice prevents the development of EAE,[90] UV-induced suppression of EAE was still observed in mice lacking the vitamin D receptor.[91] Interestingly, in a recent cross-sectional study of 29 NMOSD patients, increased sun exposure and serum calcifediol (a vitamin D metabolite) were seen in AQP4 Ab-negative NMOSD patients compared to AQP4 Ab-positive patients, potentially implicating a role of vitamin D in AQP4 Ab synthesis.[92] Presently, associations of vitamin D and sun exposure have yet to be explored in MOGAD cohorts.[93]

Paraneoplastic syndromes

A paraneoplastic association has been described in a few cases of MOGAD and AQP4 Ab-positive NMOSD and may be associated with the pathogenesis of demyelination. More recently, expression of oligodendrocyte markers, including MOG, and $CD4^+$ and $CD8^+$ T cell infiltration have been described in the teratoma tissue of a MOG Ab-positive ON patient with ovarian teratoma.[94] This is in contrast to the more frequently associated lung and breast adenocarcinomas in a small number of patients with NMOSD[95]; however, cases of ovarian teratomas in NMOSD have also been reported.[96] A patient positive for CSF MOG Ab and presenting with longitudinally extensive TM, BON, and brainstem encephalitis coincidentally with lung adenocarcinoma has been recently reported[97]; however, it is clear that the paraneoplastic nature of demyelination is rare and warrants further investigation.

Gut microbiota

Intestinal microbiota influence both local and systemic immune responses through its interaction with the gut–brain axis and offer several hypotheses regarding the origin of the autoimmune response. A recent study found that RRMS patients with active disease had increased numbers of intestinal Th17 cells, and expansion of this population was reliant on the composition of gut microbiota.[98] An increased relative abundance of anti-inflammatory *Prevotella* strains was seen in healthy controls and RRMS patients without active disease.[98] More recently, clonally expanded IgA-expressing B cells have been found to actively traffic to the CNS with specificity against certain phyla of gut microbiota and were detected in the CSF and tissue of active MS-associated lesions and could therefore serve as a systemic biomarker for active disease in MS.[99] Recent investigations into the involvement of gut microbiota in NMOSD pathogenesis have revealed the role of *Clostridia perfringens* in the disease. This strain was enriched in NMOSD patients and has been implicated in the regulation of Treg and Th17 cell populations. Specifically, AQP4-specific T cells in NMOSD patients exhibited a Th17 phenotype and cross-reacted with a *C. perfringens* peptide sequence.[100] A newly isolated Erysipelotrichaceae bacterium has been recently described that when co-cultured with *Lactobacillus reuteri* which has homology to MOG peptides, Th17 inflammatory responses were induced from MOG-specific Th17 cells and increased EAE severity.[101] Other instances of molecular mimicry to MOG have been demonstrated in a small proportion of MS patients harbouring antibodies targeting MOG peptides which cross-reacted with the bovine milk protein butyrophilin.[102] Additionally, butyrophilin has been shown to induce a MOG-specific T-cell response in rats, while also having the potential to produce a tolerogenic response and alleviate EAE.[103] As this was investigated in the context of MS, which is now known to comprise a small minority of MOG Ab-positive patients, these findings have yet to be investigated in a MOGAD cohort.

PATHOGENIC MECHANISMS IN AUTOIMMUNE DEMYELINATION

While MS has been classically considered a T cell-driven disease, the efficacy of B-cell-targeted therapies has warranted recent investigation into the regulatory or antigen-presenting role of B cells.[104–106] Conversely, even though NMOSD and MOGAD have a clear antibody association, the role of antigen-specific T cells in these disorders

remains largely undefined. Overall, dysregulation of both cell-mediated and humoral compartments of the adaptive immune system likely exists across MS, NMOSD and MOGAD.

T cells

The contribution of pathogenic T cells has been considerably explored in the context of MS which has been classically described as a T cell-mediated disease. In particular, in EAE, the role of $CD4^+$ Th17 cells is well established as being the primary mediators of disease pathogenesis[107] with recent findings showing increased frequencies of distinct Th17 subsets in the blood and CSF of patients with RRMS compared to SPMS.[108] Regardless of disease course, $CD8^+$ T cells in MS lesions far outweigh the frequency of other infiltrating lymphocytes such as B cells and $CD4^+$ T cells.[109] $CD8^+$ T cells are enriched in the CSF of RRMS patients early in disease,[110] and these $CD8^+$ T cells found in the CSF shared the same repertoire as CNS-resident $CD8^+$ T cells.[111] However, the role these $CD8^+$ T cells play in disease is not well understood. For instance, myelin-specific $CD8^+$ T cells from MS patients have demonstrated a proinflammatory profile when expanded *in vitro* and expressed CD20 in greater proportions compared to control subjects.[105] These myelin-specific $CD20^+CD8^+$ T cells were preferentially depleted by anti-CD20 therapy which has been shown to be effective in MS treatment.[105] On the contrary, a subset of clonally expanded regulatory $CD8^+$ T cells have been recently described to suppress the pathogenicity of $CD4^+$ T cells in EAE,[112] and thus, $CD8^+$ T cells may play a multifaceted role as either a regulatory or pathogenic mediator of human demyelination.

Antigen-specific T cells in NMOSD and MOGAD have been seldom detected despite central dogma for the necessity of these cells in their role for autoantibody production and pathogenicity. Interestingly, AQP4-specific $CD4^+$ T cells were detected in AQP4 Ab-positive patients, with T cell reactivity observed in a peptide sequence at amino acids 156–170 which overlaps with the epitope recognised by AQP4 Ab.[113,114] Contrastingly, the same study could not detect MOG-specific T cells in MOG Ab-positive patients and this was postulated to be because of the failure of synthetic peptides in mimicking antigen processing and MHC presentation.[113] Indeed, a previous study using *Escherichia coli*-expressed MOG coupled to fluorescent beads was able to detect MOG-specific $CD4^+$ T cells producing IFN-gamma, IL-22 and IL-17A in 16 out of 29 MS patients.[115] However, MOG Ab was detected in only one of these patients reinforcing the notion that MOG Ab seropositivity in MS patients is rare and that the role of MOG-specific T cells in MS patients remains difficult to explore.[115] Although antigen-specific T cells in demyelination have been challenging to isolate, the cytokine profile of demyelination patients implicates the role of specific T cell subpopulations. The proinflammatory Th17-related cytokines IL-6 and G-CSF were elevated in paediatric MOGAD patients compared to MOG Ab-negative patients with demyelination.[116] In a cross-sectional study, adult and paediatric MOGAD patients were found to have an upregulation of Th17, Th1-related and Treg-related cytokines.[117] These cytokines were similar to those upregulated in the CSF of AQP4 Ab-positive NMOSD patients; however, they differed significantly from MS patients.[117]

B cells and antibodies

The initiation of an autoimmune response against CNS antigens can lead to the breach of the blood–brain barrier (BBB) to allow leukocyte infiltration, antibody deposition and inflammation in the local CNS region.[118–120] Autoantibodies are implicated in the exacerbation of autoantigen destruction through executing effector functions such as the activation of complement-dependent cytotoxicity (CDC) or antibody-dependent cellular cytotoxicity (ADCC).[121]

Even though a central autoantigen in MS remains unidentified, evidence exists for the contribution of humoral mechanisms in disease pathogenesis in addition to the T cell-driven response.[109,122] Intrathecal OCBs are a hallmark feature of MS, in which the presence and quantity are strongly associated with disease severity and disability in patients.[123–127] Several studies have evidenced the role of B cells in the production of OCBs,[128–130] thus implicating the importance of the humoral response in promoting characteristic MS demyelination. This is further supported by the observation that B cells are responsible for mediating brain homing Th1 cell autoproliferation, and B-cell depletion by anti-CD20 therapies reduces T cells and inflammation both *in vitro* and in patients with MS.[104] MS patients commonly display elevated intrathecal Ig,

specifically IgG1 and IgG3.[131] These findings have been supported by recent studies observing higher serum IgG3 may be predictive of the progression of CIS towards MS.[132,133] Subsequent functional assays on antibody pathogenicity in animal and human models have confirmed MS lesion observations. Injection of CSF from MS patients was observed to induce demyelination and axonal damage in mice.[134] Evidencing the specific role of antibodies in this process, recombinant IgG1 from MS patient CSF was observed to initiate CDC, rapid demyelination and microglia activation on mouse organotypic cerebellar slices.[135] In addition to CSF antibodies, serum autoantibodies have the capacity to disrupt the BBB, target brain microvessels and initiate destruction of myelin.[136]

Defining a putative autoantibody responsible for MS demyelination is encumbered by the potential heterogeneity of target autoantigens in MS. Various autoantibody targets have been investigated (Table 1). For instance, the presence of isotype-switched antibodies against myelin PLP is significantly elevated in patients with RRMS and SPMS who have specific HLA types, and PLP Ab titres correlated with disease severity.[137] Additionally, a subgroup of MS patients with brainstem and cerebellar lesions have been identified with PLP antibodies.[138] In other cases, the pathogenic potential of these autoantibodies has been evidenced through the initiation of CNS inflammation following the passive transfer to rodent models[139]; however, validation of their pathogenic roles in humans remains unprecedented. Distinct subgroupings of MS patients with precise disease course, clinical and radiological features may facilitate discovery of new autoantigenic targets and discrete clinical entities, as has been the case for the discovery of AQP4 Ab and MOG Ab.

The mechanisms of AQP4 Ab pathogenesis have been investigated extensively through functional assays in animals and human tissue. An early *in vitro* study revealed that serum-derived IgG from NMOSD patients binds to astrocytes and increases BBB permeability to permit autoimmune reactivity within the CNS.[140] Further, human AQP4 Ab binding to astrocytes initiates injury, secondary oligodendrocytopathy and demyelination through CDC, ADCC or induction of inflammation through granulocyte activation.[141–143] The process by which astrocytopathy leads to demyelination in NMOSD remains unclear. Bystander formation of membrane attack complexes in the process of CDC has been shown in neurons and oligodendrocytes co-cultured with astrocytes.[144,145] Other studies demonstrate internalisation and downregulation of the astrocytic glutamate receptor, EAAT2, alongside AQP4 upon Ab binding,[146] and have therefore implicated glutamate excitotoxicity to oligodendrocytes as a contributing factor in disease pathogenesis.[147] The production of recombinant antibodies from NMOSD patient periphery-[148–150] and CSF-derived[149,151,152] B cells revealed that AQP4 Ab initiates pathogenic effects both *in vitro* and *in vivo* because of defective central and peripheral B cell tolerance mechanisms. Recombinant AQP4 Ab was observed to specifically bind to the H101/L104 epitope and initiate CDC.[152] Supporting these findings, recent clinical trials indicate that eculizumab, a complement inhibitor, reduces relapse rates in patients.[153] Additionally, the IL-6 cytokine pathway has been strongly implicated in NMOSD pathogenesis[154–156] and using antibodies against the IL-6 receptor has demonstrated a strong potential to block this pathway through reducing the survival of AQP4 Ab-secreting plasmablasts.[157]

Evidence of disease initiation and exacerbation following passive transfer of AQP4 Ab further outlines the pathogenic role of these autoantibodies. Immunisation with AQP4 peptides exacerbated experimental autoimmune myasthenia gravis symptoms in mice, including fatigue, weakness and decreased nerve responsiveness.[158] The administration of recombinant AQP4 Ab to rodents has provided strong evidence to support *in vivo* studies. Recombinant AQP4 Ab generated from NMOSD patient CSF-derived plasma cells was observed to initiate perivascular astrocyte depletion, myelinolysis, and Ig and complement deposition in EAE rats.[151] In line with functional assays on pathogenicity, the observation that seropositivity is associated with increased chances of opticospinal involvement, longitudinally extensive spinal cord lesions, relapse rate and lower EDSS scores further evidences the role of the autoantibodies in driving demyelinating pathogenesis.[159] Although the mechanism of pathogenesis initiation within the CNS is still debated, current evidence points towards a peripherally initiated response in NMOSD. For instance, intrathecal production of AQP4 Ab is rarely observed in NMOSD patients.[160] Additionally, a recent report demonstrated that

Table 1. Summary of evidence for the pathogenicity of demyelinating autoantibodies

Pathogenicity criteria	MS	NMOSD	MOGAD
Autoantibodies present in affected patients	*MOG Ab* 0–5% of adult MS patients[47–49] (dependent on selection criteria and cohort size) ADEM patients with persistent MOG Ab titres over 5 years were eventually diagnosed with MS[166] *PLP Ab* Isotype-switched PLP Ab present in 84% of MS patients[137] *NFL Ab* Progressive and relapsing–remitting MS associated with higher levels of NFL and NFL Ab[197] *NFM Ab* Increased NFM Ab in MS patients[198] *HERV-W Ab* 19/22 (86%) patients with relapsing–remitting MS (RRMS) harboured HERV-W Ab; compared to 7/22 (32%) AQP4 Ab-positive and 20/22 (91%) MOG Ab-positive patients[199] *Kir4.1 Ab* 46.9% MS patients harboured Kir4.1 Ab,[139] but varied prevalence in subsequent studies; from 8 to 28%,[200–203] and a number of studies detected no significant level of Kir4.1 Ab in MS patient serum[204–206] *Talin1 Ab* Talin1 Ab levels increased in MS compared to controls, but negatively correlate to demyelination activity[207]	*AQP4 Ab* Inflammatory demyelinating CNS diseases: 18.1%[164] NMOSD and rheumatic disease: 78%[192]SLE: 6.7%[193] *ANA Ab* 36% (52/143) in AQP4-positive NMOSD cohort[196]	*MOG Ab* Optic neuritis: 1.7–4%[194,195] Paediatric ADEM: 40%[31] AQP4 Ab-negative NMOSD: 39%[35]
Antibody interacts with target antigen	Recombinant IgG1 from MS patient CSF target myelin and astrocyte-specific antigens on mouse organotypic cerebellar slices and cause oligodendrocyte loss and demyelination through CDC and microglia activation[135] Autoreactive antibodies found in phagocytic macrophages within active demyelinating lesions; may be contributing to lesion formation or initiation[208] Astrocytes in active MS lesions are immunoreactive to and express Kir4.1[25] Antibody and complement deposition on CNS lesions in patients with MS[209,210] Deposition of Ig and complement (C9neo) in areas of active demyelination, alongside activated macrophages with immunoreactivity to myelin antigens, Ig and C9neo[211]	AQP4 Ab induces demyelination through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity and inflammation initiated by granulocytes and macrophages[141] Necrotic CNS lesions display AQP4 loss and deposits of Ig and complement[30,209,212] Serum AQP4 IgG1 from NMO patients binds to AQP4-expressing cells to activate complement and initiate endocytosis[213,214] ADCC-mediated cell death when incubated with AQP4 Ab-positive patient serum and NK cells[140]	Human MOG Ab induces complement-mediated myelin loss in murine organotypic brain slices[215] Human[37] and murine[171] MOG Ab causes rearrangement and destabilisation of oligodendrocyte cytoskeleton Children with MOG Ab harbour elevated IL-6, G-CSF and deposits of IgG, C1q and activated microglia around early brain lesions[169]

(Continued)

Table 1. Continued.

Pathogenicity criteria	MS	NMOSD	MOGAD
Passive antibody transfer reproduces disease features	Injection of Kir4.1 Ab in mice increased astrocyte expression of glial fibrillary acidic protein, activated complement cascade surrounding Kir4.1 and decreased Kir4.1 expression.[139] However, importance of this autoantigen in MS patients is debated	Monoclonal AQP4 Ab transferred to rats induces CNS lesion formation and AQP4 loss without assisted antibody entry into CNS[161] Passive transfer of human AQP4 Ab to rats causes infiltration of inflammatory cells to CNS and exacerbation of lesion formation[216] Recombinant AQP4 Ab derived from NMOSD patients initiates perivascular astrocyte depletion, myelinolysis and deposition of complement and Ig in rats with EAE[151]	Affinity-purified MOG Ab induces complement-dependent demyelination when co-transferred with MOG-specific T cells in rat models of EAE[173]
Immunisation with antigen produces model disease	*MOG* Mice sensitised with $MOG_{35–55}$ peptide induces an acute and reproducible EAE phenotype[61] Immunisation with non-inflammatory MOG mRNA suppresses EAE in mice[191] EAE exacerbated after passive transfer of MOG monoclonal IgG in mice, causing extensive demyelinating plaques and fatal relapses[217] *PLP* Mice immunised with $PLP_{139–151}$ produce EAE which models clinical relapses and RRMS[62] *MBP* Mice immunised with bovine[63] or rat[64] MBP produce a monophasic EAE model	Injection of AQP4 peptide to mice with experimental autoimmune myasthenia gravis aggravates disease symptoms[158] Rats immunised with mimotopes of conformational AQP4 epitopes produce AQP4 Ab detectable in sensitive cell-based assays; however, no concurrent pathology was observed[218] Encephalomyelitic syndrome was initiated when $Rag1^{-/-}$ mice reconstituted with mature T cells of $AQP4^{-/-}$ mice were immunised with AQP4. NMO-specific lesions within CNS occur only with the additional presence of AQP4 Ab[163]	Macaques immunised with rhMOG/IFA develop EAE comparable to MOGAD in children; increased IL-6 and G-CSF cytokines and early brain lesions with deposits of IgG, C1q and activated microglia[169]
Reduction of antibody levels ameliorates disease	Therapeutics reducing inflammation and immune response ameliorate MS symptoms and treat relapse, including prednisone, methylprednisone, plasmapheresis and ocrelizumab[104] Relapse rate higher in MOG Ab-seropositive patients[131,219]	AQP4 Ab seropositivity is predictive of relapse and titres increase during relapse[220–222] High titres associated with increased disease activity (complete blindness or extensive CNS involvement)[223] Treatment with rituximab causes significant improvement of disease activity most patients,[224] and AQP4 Ab concentration decreases in serum after immunosuppressive therapy[222] Chimeric, high avidity AQP4 Ab blocks patient IgG binding to AQP4, thus preventing CDC *in vitro*[225] Coexistence of AQP4 and ANA Ab associated with more severe disease phenotypes[196]	Disease ameliorated upon treatment with steroids and rituximab[44] High MOG Ab titres are predictive of a more severe, relapsing course and increase during active disease[56,168]

Ab, antibody; ADCC, antibody-dependent cellular cytotoxicity; ADEM, acute disseminated encephalomyelitis; ANA, anti-nuclear antibody; AQP4, aquaporin-4; CDC, complement-dependent cytotoxicity; CSF, cerebrospinal fluid; EAE, experimental autoimmune encephalitis; EAMG, experimental autoimmune myasthenia gravis; G-CSF, granulocyte colony-stimulating factor; HERV-W, human endogenous retrovirus-w; Ig, immunoglobulin; IL-6, interleukin 6; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; MOGAD, MOG antibody-associated disorder; mRNA, messenger ribonucleic acid; MS, multiple sclerosis; NFL, neurofilament light; NFM, neurofilament medium; NK cell, natural killer cell; NMOSD, neuromyelitis optica spectrum disorder; PLP, myelin proteolipid protein; rAb, recombinant antibody; rhMOG/IFA, recombinant human MOG/incomplete Freund's adjuvant; RRMS, relapsing–remitting multiple sclerosis; SLE, systemic lupus erythematosus.

systemic injection of AQP4 Ab has a number of entry sites into the CNS and produced NMOSD-like lesions.[161] Although some studies report the necessity for T cells in AQP4 Ab lesion formation,[162] others suggest that AQP4 Ab alone can induce NMOSD pathology without T cell help.[161] It is likely that both pathways are required in NMOSD pathogenesis, as indicated in a study which observed that while immunisation with AQP4 initiates encephalomyelitis in $Rag1^{-/-}$ mice with the presence of T cells alone, lesions are only produced in the presence of both antibodies and T cells against AQP4.[163]

MOG Ab has been shown to contribute to CNS demyelination through CDC or ADCC-mediated lysis of MOG-expressing cells.[31,164,165] These findings are supported by the observation that the majority of MOG Ab are IgG1,[33,166–169] a subclass efficient in fixing complement and binding to Fc receptors for ADCC initiation although the potency of these effector mechanisms may be dependent on autoantibody affinity.[170] Further studies suggest murine and human MOG Ab induce cytoskeleton disruption and microtubule destabilisation.[37,171]

Several studies have further observed CNS inflammation and complement-dependent lysis of MOG-expressing cells following passive transfer of high-affinity patient MOG Ab to rodents.[172,173] A recent report demonstrated the pathogenicity of an antibody derived from the RNA of post-mortem human brain tissue and showed similar demyelinating activity to a prototypical murine-derived MOG Ab.[174] However, these studies use rodent-reactive antibodies which are only present in a minor proportion of MOGAD patients, with between 70 and 80% of human MOG Ab recognising a conformational epitope at position 42 of the extracellular domain of MOG where proline exists in humans as opposed to serine in rodents.[168,175] Autoantibody pathogenicity in a primate model has since been demonstrated in an *in vivo* macaque model in which complement-dependent vacuolisation of myelin, lesion pathology, EAE and MOG Ab were observed after injection of recombinant human MOG.[169]

CURRENT TRENDS AND FUTURE DIRECTIONS

Standardised serological testing

With ongoing attempts to make the delineation between MS, NMOSD and MOGAD progressively clearer, discernment of the correct disease entity remains reliant on evaluation of clinical presentations and accurate paraclinical testing. Increasingly evident is the need to standardise assay methodologies for the accurate detection of demyelination-associated autoantibodies.[109,176] Several multicentre studies over recent years have evaluated the accuracy, sensitivity and specificity of antibody testing in NMOSD and MOGAD. A multicentre study of 21 AQP4 Ab assays across 15 European centres found that cell-based assays using microscopy produced the highest sensitivities and specificities.[177] It also further reinforced the use of the M23 isoform of AQP4, with improved sensitivity in contrast to the M1 isoform,[177] attributed to findings that formation of orthogonal array of particles (OAPs) exclusive to the M23 isoform, is important for pathogenic human AQP4 Ab binding.[141] Recent validation studies have demonstrated lower concordance in MOG Ab testing when determining the presence of MOG Ab in patients with borderline and low MOG Ab titres tested across international centres.[178] Differences in assay methodologies, data analyses and cut-offs for MOG Ab positivity largely account for these discrepancies.[179,180] Moreover, studies on the isoform of MOG have shown that C-terminal truncation of the full-length protein decreases binding of human MOG Ab[181] and is likely because of the effect of truncation on the second hydrophobic domain of MOG which has recently been revealed to be important in the bivalent binding of human MOG Ab.[170] Although major human MOG Ab epitopes have been described in the extracellular domain of the protein,[168,175] it has been postulated that the transmembrane domains and cytoplasmic tail may play an important role in the surface expression and oligomerisation of the antigen. Further, the use of fixatives in cell-based assays has been shown to alter the native conformation of MOG and significantly decrease the sensitivity of the MOG Ab test.[168,178] Hence, cell-based assays using live cells are the current gold standard in the detection of these antibodies,[38,178,182] and therefore, translation and standardisation of these assays for routine diagnostic testing are highly warranted.

Recent studies are also shedding light on the co-occurrence of disease-associated autoantibodies in CNS neurological disorders. For instance, the co-existence of NMDAR Ab and other autoantibodies associated with autoimmune encephalitis in MOGAD and AQP4 Ab-positive NMOSD patients

has been observed.[183,184] AQP4 Ab-positive NMOSD has been found to occur in patients with AChR Ab-positive myasthenia gravis with NMOSD onset most commonly occurring after diagnosis of MG.[185] This was further reflected in antibody titres, with AChR Ab decreasing as AQP4 Ab increased over the disease course.

Predictors of disease

Predicting disease course remains a significant challenge as residual disability and worsening of clinical outcomes often accumulates with further relapses in MS, NMOSD and MOGAD. Intriguingly, a recent study found an association between epitope binding patterns and likelihood to relapse, with 75% of adult MOGAD patients that did not recognise the Proline42 epitope, the major immunodominant binding region of human MOG Ab, presented with a relapsing disease course.[168] This provides evidence that characterising the epitope of autoantibodies in demyelination may prove useful in predicting disease course, thereby enabling refinement of therapeutic pathways. Characterisation of binding patterns in AQP4 Ab-positive NMOSD showed a change in AQP4 Ab epitope in only a minority of patients over the disease course.[186] Similarly, the immunodominant epitope in MOGAD patients also remains stable over time.[168] Additionally, while MOGAD patients exhibited the same Ab characteristics in serum and CSF, paired CSF-serum samples containing AQP4 Ab taken at the same time exhibited different binding patterns potentially suggesting the contribution of two independent sources of antibody production in NMOSD.[186]

Given the exemplars of MOG Ab and AQP4 Ab, the discovery and validation of new biomarkers may have significant implications in predicting disease features. Axonal damage is variable across demyelinating diseases and can be measured by neurofilament levels. Recent findings have shown elevated blood and CSF neurofilament levels in RRMS patients associated with disease activity, disability score and more frequent relapse.[187] Additionally, in 18 MOGAD patients followed longitudinally, elevated neurofilament light-chain levels at baseline remained stable or decreased over time, signifying peak axonal damage occurring at disease onset.[188] Interestingly, similar associations have been reported between elevated serum levels of glial fibrillary acidic protein (GFAP)[189] and NMOSD, in which higher GFAP levels were correlated with greater disability and shorter time to relapse.[190]

Preventative treatment

Evolution of new technologies such as single-cell RNA sequencing has shed light on impairments to immune tolerance checkpoints that result in CNS autoreactivity (reviewed in Zou *et al*.[150]). Delivery of mRNA to lymphoid tissues in order to mimic and correct peripheral tolerance mechanisms has recently been demonstrated in an EAE mouse model.[191] In this study, vaccination using MOG peptide-encoding mRNA enabled the expansion of MOG-specific Foxp3$^+$ Treg cells and prevented the development and worsening of symptoms in MOG-induced EAE mice.[191] Single-cell RNA sequencing revealed that the expansion of effector Tregs played a significant role in suppressing proinflammatory Th1 and Th17 cells that would otherwise cause disease. Further, the importance of PD-1 and CTLA-4, which are inhibitory receptors on activated T cells, were emphasised when blockade of these receptors abolished the protective effect of MOG mRNA vaccination. Overall, the study demonstrated the first instance of a protective mRNA vaccine in an autoimmune disease, and showed that pathogenic T cells are inhibited rather than deleted and were reliant on PD-1 and CTLA-4 signalling.

CONCLUSION

In summary, MS, NMOSD and MOGAD can present with similar and often overlapping clinical and radiological characteristics that have made the differential diagnoses of these disorders challenging. The discovery of AQP4 Ab and MOG Ab has become essential in the diagnoses of NMOSD and MOGAD, respectively. Remarkably, despite expression of these autoantigens on distinct cell types of the CNS with heterogeneous pathologies, their immunopathogenic mechanisms lead to similar clinical features. Although the pathogenic role of AQP4 Ab has been more thoroughly investigated, evidence of MOG Ab pathogenicity is emerging. While current focus lies on the autoantibodies in NMOSD and MOGAD, there remains a need to clarify the contribution of T cells in pathogenesis. Although extensive research in MS disease models has demonstrated a primary pathogenic role of CD4$^+$ T cells, B cell and antibody

involvement in MS is being investigated, with a present demand to define patient subgroups in MS with regard to specific autoantigens. Along with associations to environmental factors such as infection, vitamin D and UV exposure, advancing research in the contribution of the gut microbiome provides a potential avenue for novel therapeutic interventions and for modifiable factors involved in brain health. As immunosuppressive and immunomodulatory therapies differ in efficacy across these disorders, a deeper understanding of the aetiology and pathogenic mediators of disease is essential to determine targeted therapeutic approaches to improve treatment decision-making and patient outcomes.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Joseph A Lopez: Conceptualization; Writing-original draft; Writing-review & editing. **Martina Denkova:** Writing-original draft; Writing-review & editing. **Sudarshini Ramanathan:** Writing-review & editing. **Russell C Dale:** Writing-review & editing. **Fabienne Brilot:** Conceptualization; Funding acquisition; Writing-original draft; Writing-review & editing.

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