Comparative immunopathogenesis of acute disseminated encephalomyelitis, neuromyelitis optica, and multiple sclerosis

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Purpose of review

Advanced immunopathological techniques hold promise for more precise diagnosis of idiopathic demyelinating diseases of the central nervous system. We review recent progress in differentiating and understanding the disease mechanisms of acute disseminated encephalomyelitis, neuromyelitis optica, and classical multiple sclerosis.

Recent findings

Four distinct immunopathological patterns have been described in multiple sclerosis patients, potentially implicating different inflammatory, demyelinating, and apoptotic mechanisms. A specific serum biomarker, neuromyelitis optica immunoglobulin G, is strongly associated with neuromyelitis optica and identifies patients with severe optic nerve and spinal cord lesions with specific pathological features such as eosinophilic and neutrophilic inflammatory infiltrates, necrosis, vascular hyalinization, and extensive vasculocentric immunoglobulin and complement deposition. This biomarker targets the water channel aquaporin-4, which is lost in neuromyelitis optica lesions. Acute disseminated encephalomyelitis still has no validated clinical diagnostic criteria but its perivenous pathological findings distinguish it from multiple sclerosis and neuromyelitis optica.

Summary

The clinically heterogeneous group of idiopathic inflammatory demyelinating diseases of the central nervous system is characterized by several immunopathological patterns that suggest the involvement of diverse pathogenic effector mechanisms. Future advances in experimental pathology, immunology, molecular genetics, and neuroimaging, as well as the discovery of specific biomarkers, will more precisely define these disorders and lead to better targeted therapies.

Keywords

acute disseminated encephalomyelitis, immunopathology, multiple sclerosis, neuromyelitis optica, pathogenesis

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Abbreviations

ADEM	acute disseminated encephalomyelitis
CNS	central nervous system
CSF	cerebrospinal fluid
EAE	experimental allergic encephalomyelitis
IL	interleukin
MAG	myelin-associated glycoprotein
MHC	major histocompatibility complex
MS	multiple sclerosis
NMO	neuromyelitis optica
OSE	opticospinal experimental allergic encephalomyelitis

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Introduction

The inflammatory demyelinating diseases of the central nervous system (CNS) are clinically heterogeneous with respect to their mode of presentation, clinical severity, rate of progression, and prognosis [1]. They are often grouped together under the umbrella term of 'multiple sclerosis' (MS). There is increasing evidence, however, that clinically recognizable syndromes, such as acute disseminated encephalomyelitis (ADEM) and neuromyelitis optica (NMO), are associated with distinct immunopathological features. Herein, we review the clinical and pathologic features that differentiate ADEM, NMO, and MS, and discuss recent advances in understanding the immunopathogenesis of each of these disorders.

Clinical diagnosis

The inflammatory demyelinating syndromes of ADEM, NMO, and MS are typically diagnosed on the basis of presenting clinical symptoms and signs, neuroimaging features, laboratory characteristics, and clinical course, especially the tendency to relapse. Comparative features are summarized in Table 1; however, it is important to note that no single clinical, neuroimaging, or cerebrospinal fluid (CSF) feature defines a disorder with absolute certainty.

Classical MS is highly variable in clinical presentation and is usually a relapsing disease [2]. White matter lesions localize to periventricular brain regions and those affecting the spinal cord are usually less than one vertebral segment in length [3,4]. Spinal fluid examination reveals a normal cell count or only a mild lymphocytic pleocytosis, and oligoclonal bands are present in 85–90% of confirmed cases.

Table 1 Comparison of the clinical, laboratory, and imaging features of multiple sclerosis (MS), neuromyelitis optica (NMO) and acute disseminated encephalomyelitis (ADEM)

Characteristic	MS	NMO	ADEM
Antecedent infection/immunization	Variable (may trigger relapse)	Absent	Typical
Age	Uncommon in children and >50 years; median = 29 years	Any; median = 39 years	Children and adults
Gender (F : M)	2 : 1	Up to 9 : 1	1 : 1.2
Clinical presentation	Usually monosymptomatic	Usually monosymptomatic; sometimes simultaneous myelitis and optic neuritis	Polysymptomatic
Typical attack severity	Mild to moderate	Moderate to severe	Moderate to severe
Typical attack-related impairment	None to mild	Moderate to severe	Mild to moderate
Clinical course	85% relapsing with most developing secondary progression, 15% primary progressive	>85% relapsing	Monophasic; rare 'multiphasic' or 'relapsing' ADEM
CSF cell count and differential	<50 WBCs; lymphocytes	Any; lymphocytes, sometimes PMNs	>50 WBCs; lymphocytes
CSF oligoclonal bands	85%	30%	Absent
Brain MRI lesion size, distribution, gadolinium enhancement	Small to medium; asymmetric, periventricular; variable enhancement	None/punctate; subcortical, increase with time; 10% meet MS criteria; less than 10% hypothalamic/ thalamic/periependymal	Larger, fairly symmetric and subcortical
Brain MRI gadolinium enhancement	Variable	None	Relatively uniform
Spinal cord MRI	Short lesions (up to two vertebral segments)	Longitudinally extensive (more than three vertebral segments)	Variable

CSF, cerebrospinal fluid; WBC, white blood cell; PMN, polymorphonuclear cell.

NMO has become a rigorously defined clinical entity with diagnosis strengthened by a highly specific serum biomarker, NMO-immunoglobulin G (IgG), which targets the water channel aquaporin-4 [5,6,7••]. NMO is recognized by its propensity to cause severe optic neuritis and 'longitudinally extensive' transverse myelitis (associated with a spinal cord MRI lesion spanning three or more vertebral segments) to the relative exclusion of other CNS regions. The disorder is typically relapsing [8••,9•], brain MRI is often normal at onset but accrues white matter lesions over time (sometimes mimicking classic MS), and the CSF may show a prominent neutrophilic pleocytosis and usually lacks oligoclonal bands.

The prevailing concept of the ADEM syndrome, which may be more confidently diagnosed in children, is that of a monophasic disorder characterized by a multifocal clinical presentation (often following an infection or vaccination), meningoencephalitic symptoms and signs including encephalopathy, cerebrospinal fluid pleocytosis without the presence of oligoclonal bands, and MRI lesions involving deep grey and cortical structures as well as the white matter [10]. Importantly, there is no validated clinical definition of ADEM, with most recent case series describing arbitrary clinical and imaging features. Furthermore, reports of multiphasic or recurrent forms of ADEM serve to complicate the nosology of demyelinating diseases by failing to convincingly distinguish these disorders from classical MS [11–13]. Even in childhood, cases of ADEM frequently evolve into a disorder highly consistent with relapsing–remitting MS [14,15].

Immunopathogenesis of multiple sclerosis

Key pathological features of MS, NMO, and ADEM are summarized in Table 2. The chronic inactive MS plaque is a sharply demarcated hypocellular lesion containing gliosis, variable axonal loss, reduced density of oligodendrocytes, variable amounts of inflammation (often perivascular) and evidence for remyelination, but without evidence of active demyelination [16•]. Active inflammatory demyelinating lesions characteristically show perivascular inflammation of variable degree together with lipid-laden macrophages and large reactive astrocytes. Although this background inflammation containing T lymphocytes and macrophages consistently underlies active MS lesions, evaluation of the earliest lesions from biopsy or autopsy material demonstrates significant pathological heterogeneity classifiable into four distinct patterns [17,18]. Pattern I refers to focal demyelinated lesions associated with macrophage and T lymphocyte infiltration. Pattern II includes additional features such as immunoglobulin deposition and complement activation at sites of active myelin breakdown. Both patterns are associated with loss of all myelin-related proteins, lesions centered on blood vessels, sharp plaque borders, and extensive remyelination. Pattern III lesions are also inflammatory but have ill-defined plaque borders, and often demonstrate myelin sparing around blood vessels. These lesions are characterized by a selective loss of myelin-associated glycoprotein (MAG), reduction in oligodendrocyte density, oligodendrocyte apoptosis, and minimal remyelination. The selective loss of MAG is interpreted as evidence for a dying-back oligodendrogliopathy, since MAG localizes to the most distal extension of the oligodendrocyte cell body. Pattern IV lesions show

Table 2 Pathologic features of multiple sclerosis (MS), neuromyelitis optica (NMO) and acute disseminated encephalomyelitis (ADEM)

Characteristic	MS	NMO	ADEM
Lesion number/location	Variable number; white >> grey matter of brain, optic nerves and spinal cord	Usually few; predilection for optic nerves and spinal cord grey and white matter (longitudinally extensive), variable brain lesions	Multifocal/diffuse; white and grey matter of brain, optic nerves, and spinal cord
Lesion age	Heterogeneous	Heterogeneous	Uniform
Perivascular infiltrates	Variable, perivenular	Scant, variable	Variable
Infiltrate cell types	Macrophage > lymphocyte; CD8+ > CD4+	Macrophage > lymphocyte; PMNs, including eosinophils may be present	Macrophages and lymphocytes
Perivascular IgG and complement	Confluent and extensive	Confluent and extensive	Limited and perivenular
Character and degree of demyelination	Variable, mild	Present	Present
Extent of acute axonal injury	Variable, usually mild	Severe	Minimal

PMN, polymorphonuclear cell; IgG, immunoglobulin G.

evidence of nonapoptotic oligodendroglial death in the adjacent normal-appearing periplaque white matter, possibly owing to metabolic or toxic factors, but the responsible mechanisms are not known. Overall, all active lesions from a given patient adhere to one lesional classification suggesting inter-individual, but not intra-individual, heterogeneity in demyelinating mechanisms in MS. Recent data suggest that biopsy-evaluated patients, despite their severe or atypical disease presentation, have MRI features and a subsequent clinical course similar to that of other MS patients [19].

The immunopathogenetic hypotheses about MS must account for the inflammatory CNS lesions, the later development of secondary progressive disease, and the lesional heterogeneity outlined above. It is postulated that several elements of the immune response in MS are governed by activated helper T-cell subsets, termed Th1 [which produce mainly proinflammatory cytokines such as interleukin (IL)-2, tumor necrosis factor-α (TNFα), and interferon-γ (INFγ)] and Th2 (producing mainly antiinflammatory cytokines, such as IL-4, IL-5, IL-6, IL-10, and IL-13) [20]. The initial step in development of an inflammatory MS lesion is considered to be activation of circulating autoreactive T lymphocytes by factors such as infection, superantigen stimulation, or effects of reactive metabolites or metabolic stress. These activated T lymphocytes interact with endothelial surface integrins [e.g. very late antigen-4 (VLA-4)] to injure and breach the blood–brain barrier, with injury mediated in part through matrix metalloproteinases (MMPs), in particular, MMP-9. Upregulation of endothelial adhesion molecules [e.g. intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule (VCAM-1), and E-selectin] permits further ingress of pathogenic inflammatory cells. The trimolecular complex of the T-cell receptor, major histocompatibility complex (MHC) molecule, and the presented antigen serves to activate antigen-specific T cells. CD4+ T lymphocytes recognize antigens in association with MHC class II molecules and CD8+ T lymphocytes do so with MHC class I molecules; both interactions are assisted by costimulatory molecules such as CD40/CD40 ligand or B7-1 and B7-2/cytotoxic T-lymphocyte antigen-4. Once activated, CD4+ T lymphocytes in MS appear to develop a Th1-dominant profile with upregulation of IL-2, IFNγ, and TNFα. Their cytokines activate macrophages, which play a direct role in demyelination. Other factors contributing to myelin and axonal injury may include production of demyelinating antibodies, direct toxicity of proinflammatory cytokines, chemokines, and other soluble mediators, cytotoxic CD8+ T-lymphocyte/MHC class I-mediated injury, production of reactive oxygen and nitrogen species, excitotoxic glutaminergic mechanisms, or oligodendrocyte injury [16•,21•,22].

There is increasing interest in the role of humoral immunity in MS pathogenesis. Unknown elements of the CNS immune response lead to intrathecal clonal B-lymphocyte expansion with production of IgG detected as CSF oligoclonal banding. In MS lesions, antibodies and the C9neo terminal lytic component of the complement system are deposited along demyelinated segments and within macrophages [17,23]. The presence of dominant B-cell clonotypes in CSF and MS lesions supports an antigen-driven selection process [24,25]. Recently, B-cell-related cytokines such as tumor-necrosis factor ligand superfamily member 13B (BAFF) have been detected in MS lesions [26] and plasma blasts and plasma cells noted in CSF [27]. Furthermore, anti-myelin oligodendrocyte glycoprotein (MOG) antibodies have been detected in MS lesions [28] and patient serum, although the association of serum antibodies with clinical disease has been inconsistent [29,30]. In sum, the findings support potential important roles for a humoral response in MS pathogenesis but the specificity of the response has not been identified.

Attention is also being paid to the factors responsible for initiating and limiting CNS remyelination and repair and

the development of progressive disease in later stages of MS. Recent observations suggest important roles for the following substances or mechanisms in remyelination and repair: growth factors; chemokines; novel molecules such as neurite outgrowth inhibitor (Nogo) receptor-interacting protein 1, which influences axonal outgrowth and myelin repair [31]; the Jagged-Notch signaling pathway important for oligodendrocyte differentiation [32]; and oligodendrocyte recruitment and signaling mechanisms. One proposed model of the development of progressive MS summarizes the effects of early and recurrent inflammation, demyelination, oligodendrocyte loss, complement deposition, and local axonal loss, leading to perpetuation of abnormal local and regional microenvironments that result in eventual failure of neural, axonal and oligodendroglial trophic and structural mechanisms [33•].

The inciting antigen responsible for the putative autoimmune pathogenesis of MS has not been identified, leaving a substantial gap in the inferences that can be made from animal models, in-vitro experiments, and human blood, CSF, and pathological data. Other elements of the pathophysiological processes described above, however, are consistent with the therapeutic benefits of drugs with known select mechanisms of action. For example, β-interferons, which reduce relapse rate and severity, are potent MMP-9 inhibitors and may limit CNS T-lymphocyte infiltration and cytokine production [34]. Natalizumab, a powerful VLA-4 inhibitor, reduces clinical relapse rate and accumulation of MRI lesions [35,36••,37]. There may be a role for treatment of MS with rituximab, a chimeric human/murine anti-CD20 monoclonal antibody that selectively depletes B lymphocytes, because of the humoral immune involvement in MS pathogenesis. Current immunomodulatory therapies have modest impact on secondary progressive MS, indicating that they fail to influence the major pathways leading to progression or that those mechanisms have triggered irreversible injury [38]. Advances in understanding the very earliest disease pathways, especially the identification of responsible autoantigens, will increase the chances of greater therapeutic successes in the future.

Immunopathogenesis of neuromyelitis optica

Most data support a humoral basis for NMO pathogenesis, including associations with systemic autoimmune diseases and myasthenia gravis, therapeutic response to plasmapheresis, and immunological and immunopathological findings [39–41,42•,43•]. Severe inflammation and demyelination in optic nerve and longitudinally extensive spinal cord lesions is often accompanied by necrosis and cavitation [40]. Eosinophils and neutrophils may predominate in the inflammatory infiltrates of active NMO lesions [40,44] and this pattern may be associated with IL-17/IL-8 axis activation [45]. Penetrating spinal vessels are often irregularly thickened and hyalinized [40,46]. These features are not seen in classical MS. Active NMO lesions also exhibit immunoglobulin and complement deposition in a characteristic vasculocentric 'rim' and 'rosette' pattern that is quite distinct from the pattern of immune complex deposition along myelin sheaths and within macrophages observed in the 'pattern II' described in MS lesions [17,40,46].

The serum autoantibody marker NMO-IgG is about 73% sensitive and more than 90% specific for clinically defined NMO [6]. The biomarker selectively binds to the abluminal surface of microvessels, pia, subpia and Virchow-Robin sheaths in a pattern reminiscent of the distribution of immune complex deposition in NMO patients' spinal cord tissues. A clue to the identification of the NMO-IgG target antigen came with the recognition that NMO-IgG immunoreactivity also included renal distal collecting tubules and basolateral membranes of gastric mucosal epithelium, regions that contain substantial concentrations of the water channel protein aquaporin-4. Aquaporin-4 is the most abundant CNS water channel and is important for maintaining water homeostasis during stresses such as ischemia or inflammation [47,48]. Interestingly, it is not expressed in myelin or oligodendrocytes; rather, it is anchored by the dystroglycan protein complex within the plasma membrane of astrocytic foot processes facing microvessels and pia (the 'glia limitans') and in the basolateral domain of ependyma [48]. The regions of high aquaporin-4 density correspond to sites of intense NMO-IgG immunoreactivity. The antigenic specificity of aquaporin-4 was demonstrated in a series of experiments showing absence of this immunoreactivity in transgenic aquaporin-4-knockout mouse tissues and selective aquaporin-4 immunoprecipitation from an aquaporin-4-transfected cell line that coexpressed dystroglycan complex proteins that are related to aquaporin-4 [5]. MRI studies of NMO patients demonstrate that a specific lesional pattern colocalizes with aquaporin-4 distribution in the CNS, specifically in the regions of the hypothalamus and periependymal areas such as near the fourth ventricle [8••,9•]. Several groups have since replicated the strong and specific association of NMO-IgG/anti-AQP4 antibodies with both NMO and longitudinally extensive transverse myelitis [49–52].

It has not yet been proven that NMO-IgG causes NMO, but Lennon and colleagues [5] hypothesized that a small fraction of peripherally circulating aquaporin-4-specific IgG that gains entry to the CNS via a relatively susceptible or breached blood–brain barrier would immediately encounter aquaporin-4, resulting in complement activation, cross-linking of aquaporin-4, or both, thereby directly perturbing CNS water homeostasis [5]. This mechanism would also explain the lack of CSF

oligoclonal banding in NMO because intra-CNS clonal B-cell expansion would not necessarily occur in this peripherally driven process. Preliminary in-vitro studies have since shown that application of serum IgG derived from NMO patients to living aquaporin-4-transfected cells results in IgG binding to the extracellular domain, activation of the membranolytic complement cascade, and endocytotic downregulation of surface aquaporin-4 [53]. In addition, the 'rim' and 'rosette' immunoglobulin staining patterns in NMO pathology specimens correspond to regions of high aquaporin-4 expression in normal astrocytic endfeet. Unlike MS lesions, NMO lesions demonstrate a striking loss of aquaporin-4 [54•], independent of stage of demyelinating activity, necrosis, or site of CNS involvement [55]. Furthermore, a novel NMO lesion type in the spinal cord and medullary tegmentum with extension into the area postrema is characterized by aquaporin-4 loss, inflammation, edema, and intense vasculocentric immune complex deposition [55]. Collectively, these findings suggest that a complement-activating, anti- aquaporin-4 antibody (NMO-IgG) has the potential to cause at least some of the primary immunopathological features of NMO.

Future development of an animal model of aquaporin-4 autoimmunity is required to further investigate the possibility that NMO-IgG causes NMO. Although such a model has not yet been reported, recent work in the field of experimental allergic encephalomyelitis (EAE), a putative animal model of human CNS demyelinating disease, resulted in production of a mouse model with spontaneous autoimmune CNS demyelination with an optic-spinal NMO-like lesion distribution pattern. This model, termed opticospinal EAE (OSE) by one group [56•], may represent an important advance in how such topographically restricted pathological patterns are generated [57•]. Independent laboratories determined that double-transgenic mice expressing T and B-cell receptors that recognize MOG can develop spontaneous inflammation of the optic nerves, spinal cord, meninges, and parenchyma [56•,58•]. A mixture of Th1 and Th2 cytokines, including IFNγ, IL-5, and IL-17, were detected in affected tissues and cell cultures. The OSE model lacks certain characteristics of human NMO, including immunoglobulin and complement deposition within lesions, longitudinally extensive spinal cord lesions, and anti-aquaporin-4 antibodies [57•]. Nevertheless, OSE illustrates the ability of some B cells to act as antigen presenting cells. These findings may also demonstrate that several pathogenic pathways, potentially independent from aquaporin-4-related mechanisms, can generate relatively restricted optic-spinal disease. One human CSF microarray study has shown the potential for identifying other candidate autoantigens associated with the NMO phenotype [59•].

The discovery of NMO-IgG has allowed further inferences about the true scope of the clinical disease. Patients with Asian optic-spinal MS are NMO-IgG seropositive approximately as frequently as North American NMO patients and have pathological features similar to NMO, indicating the disorders may well be identical [6,60•,61•]. Furthermore, patients with systemic lupus erythematosus or Sjögren's syndrome are uniformly NMO-IgG seronegative unless they have the neurological NMO syndrome. In contrast, NMO patients frequently harbor multiple serum autoantibodies, including antinuclear antibody and extractable nuclear antigen (such as SSA and SSB), suggesting that in most instances NMO coexists with lupus or Sjögren's syndrome rather than occurring as a vasculitic complication of those systemic diseases.

Recent observations indicate that secondary progressive NMO is quite uncommon [62]. If occurrence of inflammatory relapses were a key mechanism in triggering a later degenerative process, one would expect an earlier and higher rate of conversion to secondary progressive disease in NMO and compared with MS owing to the severe and frequent nature of early relapses. These observations contribute to evidence that dissociates inflammatory relapses from degenerative progression in CNS demyelinating diseases.

Immunopathogenesis of acute disseminated encephalomyelitis

The immunopathogenesis of ADEM is the least well developed of the syndromes owing to the lack of a validated clinical disease definition. Autopsy studies dating from the 1920s describe a diffuse pattern of perivenular inflammation and demyelination affecting the brain and spinal cord after small pox vaccination or measles, mumps, and rubella vaccination or infection [63,64]. Similar cases were reported without a clear preceding infection or history of immunization. In recent years, few case reports document pathological findings in association with an ADEM diagnosis.

The distinct findings in pathologically confirmed cases of ADEM are 'sleeves' of demyelination that surround venules and are associated with significant inflammatory infiltrates dominated by macrophages [63]. These lesions are distributed throughout the brain and spinal cord and appear of similar histological age. The meninges (lymphocytes) and subpial regions (microglia) may also be inflamed. The lesions may be further differentiated from MS in that their margins are rather indistinct in contrast to the usual well demarcated leading edge of a demyelinating MS plaque [65,66]. Further studies of biopsy or autopsy specimens from patients studied with contemporary neuroimaging and CSF examination are required to determine whether this pathological pattern

underlies the monophasic, multiphasic, and relapsing ADEM syndromes reported in more recent literature [10,14,67].

The animal models of encephalomyelitis, especially EAE and Theiler murine encephalomyelitis, have long been utilized to make inferences about MS disease mechanisms but probably have greater relevance to ADEM [68•,69]. In EAE, animals are immunized with a combination of either homogenized CNS tissues or encephalitogenic myelin peptides with Freund adjuvant, resulting in a monophasic syndrome of motor weakness and incontinence associated with diffuse CNS inflammatory demyelination with a pattern most closely resembling human 'pattern I' active demyelinating MS lesions. EAE induced using MOG can result in a pathological pattern resembling human 'pattern II' pathology [70]. Another animal model, putatively mimicking postinfectious ADEM, is created by direct inoculation of genetically susceptible mice with Theiler murine encephalomyelitis virus, inducing widespread CNS inflammatory demyelination [71]. Translation of studies of these models to human ADEM indicates that mechanisms such as molecular mimicry or direct CNS infection with a secondary inflammatory cascade may play leading roles in ADEM pathogenesis. Introduction of pathogens to the CNS may result in tissue damage with leaking of autoantigens into the systemic circulation where they are processed by peripheral immune mechanisms, leading to a self-directed autoimmune attack against the CNS driven by encephalitogenic T cells. The molecular mimicry hypothesis suggests that structural similarities between the pathogen and the host are sufficient to induce T-cell activation but not sufficient to induce tolerance [72]. Activated T cells (and secondarily activated B cells) may then reactivate when encountering local antigen presenting cells while patrolling the CNS. ADEM associated with vaccines may be related to contamination with myelin antigens from CNS culture tissue [73,74]. Recent data suggest that Th1 and Th2-related chemokines are produced in ADEM and MS but that relatively selective upregulation of chemokines active on neutrophils and Th2 cells may occur in ADEM [75,76]. Preliminary studies also support involvement of MMP-9 and ICAM-1 in the ADEM immune response [77•,78].

Conclusion

Improvements in neuroimaging and laboratory techniques, especially immunopathology and development of specific biomarkers, promise to further clarify the nosology of CNS demyelinating diseases. The momentum of recent research suggests that NMO may be the first of the disorders to be confirmed as a distinct clinical and immunopathological entity with a known cause. Much more work is needed in the area of ADEM, where clinical diagnosis and lack of readily available CNS pathology hinders addressing important issues, such as the clinical spectrum of disorders associated with perivenular encephalomyelitis and identifying the underlying mechanisms of 'multiphasic' and 'relapsing' ADEM. Clinical and neuroimaging phenotypes are likely to overlap amongst these disorders regardless of their working definitions, but careful clinicopathological correlations should help overcome some of these challenges.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 379).

1 Kantarci OH, Weinshenker BG. Natural history of multiple sclerosis. Neurol Clin 2005; 23:17–38.

2 Polman CH, Reingold SC, Edan G, *et al.* Diagnostic criteria for multiple sclerosis: 2005 revisions to the 'McDonald criteria'. Ann Neurol 2005; 58: 840–846.

3 Bot JC, Barkhof F, Polman CH, *et al.* Spinal cord abnormalities in recently diagnosed MS patients: added value of spinal MRI examination. Neurology 2004; 62:226–233.

4 Frohman EM, Goodin DS, Calabresi PA, *et al.* The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 2003; 61:602–611.

5 Lennon VA, Kryzer TJ, Pittock SJ, *et al.* IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med 2005; 202:473–477.

6 Lennon VA, Wingerchuk DM, Kryzer TJ, *et al.* A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 2004; 364:2106–2112.

7 •• Wingerchuk DM, Lennon VA, Pittock SJ, *et al.* Revised diagnostic criteria for neuromyelitis optica. Neurology 2006; 66:1485–1489.
The authors used a quantitative approach to derive new diagnostic criteria for NMO. The criteria are 99% sensitive and 90% specific for distinguishing NMO from MS with an optic-spinal presentation.

8 •• Pittock SJ, Lennon VA, Krecke K, *et al.* Brain abnormalities in neuromyelitis optica. Arch Neurol 2006; 63:390–396.
This paper describes the spectrum of brain MRI findings in NMO, emphasizing that brain lesions are compatible with the diagnosis and that up to 10% of cases will meet MS MRI criteria.

9 • Pittock SJ, Weinshenker BG, Lucchinetti CF, *et al.* Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol 2006; 63:964–968.
A small number of patients with NMO have lesions involving the hypothalamic, thalamic, and periependymal regions which correlate with areas of known high aquaporin-4 density.

10 Menge T, Hemmer B, Nessler S, *et al.* Acute disseminated encephalomyelitis: an update. Arch Neurol 2005; 62:1673–1680.

11 Dale RC, Branson JA. Acute disseminated encephalomyelitis or multiple sclerosis: can the initial presentation help in establishing a correct diagnosis? Arch Dis Child 2005; 90:636–639.

12 Wingerchuk DM. The clinical course of acute disseminated encephalomyelitis. Neurol Res 2006; 28:341–347.

13 Wingerchuk DM. Acute disseminated encephalomyelitis: distinction from multiple sclerosis and treatment issues. Adv Neurol 2006; 98:303–318.

14 Leake JA, Albani S, Kao AS, *et al.* Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. Pediatr Infect Dis J 2004; 23:756–764.

15 Mikaeloff Y, Suissa S, Vallee L, *et al.* First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. J Pediatr 2004; 144:246–252.

16 • Frohman EM, Racke MK, Raine CS. Multiple sclerosis: the plaque and its pathogenesis. N Engl J Med 2006; 354:942–955.
A timely update of the known pathogenesis of MS lesions and delineation of unanswered questions.

17 Lucchinetti C, Bruck W, Parisi J, *et al.* Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000; 47:707–717.

18 Ludwin SK. The pathogenesis of multiple sclerosis: relating human pathology to experimental studies. J Neuropathol Exp Neurol 2006; 65:305–318.

19 Pittock SJ, McClelland RL, Achenbach SJ, *et al.* Clinical course, pathological correlations, and outcome of biopsy proved inflammatory demyelinating disease. J Neurol Neurosurg Psychiatry 2005; 76:1693–1697.

20 Cannella B, Raine CS. The adhesion molecule and cytokine profile of multiple sclerosis lesions. Ann Neurol 1995; 37:424–435.

21 • Charo IF, Ransohoff RM. The many roles of chemokines and chemokine receptors in inflammation. N Engl J Med 2006; 354:610–621.
This wide-ranging summary provides an excellent account of chemokines research.

22 Hemmer B, Nessler S, Zhou D, *et al.* Immunopathogenesis and immunotherapy of multiple sclerosis. Nat Clin Pract Neurol 2006; 2:201–211.

23 Storch MK, Piddlesden S, Haltia M, *et al.* Multiple sclerosis: in situ evidence for antibody- and complement-mediated demyelination. Ann Neurol 1998; 43:465–471.

24 Baranzini SE, Jeong MC, Butunoi C, *et al.* B cell repertoire diversity and clonal expansion in multiple sclerosis brain lesions. J Immunol 1999; 163:5133–5144.

25 Colombo M, Dono M, Gazzola P, *et al.* Accumulation of clonally related B lymphocytes in the cerebrospinal fluid of multiple sclerosis patients. J Immunol 2000; 164:2782–2789.

26 Krumbholz M, Theil D, Derfuss T, *et al.* BAFF is produced by astrocytes and up-regulated in multiple sclerosis lesions and primary central nervous system lymphoma. J Exp Med 2005; 201:195–200.

27 Cepok S, Rosche B, Grummel V, *et al.* Short-lived plasma blasts are the main B cell effector subset during the course of multiple sclerosis. Brain 2005; 128 (Pt 7):1667–1676.

28 Genain CP, Cannella B, Hauser SL, Raine CS. Identification of autoantibodies associated with myelin damage in multiple sclerosis. Nat Med 1999; 5:170–175.

29 Berger T, Rubner P, Schautzer F, *et al.* Antimyelin antibodies as a predictor of clinically definite multiple sclerosis after a first demyelinating event. N Engl J Med 2003; 349:139–145.

30 Reindl M, Khalil M, Berger T. Antibodies as biological markers for pathophysiological processes in MS. J Neuroimmunol 2006; 180 (1–2):50–62.

31 Wang KC, Koprivica V, Kim JA, *et al.* Oligodendrocyte-myelin glycoprotein is a Nogo receptor ligand that inhibits neurite outgrowth. Nature 2002; 417:941–944.

32 John GR, Shankar SL, Shafit-Zagardo B, *et al.* Multiple sclerosis: re-expression of a developmental pathway that restricts oligodendrocyte maturation. Nat Med 2002; 8:1115–1121.

33 • Imitola J, Chitnis T, Khoury SJ. Insights into the molecular pathogenesis of progression in multiple sclerosis: potential implications for future therapies. Arch Neurol 2006; 63:25–33.
The authors propose a model of how MS evolves into a progressive disorder.

34 Yong VW, Chabot S, Stuve O, Williams G. Interferon beta in the treatment of multiple sclerosis: mechanisms of action. Neurology 1998; 51:682–689.

35 Miller DH, Khan OA, Sheremata WA, *et al.* A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2003; 348:15–23.

36 •• Polman CH, O'Connor PW, Havrdova E, *et al.* A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354:899–910.
This landmark trial demonstrated that integrin inhibition could result in efficient control of brain MRI activity of MS and reduce clinical relapses and disability.

37 Rice GP, Hartung HP, Calabresi PA. Antialpha4 integrin therapy for multiple sclerosis: mechanisms and rationale. Neurology 2005; 64:1336–1342.

38 Kappos L, Weinshenker B, Pozzilli C, *et al.* Interferon beta-1b in secondary progressive MS: a combined analysis of the two trials. Neurology 2004; 63:1779–1787.

39 Keegan M, Pineda AA, McClelland RL, *et al.* Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology 2002; 58:143–146.

40 Lucchinetti CF, Mandler RN, McGavern D, *et al.* A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. Brain 2002; 125 (Pt 7):1450–1461.

41 Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999; 53:1107–1114.

42 • Furukawa Y, Yoshikawa H, Yachie A, Yamada M. Neuromyelitis optica associated with myasthenia gravis: characteristic phenotype in Japanese population. Eur J Neurol 2006; 13:655–658.
This paper contributes to the clinical association of NMO with other humoral autoimmune diseases.

43 • Kister I, Gulati S, Boz C, *et al.* Neuromyelitis optica in patients with myasthenia gravis who underwent thymectomy. Arch Neurol 2006; 63:851–856.
This paper contributes to the clinical association of NMO with other humoral autoimmune diseases.

44 Correale J, Fiol M. Activation of humoral immunity and eosinophils in neuromyelitis optica. Neurology 2004; 63:2363–2370.

45 Ishizu T, Osoegawa M, Mei FJ, *et al.* Intrathecal activation of the IL-17/IL-8 axis in opticospinal multiple sclerosis. Brain 2005; 128 (Pt 5):988–1002.

46 Lefkowitz D, Angelo JN. Neuromyelitis optica with unusual vascular changes. Arch Neurol 1984; 41:1103–1105.

47 Agre P, Kozono D. Aquaporin water channels: molecular mechanisms for human diseases. FEBS Lett 2003; 555:72–78.

48 Amiry-Moghaddam M, Ottersen OP. The molecular basis of water transport in the brain. Nat Rev Neurosci 2003; 4:991–1001.

49 Jarius S, Friedemann P, Aktas O, *et al.* Antibodies to aquaporin-4 in the diagnosis and differential diagnosis of neuromyelitis optica. In: Program and Abstracts of the 22nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS); 2006; Madrid, Spain.

50 Littleton ET, Jacob A, Boggild M, Palace J. An audit of the diagnostic usefulness of the NMO-IgG assay for neuromyelitis optica. Mult Scler 2006; 12:S156.

51 Marignier R, De Seze J, Durand-Dubief F, *et al.* NMO-IgG: a French experience. Mult Scler 2006; 12:S4.

52 Zuliani L, Blanco Y, Tavolato B, *et al.* Neuromyelitis optica autoantibody (NMO-IgG) in patients with suspected NMO or limited forms of NMO. Mult Scler 2006; 12:S155–S156.

53 Lennon VA. Changing concepts in CNS demyelinating disorders: autoimmune water channelopathies. In: Program and abstracts of the American Academy of Neurology 58th Annual Meeting; 1–8 April 2006; San Diego, California. Plenary session.

54 • Misu T, Fujihara K, Nakamura M, *et al.* Loss of aquaporin-4 in active perivascular lesions in neuromyelitis optica: a case report. Tohoku J Exp Med 2006; 209:269–275.
This paper describes loss of aquaporin-4 in NMO lesions with relative sparing in MS lesions.

55 Roemer SF, Parisi JE, Lennon VA, *et al.* Pattern specific loss of aquaporin 4 immunoreactivity distinguishes neuromyelitis optica from multiple sclerosis. Brain (in press).

56 • Krishnamoorthy G, Lassmann H, Wekerle H, Holz A. Spontaneous opticospinal encephalomyelitis in a double-transgenic mouse model of autoimmune T cell/B cell cooperation. J Clin Invest 2006; 116:2385–2392.
Describes the development of an NMO-like EAE model and the accompanying editorial nicely outlines the relevance of the model and comparisons with human NMO.

57 • Ransohoff RM. A mighty mouse: building a better model of multiple sclerosis. J Clin Invest 2006; 116:2313–2316.
Describes the development of an NMO-like EAE model and the accompanying editorial nicely outlines the relevance of the model and comparisons with human NMO.

58 • Bettelli E, Baeten D, Jager A, *et al.* Myelin oligodendrocyte glycoprotein-specific T and B cells cooperate to induce a Devic-like disease in mice. J Clin Invest 2006; 116:2393–2402.
Describes the development of an NMO-like EAE model and the accompanying editorial nicely outlines the relevance of the model and comparisons with human NMO.

59 • Lalive PH, Menge T, Barman I, *et al.* Identification of new serum autoantibodies in neuromyelitis optica using protein microarrays. Neurology 2006; 67:176–177.
About 25% of patients with NMO are NMO-IgG seronegative. This paper describes use of microarrays to identify other potential candidate autoantibodies associated with NMO.

60 • Nakashima I, Fujihara K, Miyazawa I, *et al.* Clinical and MRI features of Japanese patients with multiple sclerosis positive for NMO-IgG. J Neurol Neurosurg Psychiatry 2006; 77:1073–1075.
This paper confirmed both the association of NMO-IgG with severe optic-spinal demyelinating disease in Asians and the fact that brain MRI lesions do not preclude the diagnosis.

61 • Weinshenker BG, Wingerchuk DM, Nakashima I, *et al.* OSMS is NMO, but not MS: proven clinically and pathologically. Lancet Neurol 2006; 5:110–111.
A succinct account of the case-supporting identity of NMO and Asian optic-spinal MS.

62 Wingerchuk DM, Pittock SJ, Lucchinetti CF, *et al.* A secondary progressive clinical course is uncommon in neuromyelitis optica. Neurology (in press).

63 Hart MN, Earle KM. Haemorrhagic and perivenous encephalitis: a clinical–pathological review of 38 cases. J Neurol Neurosurg Psychiatry 1975; 38:585–591.

64 Prineas JW, McDonald WI, Franklin RJM. Demyelinating diseases. 7th ed London: Arnold; 2002.

65 Oppenheimer DR. Demyelinating diseases. London: Edward Arnold; 1976.

66 van Bogaert L. Postinfectious encephalomyelitis and multiple sclerosis: the significance of perivenous encephalomyelitis. J Neuropathol Exp Neurol 1950; 9:219–249.

67 Dale RC, de Sousa C, Chong WK, *et al.* Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain 2000; 123 (Pt 12):2407–2422.

68 • Gold R, Linington C, Lassmann H. Understanding pathogenesis and therapy of multiple sclerosis via animal models: 70 years of merits and culprits in experimental autoimmune encephalomyelitis research. Brain 2006; 129 (Pt 8): 1953–1971.
A comprehensive account of what has been gleaned from several decades of EAE research.

69 Sriram S, Steiner I. Experimental allergic encephalomyelitis: a misleading model of multiple sclerosis. Ann Neurol 2005; 58:939–945.

70 Storch MK, Stefferl A, Brehm U, *et al.* Autoimmunity to myelin oligodendrocyte glycoprotein in rats mimics the spectrum of multiple sclerosis pathology. Brain Pathol 1998; 8:681–694.

71 Fuller KG, Olson JK, Howard LM, *et al.* Mouse models of multiple sclerosis: experimental autoimmune encephalomyelitis and Theiler's virus-induced demyelinating disease. Methods Mol Med 2004; 102:339–361.

72 Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin basic protein and virus: mechanism for autoimmunity. Science 1985; 230:1043–1045.

73 Hemachudha T, Griffin DE, Giffels JJ, *et al.* Myelin basic protein as an encephalitogen in encephalomyelitis and polyneuritis following rabies vaccination. N Engl J Med 1987; 316:369–374.

74 Plesner AM, Arlien-Soborg P, Herning M. Neurological complications to vaccination against Japanese encephalitis. Eur J Neurol 1998; 5:479–485.

75 Franciotta D, Zardini E, Ravaglia S, *et al.* Cytokines and chemokines in cerebrospinal fluid and serum of adult patients with acute disseminated encephalomyelitis. J Neurol Sci 2006; 247:202–207.

76 Ishizu T, Minohara M, Ichiyama T, *et al.* CSF cytokine and chemokine profiles in acute disseminated encephalomyelitis. J Neuroimmunol 2006; 175 (1–2): 52–58.

77 • Ichiyama T, Kajimoto M, Suenaga N, *et al.* Serum levels of matrix metalloproteinase-9 and its tissue inhibitor (TIMP-1) in acute disseminated encephalomyelitis. J Neuroimmunol 2006; 172 (1–2):182–186.
The near future will see more studies like this: comparisons of new immunologic adrances amongst cases defined clinically as MS or ADEM.

78 Martino D, Branson JA, Church AJ, *et al.* Soluble adhesion molecules in acute disseminated encephalomyelitis. Pediatr Neurol 2005; 33:255–258.