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Update on pathology of central nervous system inflammatory demyelinating diseases

Alicja Kalinowska-Łyszczarz[1], Yong Guo[2], Claudia F. Lucchinetti[2]

[1]Department of Neurology, Division of Neurochemistry and Neuropathology, Poznan University of Medical Sciences, Poznan, Poland

[2]Department of Neurology, Mayo Clinic, Rochester, Minnesota, United States

ABSTRACT

Multiple sclerosis (MS) is by far the most common central nervous system inflammatory demyelinating disease (CNS-IDD). It is diagnosed according to detailed criteria based on clinical definitions, magnetic resonance imaging (MRI) and cerebrospinal fluid findings. However, in rare instances, atypical syndromes associated with CNS demyelination, such as unusual MRI findings or poor response to standard treatment, may eventually necessitate a CNS biopsy with neuropathological examination.

Pathology remains the gold standard in the differentiation of atypical CNS-IDDs, the recognition of which is essential for establishing the correct prognosis and optimal therapy. However, one must bear in mind that between different CNS-IDDs there are still overlapping features, even in the pathology.

In this review, we compare and highlight contrasts within a spectrum of CNS-IDDs from the neuropathological perspective. We characterise pathological hallmarks of active *vs.* chronic multiple sclerosis. Also, we define differences in the pathology of MS, acute disseminated encephalomyelitis (ADEM), aquaporin 4-IgG positive (AQP4-IgG+) neuromyelitis optica spectrum disorder (NMOsd), and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD).

Detailed description of the particular CNS-IDD pathology is crucial on an individual patient level (when clinically justified in atypical cases) but also from a broader perspective i.e. to advance our understanding of the complex disease mechanisms. Recent immunobiological and pathological discoveries have led to the description of novel inflammatory CNS disorders that were previously classified as rare MS variants, such as NMOsd and MOGAD. Multiple sclerosis remains an umbrella diagnosis, as there is profound heterogeneity between patients. Advances in neuropathology research are likely to disentangle and define further CNS-IDDs that used to be categorised as multiple sclerosis.

Key words: multiple sclerosis, acute disseminated encephalomyelitis, neuromyelitis optica spectrum disorder, myelin oligodendrocyte glycoprotein antibody-associated disease, neuropathology, central nervous system demyelination

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Introduction

Although rarely required in multiple sclerosis (MS) patients, neuropathological studies have been crucial in progressing the understanding, differentiation, and therapy of central nervous system inflammatory demyelinating diseases (CNS-IDDs) [1]. MS is an umbrella diagnosis applied to patients with clinical symptoms suggestive of inflammatory demyelinating disease AND typical magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) findings, all of which allow it to be established that the pathological process is indeed disseminated in time and space [2, 3].

The profound heterogeneity of MS in its clinical course, radiographic presentation and response to therapy has led to the distinction of several MS variants (i.e. Marburg variant or Baló concentric sclerosis alongside tumefactive demyelination)

Address for correspondence: Alicja Kalinowska-Łyszczarz, Department of Neurology, Division of Neurochemistry and Neuropathology, Poznan University of Medical Sciences, 49 Przybyszewskiego St., 60-355 Poznan, Poland; e-mail: akalinowskalyszczarz@ump.edu.pl

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and neuromyelitis optica spectrum disorders (NMOsd), with the latter turning out to be an antibody-mediated astrocytopathy [4], and not in fact a primarily demyelinating disorder. Although anti-aquaporin 4 antibodies (AQP4-IgG, NMO-IgG), directed against an astrocytic water channel protein have been found to be pathogenic in NMOsd and became a useful biomarker, subsequently a subset of seronegative patients has emerged.

Some of these patients were found to be positive for antibodies against myelin oligodendrocyte glycoprotein (anti-MOG IgG) [5, 6]. In fact, anti-MOG antibodies are not specific for NMOsd but have also been identified in up to 64% of paediatric patients with acute disseminated encephalomyelopathy (ADEM) [7]. Despite several clinical, radiographic, and pathogenic overlaps with MS and NMOsd, MOG antibody-associated disease (MOGAD) has been distinguished as a separate diagnosis [8, 9], presenting with a different frequency among adults and children as optic neuritis, transverse myelitis, brainstem demyelination or ADEM, the latter much less common in adults (< 8%) [10]. Importantly, it has been shown that patients initially diagnosed as having ADEM, estimated to be 8.5% of children [11, 12] and 35% of adults [13] within a one year observation, were eventually given the diagnosis of MS. The apparent clinical and radiological overlap between different CNS-IDDs is verified and challenged by the pathological studies which demonstrate clear discriminating features between the overlapping phenotypes.

The pathological heterogeneity is further underlined by the fact that four different immunopatterns of early active plaques have been described among MS patients [14] (see Fig. 1). These immunopatterns have been shown to differentially respond to acute treatment, with relapses in patients with humoral pathology-dependent type II lesions responding better to plasma exchange than other immunopatterns [15]. On the other hand, relapse-related disability seems higher in patients with immunopattern III lesions [16]. However, in the long term, patients with biopsy-established immunopathology appear to have similar outcomes, regardless of their immunopattern [16]. The heterogeneity of the active disease, with differences in immunopathology, clinical (relapse severity and frequency, relapse-related residual disability) and radiographic (MRI-obtained total lesion count, individual and total lesion volume, spinal cord involvement, measures of global and localized CNS atrophy) features, are in opposition to a relatively unified progressive MS phenotype, which suggests convergence into a final common pathway related to the chronically denuded axon [16].

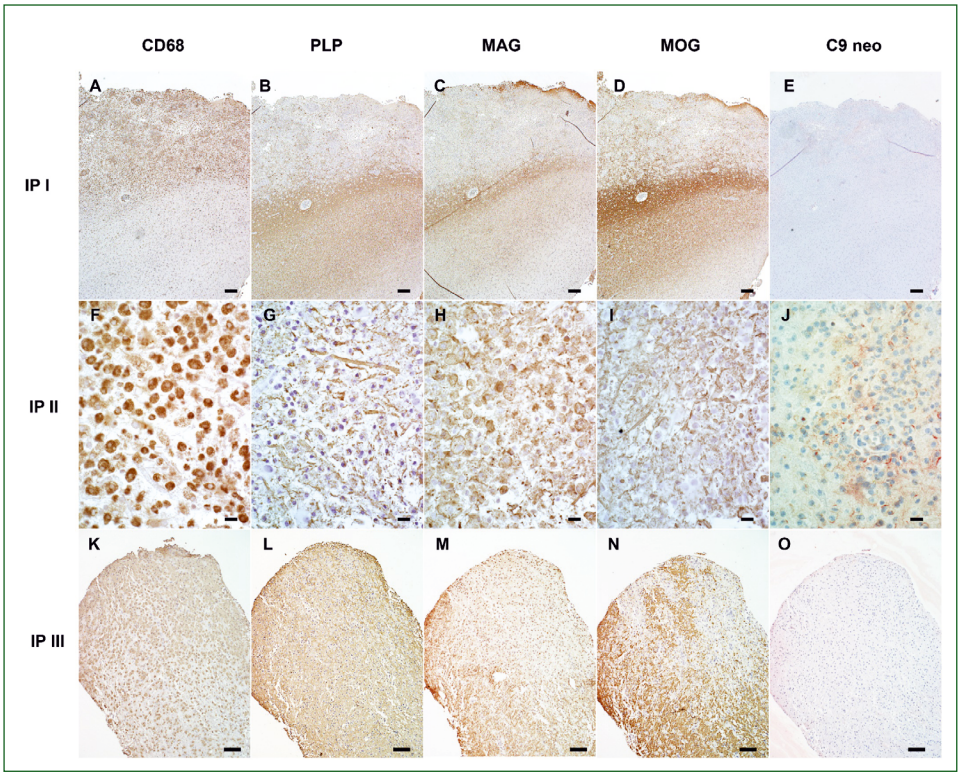

Figure 1. Pathological features in different immunopatterns of MS. IP-I shows typical macrophages enriched (**A**, CD68) lesions with equal loss of major myelin protein (**B**, PLP) and minor myelin protein components (**C** and **D**, MAG and MOG), no complement deposition (**E**). IP-II (**F–J**) MS shows similar findings, but is characterised by complement activation products within macrophages in active demyelinating lesion (**J**). IP-III MS (**K–O**) shows preferential MAG loss (**M**) compared to MOG (**N**). No complement activation products are present in macrophages in IP-III lesion (**O**). Scale bars: 200 µm (A-E), 20 µm (**F–J**), and 100 µm (**K–O**)

In this review, we present the current perspective on pathological hallmarks of active and chronic MS and pathological differences between MS, ADEM, AQP4-IgG positive NMOsd, and MOGAD.

Multiple sclerosis

Multiple sclerosis is an inflammatory CNS disease characterised pathologically by macrophage-enriched demyelinating white matter lesions with relative axonal sparing and reactive glial scar formation [17–19]. Importantly, the pattern of MS-related demyelination is *confluent*, as opposed to the perivascular (and sometimes coalescing) pattern seen in ADEM or AQP4-IgG positive NMOsd.

The classic neuropathological features of active macrophage-driven demyelination with relative axon sparing and astrogliosis, as described by Charcot, relate to the active MS lesion which is equivalent to a clinical relapse. However, MS lesion formation and repair are part of a dynamic process. While most plaques in early MS are marked by active inflammatory demyelination, inactive plaques predominate in chronic MS [20]. MS plaques are categorised based on the density of the inflammatory infiltrate and the degree of microglia activation into *active vs. inactive* plaques, the latter containing few if any activated microglia cells. Active lesions also contain major histocompatibility complex (MHC) class I restricted CD8 T lymphocytes, which dominate over CD4 T cells [21], with only sparse B lymphocytes and plasma cells within the infiltrate [22].

Active plaques can be further staged into *early active vs. late active* plaques based on the composition of myelin debris identified within macrophages. Specifically, in the early stages of lesion formation, all myelin components can be identified within myelin-laden macrophages, including minor myelin proteins such as myelin oligodendrocyte glycoprotein (MOG), myelin-associated glycoprotein (MAG), and 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) [23]. The plaques containing these proteins within macrophages, which can be seen on pathology with immunohistochemistry staining, are defined as *early active* (EA) lesions. On the other hand, in *late active* lesions, minor myelin proteins are already fully degraded (and hence absent) and only major myelin proteins can be identified, namely myelin basic protein (MBP) and proteolipid protein (PLP) [23]. When all myelin proteins are fully degraded, macrophages will remain positive for lipids and Periodic Acid-Schiff (PAS).

Early active plaques have been further categorised according to the effector mechanism of demyelination, which is patient-specific (but differs between patients), into four basic immunopatterns: *immunopattern I*, which is associated with T lymphocyte and macrophage infiltration; antibody/ /complement-associated *immunopattern II* (the most commonly encountered EA lesions in biopsy specimens); *immunopattern III* characterised by preferential MAG loss; and *immunopattern IV* (found in fewer than 1% of patients), which is defined by primary oligodendrocyte degeneration [14, 24].

Although frequent in early relapsing-remitting MS and active secondary progressive MS, active plaques are much less frequent in primary progressive and secondary progressive MS without clinical attacks. They are rare in established MS; with less than 13% probability a lesion will be active at 20 years of disease duration [20]. In fact, as shown in a large sample of MS autopsies the distribution of active and inactive plaques reaches an equilibrium at 47 years of age [20]. At the same age (i.e. 18-20 years of disease duration) the number of *smouldering lesions* starts to peak. Smouldering lesions, also known as *slowly expanding lesions*, are only seen in the progressive forms of MS and are characterised by a rim of MBP- or PLP-positive macrophages/microglia surrounding an inactive centre that is depleted of macrophages [22, 25]. Smouldering lesions are considered one of the correlates of MS-related progression [26, 27].

With regards to myelin repair, or remyelination, this is common and relatively effective in early MS [28] but often incomplete in progressive MS. Remyelinated axons can be distinguished by thinner myelin sheaths and consequently a paler staining intensity [25]. The plaques where remyelination is extensive are called *shadow plaques*, and are present in both relapsing and progressive MS [25].

In recent years, beyond focal white matter pathology, cortical lesions have also emerged as key MS characteristics. Cortical demyelination begins early and accumulates with disease duration [29, 30]. In early MS, it typically occurs on a background of inflammation [30, 31] but it is most prominent in the progressive disease [32]. Three types of cortical plaques have been distinguished, namely *leukocortical* (type 1), *intracortical* (type 2), and *subpial* (type 3) [33–35]. Importantly, their distribution reflects correlates of irreversible disability and cognitive impairment [33, 36].

Cortical lesion load is one of the strongest predictors of MS-related disability [37, 38]. Yet on the other hand, cortical lesion load is low in MS patients with clinically 'benign' disease [39]. Interestingly, extensive cortical demyelination can be present in the near absence of focal white matter lesions [32, 40].

Another important neuropathological feature of MS is *meningeal inflammation*, which is associated with cortical demyelination, microglial activation and neuritic damage [41, 42]. Clinically, meningeal inflammation has been associated with a more severe course of primary progressive MS, shorter disease duration, and younger age at death [43]. Moreover, meningeal follicular structures have been reported in secondary progressive MS [44]. These lymphoid structures have been reported to be immunoreactive for EBV [45].

As for axonal damage in MS, signs of acute axonal injury, namely axonal spheroids and end bulbs, are visible mainly within active plaques but also, to a smaller extent, within normal-appearing white matter and chronic lesions [46]. In

active lesions, axonal damage is probably the by-stander result of the toxic inflammatory milieu [47]. As for chronic axonal damage, the pathomechanism is even more complex, including lack of trophic support from myelin and oligodendrocytes and mitochondrial failure [46]. The mean reduction of axon density in cerebral plaques is estimated between 59–64% [48]. A significant (57-68%) reduction in the number of axons/ /mm^2 is also seen in spinal cord lesions [49]. Global axonal loss is a major correlate of end-point disability in MS patients [50].

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a typically monophasic immune-mediated primarily demyelinating CNS disorder that usually affects children and follows an infection or vaccination. It is distinguished clinically by a first multifocal neurological episode with suspected demyelinating aetiology associated with encephalopathy and no clinical or radiological dissemination in time, usually with a favourable prognosis [51]. While several MRI features are suggestive of ADEM rather than MS, e.g. large, poorly demarcated lesions, frequent basal ganglia involvement, and lack of T1 hypointensities, often simultaneous gadolinium enhancement and CSF analysis can be of help (ADEM patients are typically negative for CSF-specific oligoclonal bands); ADEM remains a diagnosis of exclusion [52]. From the neuropathological perspective, ADEM is characterised by *perivenous demyelination* (sometimes *coalescent*), as opposed to an MS-related confluent pattern [53]. The inflammatory infiltrate consists mainly of macrophages, T and B lymphocytes. Granulocytes and plasma cells can also be identified, albeit only occasionally [54]. Interestingly, all three types of cortical lesion described in MS have also been identified in ADEM cases, namely subpial, intracortical and leukocortical. A unique pattern of cortical microglial activation and aggregation that is not associated with cortical demyelination has been described in patients with ADEM [54]. One could speculate that these diffuse microglial aggregates are a substrate of ADEM-associated encephalopathy.

It is of the utmost importance to reliably distinguish ADEM from MS, because the latter necessitates a prompt disease-modifying treatment strategy in order to improve patient prognosis [55]. However, the criteria used to distinguish relapsing ADEM from MS can be vague. Moreover, the currently used ADEM criteria are in fact only applicable to children and have never been adjusted for the adult population [11]. Pathology (if available) remains the gold standard for ADEM diagnosis. However, cases of concurrent perivenous and confluent demyelination in the same patient have been described [54], highlighting the possibility that, in rare cases, even a neuropathological study may not definitively distinguish ADEM from MS.

Aquaporin 4-antibody positive neuromyelitis optica spectrum disorders

Our understanding regarding the pathology of NMOsd has been revolutionised by the discovery of anti-aquaporin-4 antibodies [4], or NMO-IgG. Previously considered an MS variant with poor prognosis and selective involvement of optic nerves and spinal cord, it is now seen as a separate autoimmune inflammatory CNS disease, with detailed diagnostic criteria [56] and novel targeted therapies [57]. As for NMOsd pathology, some features are shared with MS, including macrophage infiltration, microglial activation and the presence of myelin-laden macrophages which suggest active demyelination. Although complement deposition is present in both NMO and early active IP-II lesions, in MS C9neo antigen is present within macrophages but not around blood vessels (on glia limitans), as seen in NMOsd cases [58]. MAG loss, which characterises early active IP-III MS lesions, can also be observed in some NMOsd lesions. Other features unique for NMO lesions include eosinophils and neutrophils infiltration, prominent perivascular immune complexes and complement deposition (often in a rosette pattern), vascular hyalinisation and prominent necrosis [59]. Given that AQP-4 is a water channel localised mainly on astrocytes, astrocytic pathology is prominent in NMOsd lesions and includes astrocyte dystrophy, disintegration of astrocyte foot processes, apoptosis and gliosis [60]. However, the observation of aquaporin 4 internalisation with loss of astrocyte surface immunoreactivity suggests antigenic modulation which reflects a functional outcome of IgG binding. Therefore, antigen-bearing cells can be compromised but not destroyed [60]. This suggests that AQP4 loss is not entirely due to astrocyte loss, but may also be a result of NMO-IgG initiated modulation of AQP4, the latter being potentially reversible.

Interestingly the relapsing course is the most common form of NMOsd, and secondary progression is unlikely, whereas the opposite is true of multiple sclerosis patients [61, 62]. This aligns with the fact that cortical demyelination and smouldering lesions, thought to be correlates of MS-related progression, are absent in NMOsd biopsies [63, 64].

Meningeal B-cell follicles, which are typically observed in progressive forms of MS [42], have not been identified in NMOsd, and meningeal infiltration differs between MS and NMOsd (Guo et al., unpublished data).

Myelin oligodendrocyte glycoprotein antibody-associated disease

MOG antibody-associated disease (MOGAD) has emerged as a subset of the AQP4-IgG negative NMOsd population, which is defined serologically by the presence of serum

anti-MOG antibodies and clinically by younger age at onset, less frequent relapses, more restricted symptomatology (i.e. only optic neuritis episodes), frequent disc oedema, spinal cord lesions localising in the conus medullaris, better recovery from relapses, and an excellent response to steroids (and sometimes even steroid dependence) [6, 65–67]. As opposed to AQP4, which is present in numerous tissues beyond the CNS, MOG is expressed exclusively in the CNS, localising on the outermost surface of the myelin sheath and the plasma membrane of mature oligodendrocytes (but not oligodendrocyte progenitor cells, OPCs [68]). A minor myelin component, it is known to be highly immunogenic [69]. MOG-IgG is not limited to NMOsd phenotype, but has also been associated with ADEM, paediatric MS, isolated optic neuritis and a single episode of transverse myelitis [70]. However, specific diagnostic criteria for MOG-IgG-Associated Disorders have been proposed [8, 9].

Neuropathologically, MOGAD is characterised by the overlap of MS and ADEM features and is different from AQP4-IgG seropositive NMOsd [64]. The coexistence of perivenous (as in ADEM) and confluent (as in MS) demyelination, complement deposition and overrepresentation of intracortical plaques are typically seen in MOGAD biopsy and post mortem material. In contrast to AQP4-IgG seropositive NMOsd, AQP4 is preserved, dystrophic astrocytes are absent, and there is a variable degree of oligodendrocyte and axonal destruction [64]. No slowly expanding/smouldering lesions have been identified in MOGAD cases [64]. Interestingly, our group did not observe preferential MOG loss in a study of two autopsies and 22 biopsies of MOGAD patients, which would suggest endocytic internalisation following antigen modulation by MOG-IgG [64]. This in turn suggests a different pathogenic mechanism than in AQP4-IgG positive NMOsd cases. However, Takai et al. did report MOG-dominant myelin loss in 60 out of 167 demyelinating lesions they studied in brain biopsies from 11 MOGAD patients [71]. Their biopsy patient population was older (median age 29 years as opposed to 10 in our joint Mayo Clinic/University of Vienna biopsy cohort) and included half the number of cases, with only two ADEM cases, whereas in our biopsy cohort, ADEM-like presentation accounted for 61% of cases. Takai et al. also found no isolated optic neuritis or transverse myelitis cases. Given the relatively recent description of MOGAD as a separate disease entity, more neuropathological studies are likely to emerge soon.

Summary, clinical implications and concluding remarks

Neuropathological studies are used for the purpose of establishing an accurate diagnosis for a patient with suspected CNS-IDD. However, in a broader perspective, they are also crucial for the understanding of disease mechanisms and for advancing the diagnostic and therapeutic landscape in MS and related disorders.

A summary of the pathological hallmarks of different inflammatory demyelinating diseases of the CNS is set out in Table 1 and Figure 2.

Undoubtedly, pathology is acquired in a minority of patients with multiple sclerosis, and usually for the reason of diagnostic uncertainty. Therefore, data obtained for this somehow atypical population needs to be interpreted and extrapolated with caution.

Reassuringly, our group and others have consistently shown that despite the atypical and/or aggressive onset of the disease, the subsequent course, acquired disability and prognosis do not differ from the classic MS population [72, 73], and in fact can even be slightly milder, as we have demonstrated with regards to ambulation, EDSS and progression conversion in a predominantly tumefactive MS cohort compared to a community-based MS patient cohort [74].

Although pathology can be extremely helpful in differentiating MS from other mimicking causes in patients with atypical presentation, MS remains a clinical diagnosis. This is exemplified by CNS demyelination reported secondarily in patients using TNF-alpha inhibitors [75, 76]. We have recently published a neuropathological study on a case of a rheumatoid arthritis patient treated with infliximab who developed CNS demyelination that was clinically and radiologically inconsistent with an MS diagnosis, yet was pathologically indistinguishable from multiple sclerosis [77].

Research in immunobiology and neuropathology of CNS-IDD is facilitated by the meticulous documentation of clinical records, biological samples and pathological data obtained from patients with atypical demyelinating syndromes. Careful analysis of this data, especially when long-term follow-ups are available, and adhering to the recommended procedures for tissue sampling and preservation [1] is likely to unravel and define further CNS-IDDs that have been previously categorised as multiple sclerosis.

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Table 1. Comparison of multiple sclerosis, aquaporin 4-IgG positive NMOsd, MOG antibody-associated disease, and acute disseminated encephalomyelitis pathology

	MS	AQP4-IgG+ NMOsd	MOGAD	ADEM
Target	Myelin/OG	Astrocyte/AQP4+ cells	Myelin/OG	Myelin/OG
Pattern of DM	Confluent	Perivascular and confluent non-DM lesions	Perivenular, coalescent, confluent	Perivenular, coalescent,
Immuno-pathology	I: (no complement) II: Complement on myelin/OG subset III: MAG loss subset	Vasculocentric complement deposition with some MAG loss overlap	Complement deposition	Fibrinous exudates around vessels
Inflammation	CD8 > CD4 T-cells B-cells	Granulocytes, eosinophils few T-cells	CD4 > CD8 T-cells, granulocytes	T-cells and B-cells, occasional plasma cells and granulocytes
AQP4 expression	Increased	Decreased/lost	Increased	Increased
Astrocyte	Hypertrophic gliosis (Creutzfeldt--Peters cells present)	Wide spectrum of astrocytopathopathies (hypertrophic, dystrophic, lysis) Creutzfeldt-Peters cells absent	Preserved/hypertrophic (Creutzfeldt-Peters cells present)	Preserved/hypertrophic
Axonal pathology	Acute/confluent denuded axons	Variable (from preserved to massive axonal destruction)	Limited (spheroids)	Axons relatively preserved but features of acute injury present
Smouldering plaques	Present	Absent	Absent	Absent
Cortical demyelination	Subpial/leukocortical > > intracortical	Absent	Intracortical > subpial, leukocortical	Intracortical, subpial, leukocortical

DM — demyelination; MS — multiple sclerosis; OG — oligodendrocytes

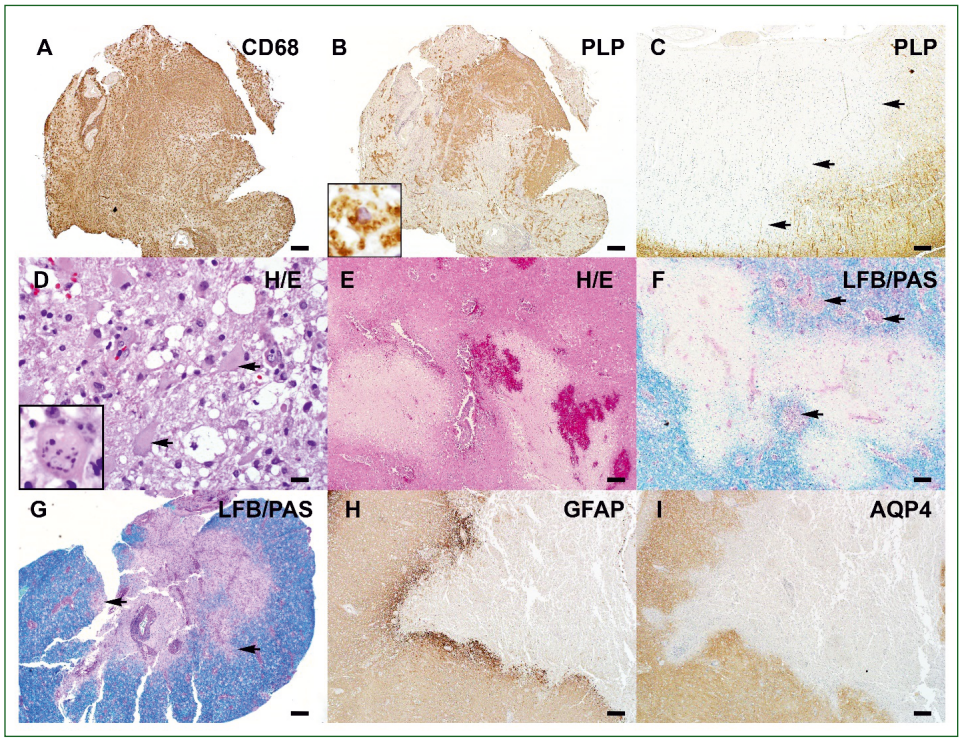

Figure 2. Typical neuropathological features associated with specific inflammatory demyelinating diseases of central nervous system. Multiple sclerosis (**A–D**): Typical MS presents as macrophage enriched CNS lesions (**A**) with demyelination involving both white matter (**B**) and cortex (**C**). Panel (**D**) shows hypertrophic astrogliosis (indicated by arrows) and Creutzfeldt-Peters cell with multiple micronuclei (inset). Acute disseminated encephalomyelitis (**E** and **F**): (**E**) White matter lesion of ADEM shows pallor stains on H/E with focal haemorrhage; **F**. LFB/PAS stain shows characteristic perivascular myelin loss (indicated by arrows) which has fused into more extensive confluent lesions. MOG antibody-associated disorder (**G**) shows similar pathology to ADEM with both confluent and focal perivascular demyelination (arrows). Neuromyelitis optica (**H** and **I**): NMO lesions show wide spectrum of astrocytopathy; **H.** Severe spinal cord lesion in NMO shows lysis of astrocyte highlighted by GFAP immunohistochemistry; **I.** AQP4 immunoreactivity shows even more extensive loss in consecutive section. Scale bars: 200 µm (**A–C**, **E–I**). 20 µm (**D**)

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