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Title: The spectrum of atypical CNS inflammatory demyelinating disease

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## **TITLE**

The spectrum of atypical CNS inflammatory demyelinating disease

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## **ABSTRACT**

Atypical demyelinating (AD) syndromes differ from both multiple sclerosis (MS) and from other demyelinating and non-demyelinating conditions in their prognosis and treatment. As with MS, the goals of treatment are, sequentially, to induce or facilitate remission from acute events and prevent future attacks. However, preventative therapies are not always indicated and when they are, they may differ from those for MS. We review AD diseases including neuromyelitis optica spectrum disorder, acute disseminated encephalomyelitis, tumefactive demyelination, Baló's concentric sclerosis, Schilder's diffuse myelinoclastic sclerosis and Marburg's multiple sclerosis. We consider the relationships of AD variants to MS and to one another and whether they are distinct and separable conditions. Advances in magnetic resonance imaging and immunobiology will improve our understanding of these conditions.

## **INTRODUCTION**

Multiple sclerosis (MS) is the umbrella diagnosis applied to patients who present with clinical syndromes compatible with inflammatory demyelination accompanied by typical findings on magnetic resonance imaging (MRI) that satisfy the principle of dissemination in time and space.<sup>1</sup> However, when patients present with an atypical syndrome, atypical MRI findings (e.g. a single, large presumed demyelinating MRI lesion, or multiple simultaneously gadolinium-enhancing demyelinating lesions), an atypical course (e.g. rapid and severe clinical deterioration), or fail to respond or deteriorate following a usually effective treatment, clinicians should consider non-demyelinating diseases including neoplasms and infarcts that mimic MS or atypical demyelinating (AD) syndromes. AD syndromes are favoured when findings suggestive of demyelination (e.g. optic neuritis (ON) or myelitis, relative lack of mass effect or "open ring" enhancement on MRI) but not typical MS are present and when other non-demyelinating diagnoses are excluded. Neuromyelitis optica spectrum disorder

(NMOSD) is usually considered with the AD syndromes although the discovery of its specific target antigen and immunopathologic studies have identified it more correctly as an inflammatory astrocytopathy rather than a primary demyelinating disease. Other AD syndromes include acute disseminated encephalomyelitis (ADEM), tumefactive demyelination (TD), Baló's concentric sclerosis (BCS), Schilder's diffuse myelinoclastic sclerosis or Schilder's disease (SD) and Marburg's MS.

Guidelines regarding diagnosis and management of AD conditions are based on less-than-adequate evidence, such as case series or even case reports, and typically involve treatments and treatment strategies applied to MS. Few of these conditions have formal internationally-approved consensus criteria. Boundaries between these conditions, and the minimum criteria for their diagnosis are often poorly defined. Furthermore, for many AD, it is uncertain whether treatments or treatment strategies different from those for MS are necessary. The discovery of a specific biomarker for NMOSD, aquaporin-4 (AQP4)-IgG, as well as recognition of distinctive neuroimaging findings, clinical syndromes and different responses to drugs used to prevent attacks of MS led to broad acceptance that NMOSD is a separate inflammatory disease from MS.<sup>2</sup> By contrast, although ADEM is likely a distinct disease from MS, and despite consensus diagnostic criteria designed to facilitate distinction,<sup>3</sup> in many patients the diagnosis of ADEM is ultimately revised to MS. Recognition of atypical inflammatory demyelinating disease is important in defining prognosis and treatment, especially considering the lack of response or even deleterious effects of MS disease modifying therapies (DMTs) for some CNS demyelinating disease.

This review addresses nosology, clinical findings, immunopathogenesis, and treatment of atypical CNS inflammatory demyelinating diseases and their relationship to MS. Some

manifestations of an AD disease may be characteristics of a given attack only, some indicative of a predilection of an individual patient to a certain type of attack and others may reflect a unique pathophysiology (i.e. distinct disease) (Table 1).

### **Neuromyelitis optica spectrum disorders (NMOSD)**

Neuromyelitis optica spectrum disorder (NMOSD), historically referred to as Devic's disease, is an inflammatory condition affecting the CNS, now recognised as distinct from MS. The hallmark clinical features of NMOSD are ON which is often bilateral or sequential, and longitudinally-extensive transverse myelitis (LETM) typically affecting three or more vertebral segments.<sup>2</sup> Patients present with subacute onset visual loss and para- or quadriparesis occurring either as separate episodes, in succession, or simultaneously. Brainstem and high cervical cord involvement occasionally result in life-threatening respiratory compromise. Prolonged episodes of nausea, vomiting or hiccups are a feature of NMOSD.<sup>2</sup>

The course of NMOSD is dominated by relapses which vary in frequency from several per year to attacks separated by many years. NMOSD is relatively more common compared to MS in South East Asia than in Western countries. Although methodological issues complicate interpretation, the prevalence of NMOSD is similar in Asian and western countries and ranges from 0.7 to 4.4 per 100 000.<sup>4</sup> NMOSD can occur at any age, including in the elderly, as reflected in a higher median age of onset than for MS (39 years vs 29 years).<sup>5</sup> Women are affected 9 times as commonly as men.<sup>5</sup> Asian optico-spinal MS was described as a unique form of relapsing demyelinating disease in Japan and Asia but it is now widely accepted that this disease largely overlaps with NMOSD. NMOSD is associated with

other antibody-mediated neurological diseases including myasthenia gravis, systemic lupus erythematosus (SLE) and Sjogren's syndrome.<sup>6-8</sup>

Most patients with NMOSD have an IgG1 antibody directed against aquaporin-4 (AQP4-IgG), a water channel concentrated on astrocytic foot processes involved in maintenance of the blood brain barrier (BBB).<sup>9</sup> Passive transfer of AQP4-IgG leads to CNS lesions in rodents,<sup>10</sup> but an *in vivo* model of AQP4-autoimmunity that reproduces the clinical and histopathological findings of NMOSD has yet to be developed. Interestingly, almost 2% of SLE patients, many of whom are asymptomatic, have serum AQP4-IgG which is pathogenic *in vitro*, and patients with myasthenia gravis may have detectable serum AQP4-IgG for years prior to developing NMOSD.<sup>6,8</sup> Breakdown in the BBB may be a critical requirement for symptoms to occur by allowing AQP4-IgG to enter the CNS.<sup>8</sup>

Historically, both ON and LETM were clinical requirements for a confident diagnosis of NMO. NMOSD was a term introduced for limited forms of the disease, (e.g. isolated, recurrent ON or recurrent LETM)<sup>11</sup> or for recently recognized NMO-typical brain lesions in the presence of a positive test for AQP4-IgG.<sup>5</sup> In 2015, the NMO diagnostic criteria were revised and the term NMOSD is now favoured over NMO to eliminate artificial distinction between limited and fully expressed phenotypes in terms of pathogenesis and treatment, and to recognise that over time, a limited form frequently evolves to meet historical criteria for NMO. However, NMOSD may also be diagnosed in AQP4-IgG seronegative individuals.<sup>2</sup>

Almost one-quarter of patients with NMOSD who are seronegative for AQP4-IgG are seropositive for myelin oligodendrocyte glycoprotein (MOG) antibodies (MOG-IgG), i.e. 5-10% of all NMOSD are MOG-IgG seropositive.<sup>12,13</sup> MOG-IgG-associated NMOSD differs in

clinical manifestations and response to treatment from AQP4-IgG-associated NMOSD.<sup>12,14,15</sup> MOG-IgG positive NMOSD patients are younger and less commonly women than AQP4-IgG seropositive cases. MOG-IgG is relatively more common in children with acquired demyelinating disease than in adults, and when detected, predicts an atypical MS syndrome.<sup>16-19</sup> MOG-IgG positive patients more commonly have bilateral than unilateral ON compared to MS patients and at a similar rate to AQP4-IgG positive patients.<sup>20</sup> Optic disc swelling due to anterior (retrobulbar) involvement of the optic nerve is more common in MOG-IgG positive patients than in either AQP4-IgG positive or MS patients<sup>20</sup> whereas, AQP4-IgG seropositive patients tend to have extensive or, when more restricted, posterior or chiasmal optic nerve involvement.<sup>20</sup> However, these conditions overlap and the location and severity of ON lesions is not diagnostic. Some NMOSD are seronegative for both current generation AQP4-IgG and MOG-IgG assays; further research is necessary to better characterize this subtype of NMOSD.<sup>21</sup>

Approximately 3% of patients with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis can have concurrent, or later develop, clinico-radiological syndromes consistent with demyelination.<sup>22</sup> Often these patients are seropositive for MOG or AQP4 IgG and phenotypes suggestive of MS, ADEM and NMOSD have been observed.<sup>22</sup> The immunopathological mechanism behind this apparent clinical and serological overlap is not understood.

Brain lesions in AQP4-IgG seropositive and seronegative NMOSD are common and often occur in characteristic locations and in typical patterns that reflect the high density of AQP4 antigen at those sites (Fig. 1).<sup>23</sup> NMOSD lesions occur in the diencephalon around the third ventricle and cerebral aqueduct, thalamus, hypothalamus and anterior midbrain.<sup>23,24</sup> Other



typical locations include dorsal brainstem including the area postrema and nucleus tractus solitarius where they may or may not be contiguous with a cervical cord lesion, and in periependymal areas. The corpus callosum (CC) is often involved, but different from MS, the lesions extend along the long axis of the CC and not in “Dawson finger” projections into the brain parenchyma.<sup>2,24-27</sup> Longitudinally-extensive lesions involving the corticospinal tracts may extend into the cerebral peduncle and brainstem. DWM lesions in NMOSD can be tumefactive and white matter lesions including non-specific T2 punctate white matter hyperintensities may be observed. Gadolinium-enhancement of any of these types of lesion is variable but tends to be less discrete than in MS and may have a “cloud-like” appearance in large NMOSD lesions.<sup>2,24,26</sup> In MOG-IgG seropositive NMOSD, the brain MRI is less frequently involved than in NMOSD with AQP4-IgG (37% vs 82%), and lesions are less distinctive from MS and include cortical and sub-cortical, deep grey nuclei T2 hyperintensities and tumefactive lesions.<sup>14,20</sup>

In MS, short-segment peripheral spinal cord lesions <1 vertebral segment are most common. In NMOSD, 90% of presenting lesions are  $\geq 3$  vertebral segments long, centrally predominant in the cord, and associated with T2 signal hyperintensity and T1 hypointensity (Fig. 1).<sup>2,24</sup> “Bright spotty lesions,” focal areas of particularly high T2 signal within ordinarily T2 hyperintense lesions are suggestive of NMOSD.<sup>28-30</sup> Acute NMOSD lesions usually enhance with gadolinium in a patchy and nonspecific pattern. Lesions may resolve completely on T2 sequences, particularly in those with a favourable outcome,<sup>31</sup> but persistent T2 hyperintensity may remain. In some instances, focal cord atrophy  $\geq 3$  vertebral segments may develop. In MOG-IgG seropositive NMOSD patients with spinal cord involvement, LETM of the thoracolumbar cord extending to the conus medullaris is relatively more common than in patients with AQP4-IgG seropositive NMOSD.<sup>12,14</sup>

Patients with AQP4-seropositive NMOSD are less likely to have CSF restricted oligoclonal bands (OCBs) in the CSF (<20%) compared to patients with MS (>80%) and CSF OCBs detected at the time of an acute attack often dissipate.<sup>2</sup> A CSF mononuclear pleocytosis >50/uL or neutrophil or eosinophil pleocytosis >5/uL during acute attacks distinguish NMOSD from MS.<sup>2</sup> CSF mononuclear pleocytosis >10/uL and OCBs are uncommon in MOG-IgG seropositive NMOSD.<sup>14,17</sup>

The pathology of AQP4-IgG seropositive NMOSD is distinctive and is helpful in distinguishing NMOSD from MS.<sup>32-35</sup> Non-destructive lesions are characterized by early preservation of astrocytes with pronounced reactivity, relative myelin preservation with focal intramyelinic oedema consistent with impaired water homeostasis,<sup>36</sup> microglial activation, loss of AQP4 immunoreactivity, granulocytic infiltrates, and variable deposition of IgG and complement components.<sup>37-40</sup> More advanced CNS lesions are characterized by pronounced BBB breakdown, oligodendrocyte loss, widespread loss of AQP4 immunoreactivity exceeding loss of other markers of astrocytes (GFAP), vasculocentric deposition of IgG, IgM and terminal complement components, leukocytic infiltration, and thickened hyalinised blood vessels. When extensive tissue destruction occurs, myelin loss, necrosis and cystic cavitation may occur, especially in central grey and white matter.<sup>32,36,38,39,41,42</sup> Eosinophilic and neutrophilic inflammatory infiltrates and a lack of Creutzfeldt cells favour NMOSD over MS but widespread loss of immunoreactivity for AQP4 in an active demyelinating lesion is the most sensitive and characteristic feature and can help biopsy to differentiate NMOSD from MS.<sup>35</sup> Cortical demyelination, a common characteristic of MS, is usually absent in NMOSD.<sup>34</sup>

The histopathology of MOG-IgG-associated neurological disease is characterised by demyelination with relative axonal preservation and complement activation markers similar to the histopathology described by some authors as MS pattern II demyelination.<sup>43,44</sup> However, distinct from AQP4-IgG-associated NMOSD, there is no evidence for an astrocytopathy.<sup>45-48</sup>

Acute attacks of NMOSD are treated with corticosteroids but may require plasma exchange (PLEX) in non-responders.<sup>49</sup> Some retrospective studies have suggested that PLEX may be more effective than corticosteroids and might be considered as an alternative or as an immediate adjunctive treatment to corticosteroids.<sup>50,51</sup> MS DMTs such as interferons, fingolimod, natalizumab and alemtuzumab are probably ineffective in NMOSD, and may be harmful.<sup>52,53</sup> Although no randomised controlled trials guide current long-term treatment choices in NMOSD, consensus guidelines favour oral corticosteroids together with an immunosuppression agent, such as azathioprine, mycophenolate mofetil or methotrexate to prevent recurrent attacks.<sup>52</sup> Mycophenolate mofetil has been proposed to be the most effective of these agents based on retrospective analysis, especially if the dose is titrated to achieve a modest lymphopenia.<sup>54</sup> For breakthrough relapses, the anti-CD20 monoclonal antibody, rituximab is beneficial as a maintenance treatment, and is being used increasingly as a first-line agent, as retrospective data suggest it may be even more effective than these other agents, and has a comparatively favourable adverse effect profile.<sup>52,54,55</sup> The complement inhibitor, eculizumab, and the interleukin-6 receptor inhibitor, tocilizumab, have shown promise in phase I trials and are currently in phase II/III trials.<sup>56,57</sup>

The prognosis for attack recovery in NMOSD with AQP4-IgG is poorer than that of MS patients. For this reason, early identification of NMOSD is important to ensure appropriate

therapy to minimise the frequency and severity of further relapses. Patients with MOG-IgG seropositive NMOSD have less acute attack-associated disability and less risk of subsequent relapse than AQP4-IgG seropositive,<sup>58</sup> but prednisolone may be necessary for 6-12 months after an attack to further reduce relapse risk. The need for longer-term immunotherapy in MOG-IgG seropositive cases is unclear, but may be justified in individual cases, particularly if there are further relapses.

### **Acute Disseminated Encephalomyelitis (ADEM)**

Acute disseminated encephalomyelitis (ADEM) is an uncommon demyelinating disorder of the CNS in children that occurs rarely in adults. It is usually multifocal. Neurologic deficits reflect the location of lesions but, unlike in MS, encephalopathy is frequent and sometimes associated with seizures. Typically, ADEM symptoms evolve rapidly, often with fever and occasionally meningismus. Symptoms peak within days, but relapses may occur over a 3 month period. Male and female children and adults are almost equally affected.<sup>59</sup> While not invariably identified, an antigenic challenge such as a nonspecific respiratory or gastrointestinal infection, or vaccination often precedes ADEM by weeks. The incidence is greatest in winter or spring, possibly reflecting higher rates of infection.<sup>59</sup>

ADEM is difficult to distinguish from an atypical first presentation of relapsing-remitting MS. Encephalopathy, including behavioural change and an altered level of consciousness or coma, favours ADEM over MS, but fulminant MS may lead to cognitive manifestations and seizures. Acceptance of multiphasic variant of ADEM further complicates the distinction from MS.<sup>60</sup> International consensus criteria have been developed to improve the accuracy of ADEM diagnosis in children.<sup>3,61</sup> According to Krupp et al. 2007, multiphasic ADEM was defined by a second attack consistent with ADEM occurring 3 months after the first attack.

However, the most recent update of paediatric consensus criteria acknowledges that 8.5% of children initially diagnosed with ADEM are ultimately diagnosed with MS,<sup>62</sup> and that a diagnosis of ADEM is no longer tenable when more than one attack occurs beyond 3 months from the onset of the initial episode.<sup>3</sup> In such patients, alternative demyelinating diseases such as MS, NMOSD or other non-demyelinating disease are more likely. Studies in adults, using 2007 ADEM diagnostic criteria, and Poser criteria for MS diagnosis, reveal that MS becomes the final diagnosis in approximately 35% of patients initially diagnosed with ADEM, with the majority developing MS within 1 year from onset.<sup>63</sup> Multiphasic ADEM is currently defined as two episodes consistent with ADEM separated by 3 months but not followed by any further events.<sup>3</sup> The criteria allow that the second event can be due to re-emergence of the original neurological symptoms, signs or MRI findings or can be due to a new neurological event.<sup>3</sup>

Typical brain MRI findings in ADEM are bilateral, asymmetric patchy areas of T2 hyperintensity within the white and grey matter (Fig.2).<sup>64</sup> Although variable in size, lesions are usually large (>1cm) and have poorly defined margins.<sup>60</sup> Gadolinium-enhancement is variable, and sometimes absent; simultaneous enhancement of all lesions is rare and may suggest ADEM, although other pathologies such as sarcoidosis or neoplasms must also be considered. TD lesions can occur in ADEM, and simultaneous enhancing lesions, makes multifocal primary CNS lymphoma an important differential diagnosis. In contrast to MS, ADEM tends to be associated with relative sparing of the periventricular white matter and affects the juxtacortical and DWM.<sup>64</sup> Thalamic and basal ganglia involvement favours ADEM over MS, while T1 hypointense “black holes” favour MS over ADEM. The optic nerves, CC, brainstem, cerebellum and spinal cord may be affected. Spinal cord lesions in ADEM are intramedullary, confluent and longitudinally extensive.

Follow-up imaging usually reveals partial or complete resolution of lesions without development of new lesions.<sup>60,65</sup> By contrast, MS lesions have more sharply defined margins than those of ADEM, and they rarely resolve completely and usually increase in number with follow-up imaging.<sup>60,65</sup>

MOG-IgG is detectable in serum of children with ADEM more frequently than in adults, including in children with multiphasic ADEM and ADEM followed by optic neuritis clinical phenotypes,<sup>18,66-68</sup> confirming that MOG-IgG is associated with a variety of AD presentations other than NMOSD.<sup>44,66,69</sup> Unlike other conditions associated with MOG-IgG such as NMOSD, titres usually decline in monophasic illnesses such as ADEM.<sup>70</sup> Whether MOG-IgG in these patients is pathogenic or an epiphenomenon reflecting tissue damage is unclear.<sup>66</sup> Passive transfer of human MOG-IgG into rodents can lead to reversible myelin damage and alteration in axonal protein expression.<sup>71</sup>

CSF examination in ADEM is useful to exclude infection, and commonly shows a mild mononuclear pleocytosis of 50/uL (range 0 to 270) with or without elevated CSF protein.<sup>59,60</sup> OCBs are usually absent but are detectable in approximately one third of patients, usually transiently.<sup>59,60,72</sup>

The pathology of ADEM differs from that of MS and is characterised by numerous perivenular ‘sleeves’ of demyelination accompanied by an inflammatory infiltrate of macrophages and fewer numbers of T and B cells<sup>34</sup> without confluent macrophage infiltration and demyelination seen in MS. Lesions in ADEM seem to be of a similar (pathological) age unlike in MS. As in other demyelinating diseases, there is relative axonal sparing. A

distinctive finding in ADEM is the presence of intracortical microglial aggregates particularly in cortical layer three that may be the substrate for encephalopathy.<sup>73</sup> The aggregates are associated with subpial microglial activation, diffuse meningeal inflammation and demyelination.<sup>34,73</sup>

ADEM is usually treated with intravenous corticosteroids initially; PLEX may be effective in non-responders.<sup>72</sup> IVIg is also used particularly in children.<sup>72</sup> Early or concurrent PLEX or IVIg may be beneficial in patients at risk of complications from cerebral oedema and raised intracranial pressure (ICP). Intractable increased ICP may require emergency neurosurgical decompression. Mortality from ADEM in predominantly paediatric cohorts approximates 5%, but survivors often recover well over several months.<sup>74</sup> Approximately 80% of patients have minimal or no residual disability.<sup>74</sup>

### **Acute Haemorrhagic Leukoencephalitis (AHL)**

Acute haemorrhagic leukoencephalitis (AHL), also known as Hurst's acute necrotizing haemorrhagic leukoencephalitis or Hurst's disease, is a very rare form of demyelinating disease thought to be a fulminant haemorrhagic form of ADEM. Patients present with rapidly progressive, severe encephalopathy and multifocal CNS symptoms, usually leading to death within one week of onset. MRI lesions are similar to those of ADEM, except for haemorrhage in some or most lesions.

The pathology of AHL is similar to that of ADEM. Fibrinoid vascular necrosis and microhaemorrhages occur in addition to perivenous demyelination and meningitis.<sup>59,75</sup> The observation that astrocytes demonstrate swelling of their end-feet, and degeneration of their processes and cell bodies in areas free of demyelination or significant oligodendrocyte

damage argues that an astrocytopathy may precede demyelination in AHL.<sup>75</sup> The perivascular infiltrate in AHL includes mononuclear cells and neutrophils, often with a neutrophil predominance. Axonal damage, haemorrhage and oedema are more extensive consistent with this being a more severe variant of ADEM.

As for ADEM, high dose corticosteroids and early PLEX are recommended treatments.<sup>76</sup>

### **Tumefactive demyelination**

Tumefactive demyelination (TD) is a term imprecisely applied to demyelinating lesions >2 cm in diameter. Symptoms and signs are those of cerebral mass lesions including seizures, impaired consciousness, cognitive deficits or focal neurological signs.<sup>77</sup> Single lesions may be mistaken for a neoplasm on MRI. The differential diagnosis includes cerebral abscess, ischaemia or infection.<sup>77</sup>

TD can be diagnosed readily in a patient with established MS, although clinicians must always consider the possibility of a superimposed disease that mimics TD. TD lesions may also occur in the context of ADEM, and in either AQP4-IgG or MOG-IgG seropositive NMOSD.<sup>20,60,78</sup> For this reason, “tumefactive demyelination” is preferred to “tumefactive MS”. TD may not be a distinct demyelinating disease, but rather a lesion type or types encountered in the context of a number of demyelinating disease processes and the international MAGNIMS collaboration has categorised the different MRI appearances of TD or TD-like lesions into ring-enhancing, infiltrative, megacystic and Baló-like subtypes.<sup>79,80</sup> TD lesions can occur multiply and simultaneously at onset. Although the majority of patients with TD will subsequently pursue a more typical course of MS, rarely, patients may develop relapsing TD.<sup>81</sup>



MRI clues that support TD include open ring-enhancement, minimal-to-moderate oedema and mass effect for size, a rim of T2 hypointensity, peripheral hypointensity on apparent diffusion coefficient (ADC) sequences at the lesion edge, and venular enhancement (Fig. 3).<sup>81-83</sup> The changes on DWI evolve rapidly over days to weeks, in contrast with relatively more stable findings in patients with tumours or abscesses. Gliomas or brain metastases lack ADC restriction, and abscesses show central rather than peripheral ADC restriction.<sup>83</sup> CT lesional hypodensity corresponding to MRI areas of enhancement also predicts TD over neoplasm.<sup>84</sup>

Magnetic resonance spectroscopy (MRS) is promising but its role in diagnosis is yet to be fully defined.<sup>85</sup> Difficulties in interpretation arise due to changes in MRS metabolites according to lesion age, whether short or intermediate echo time proton MRS (TE 1H-MRS) is used and lack of standardised studies comparing between all relevant differential diagnoses on a single type of scanner. Increased glutamate/glutamine peaks on short TE 1H-MRS may favour TD.<sup>85</sup> An increase in choline to N-acetyl-aspartate ratio (NAA) on either short or intermediate TE 1H-MRS is commonly seen in TD lesions but does not reliably distinguish TD from tumour.<sup>86,87</sup> TD lesions are not yet reliably distinguished from neoplasm based on MRS characteristics alone.

CT-PET may also be helpful in distinguishing TD from neoplasms, which have greater metabolic activity than TD. However, some inflammatory disorders such as neurosarcoidosis may also be hypermetabolic on CT-PET).<sup>88</sup> Combined MRS and CT-PET may be useful in future for distinguishing TD from neoplasm.<sup>89</sup>

Mildly elevated CSF protein or mild CSF pleocytosis are common in patients with TD lesions.<sup>81</sup> Patients who present with a TD lesion at their first clinical event less frequently have OCBs than those in whom a TD lesion develops during the course of established MS (52% vs 90%).<sup>90</sup> Detection of CSF OCBs favours MS demyelination when the diagnosis of TD is radiologically uncertain, although OCBs may be detected in individuals with CNS lymphoma.<sup>91</sup>

Biopsy is usually unnecessary for diagnosis unless atypical clinical or imaging features cast doubt on the diagnosis.<sup>77</sup> Experience is required to avoid pathologic misdiagnosis of TD lesions as glioblastoma given the high cellularity of the lesion and misinterpretation of Creutzfeldt cells as mitotic figures.<sup>81</sup> The presence of extensive macrophage infiltration should defer a pathologic diagnosis of malignancy and suggests demyelination. The pathology of TD lesions is similar to that of typical MS lesions and consists of confluent areas of demyelination with relative axonal sparing, although widespread axonal damage can occur; additionally, inflammatory infiltrates of foamy macrophages admixed with reactive astrocytes, and perivascular and parenchymal lymphocytic infiltrates are characteristic, as they are for active MS.

The prognosis of patients with TD lesions reflects the underlying disease process such as MS, NMOSD or ADEM, although the underlying diagnosis may not be apparent at presentation. Some patients experience fulminant attacks unresponsive to immunotherapies; however, approximately half of those presenting with TD recover fully, usually after receiving corticosteroid treatment.<sup>92</sup> Patients presenting with isolated, diagnostically undifferentiated TD lesions may have a better long-term prognosis than patients with conventional MS<sup>93,94</sup>, but long-term follow-up data are limited.

Treatment of acute TD is based on case reports and series and usually consists of corticosteroids initially and PLEX in non-responders.<sup>77</sup> For patients with fulminant or rapidly-evolving TD, both treatments can be administered simultaneously at the outset. Decompressive craniectomy is an option when brainstem herniation either due to direct mass effect or raised ICP appears imminent<sup>95</sup> and should be strongly considered given the favourable long term prognosis.

Cyclophosphamide and rituximab are therapeutic options for those failing to respond to corticosteroids and may protect against relapse by virtue of their longer immunosuppressive effect, although most case report evidence for cyclophosphamide comes from experience in children with TD lesions.<sup>96-98</sup> In patients with TD lesions in the context of established demyelinating diseases such as MS or NMOSD, standard immunotherapies for these conditions should be considered.<sup>77</sup> TD lesions have been reported in patients receiving fingolimod therapy.<sup>99</sup> Although the association is unproven, caution should be applied before using fingolimod in MS patients with TD.

### **Baló's concentric sclerosis**

Baló's concentric sclerosis (BCS) is a term applied to a lesion or lesions in the CNS composed of alternating rings of demyelination and relatively preserved myelin.<sup>100</sup> BCS usually presents with focal neurological signs and symptoms, but additionally may present with symptoms of a cerebral mass lesion including headache, reduced level of consciousness, cognitive dysfunction and seizures.<sup>100</sup> A prodromal illness of fever and headache may occur.<sup>101</sup> Women are affected more often than men.<sup>100</sup> BCS is rare but may be more common

in patients of Han Chinese and Filipino descent in whom MS is less common than in Caucasians.<sup>102</sup>

As with TD, BCS lesions are often mistaken for primary brain tumours and biopsied.

Although multiple BCS lesions can occur simultaneously, relapsing BCS is exceedingly rare.<sup>101</sup> Caution must apply when interpreting data regarding BCS as the condition is rare and usually derived from individual cases and small case series. In one comparatively large series of seven patients, approximately 40% who presented with an initial isolated BCS lesion developed relapses, either with typical MS-like or recurrent Baló-like lesions.<sup>103</sup> BCS lesions may also occur in aquaporin-4 seropositive and seronegative NMOSD.<sup>102,104</sup>

MRI demonstrates whorled concentric or “onion ring” lesions consisting of alternating rings of T2 and/or FLAIR of differing degrees of intensity and alternating T1 hypointensity and isointensity with minimal surrounding oedema (Fig. 4).<sup>100</sup> DWI changes and gadolinium-enhancement are often apparent at the lesion edge, but may also be layered concentrically. Other typical MS MRI lesions may occur in as many as 55% at presentation.<sup>103</sup>

One patient from a series of 11 patients with Baló-like lesions had CSF OCBs,<sup>79</sup> a frequency much lower than patients with MS or TD

The pathophysiology underlying the concentricity of BCS lesions has long been debated. The pre-eminent hypothesis is that lesions arise from a central “leaky” venule, from which inflammatory mediators spread radially in successive waves triggering macrophage-mediated demyelination.<sup>105</sup> According to the ischaemic preconditioning hypothesis (IPH), hypoxia-inducible factors are expressed at the leading edge of each successive wave and confer partial

neuronal and myelin protection leading to the concentric appearance. Upregulated expression of hypoxia-inducible proteins such as heat-shock protein 70, hypoxia-inducible factor -1 $\alpha$ , and D-110 at lesion borders in the lesion support IPH<sup>105</sup> as does a report of a patient with CADASIL-associated *Notch3* mutation who developed BCS.<sup>106</sup>

Alternative theories also propose centrifugal lesion development from a central origin<sup>102,107</sup> as supported by the evolution of lesions on serial MRIs.<sup>108</sup> Reports of BCS and TD occurring in the same patient,<sup>109</sup> and individual lesions having mixed features radiologically and in some cases pathologically,<sup>110</sup> suggest overlap of mechanisms underlying TD and BCS such that BCS might be thought of as a subtype of TD.

Historically, BCS was deemed to have a poor prognosis based on autopsy reports. MRI-based ascertainment has better elucidated the clinical spectrum of BCS. Many patients have been documented to recover fully from BCS.<sup>100</sup>

Based on case reports, acute BCS lesions are usually treated with corticosteroids and/or PLEX and with immunosuppression in refractory cases.<sup>100</sup> It is unknown whether DMTs are necessary or helpful for patients with BCS lesions whether or not they have established MS.<sup>100</sup>

### **Schilder's diffuse myelinoclastic sclerosis (Schilder's disease)**

Schilder's diffuse myelinoclastic sclerosis or Schilder's disease (SD) is a rare demyelinating disease seen most commonly in children. Whether it is distinct from other atypical demyelination syndromes is contentious. Poser and colleagues defined SD as "a subacute or chronic myelinoclastic disorder resulting in the formation of one, or more commonly, two

roughly symmetrical bilateral plaques measuring at least 3 x 2 cm in two of the three dimensions, involving the centrum semiovale of the cerebral hemispheres”.<sup>111</sup> Patients can present with focal signs or with encephalopathy and/or seizures, depending on the size and location of the lesions. The course is monophasic.

While the first case described by Schilder in 1912 was of an inflammatory demyelinating condition, latter cases described by Schilder in 1913 and 1924 were subsequently recognised to be due to adrenoleukodystrophy and subacute sclerosing panencephalitis respectively.<sup>111</sup> This confusion has meant that the published literature on SD now includes cases of both demyelinating and non-demyelinating diseases, and SD is still sometimes used as an eponym to refer to leukodystrophies.

The criteria of Poser and colleagues were developed to attempt to clarify the issue.<sup>111</sup> Importantly, these criteria specify that lesions elsewhere in the CNS must be absent, that the peripheral nervous system is not involved, and that patients have normal adrenal function and fatty acid carbon-chain length. Updated versions of the criteria focus on excluding features of ADEM such as fever or prodromal infection, the MS-atypical nature of the clinical features, that the frequent absence of CSF OCBs and, the mandatory presence of *bilateral* large areas of demyelination.<sup>112</sup> Confluent, mostly symmetrical T2 and FLAIR hyperintensity in the white matter of the frontoparietal lobes involving the centrum semiovale and the CC are typical.<sup>113</sup> Lesions are minimally-enhancing, demonstrate restricted diffusion when acute, and when chronic can resemble confluent demyelination seen in leukodystrophies. Other published cases resemble the more discrete, ovoid, ring-enhancing lesions of TD or ADEM.

Indeed, the updated diagnostic criteria do not easily distinguish multifocal presentations of TD, ADEM or even NMOSD. A subset of TD or ADEM patients with bilateral symmetrical lesions may be labelled as SD. SD description predates contemporary studies on other atypical demyelinating conditions and AQ4-IgG or MOG-IgG testing.

The pathology of SD is said to be “identical” to MS,<sup>111</sup> including well-defined lesion regions of demyelination with reactive gliosis, relative axonal sparing, perivascular lymphocytic infiltration, foamy macrophages and GFAP positive astrocytes.<sup>113</sup> The lack of a distinctive pathological features also argues against SD being a separate demyelinating disease.

Given the lack of distinctive features of SD and controversies about its existence as an independent disease entity, it is difficult to comment on prognosis and treatment.

### **Marburg’s variant of multiple sclerosis**

Marburg’s variant of MS refers to an acute, fulminant form of demyelinating disease first described post-mortem by Otto Marburg in 1906. Patients present with seizures, headache, vomiting, bilateral ON and gait disturbance with hemi- or quadri-paresis. Symptoms progress rapidly, either stepwise or continuously. Marburg’s MS may present with “multifocal” cognitive syndromes such as aphasia and apraxia rather than with diffuse encephalopathy manifest as confusion and coma that is the clinical hallmark of ADEM.

The typical MRI appearance of Marburg’s MS is multifocal demyelinating lesions in the periventricular, juxtacortical and DWM, brainstem, cerebellum or cord, which are frequently large and gadolinium-enhancing (Fig. 5).<sup>34,114</sup> Lesions often have marked perilesional oedema like ADEM, but early clinical and MRI distinction between Marburg’s MS and ADEM is

based on nuances rather than absolute criteria. Lesions of different ages favour Marburg's MS, and the majority of lesions may enhance or show other signs of activity, blurring the distinction. OCBs in Marburg's MS are commonly absent.<sup>115</sup> Marburg's MS may be an intermediate entity between TD and ADEM clinically and radiologically, although pathologically, as described below, it is much closer to TD.

The pathology of lesions resembles that of MS but is more destructive and lacks the perivenular demyelination pattern of ADEM. Confluent macrophage infiltration, axonal injury, necrosis and areas of focal or confluent hypercellular demyelination are seen.<sup>34,114</sup> Hypertrophic and giant astrocytes may also be detected.<sup>31,114</sup> Cavitating lesions may be infiltrated by neutrophils and eosinophils<sup>34</sup> as seen in NMOSD, a diagnosis that cannot be adequately excluded in historical cases. A recent autopsy case also noted meningeal inflammation and grey matter lesions and perivascular inflammation comprised of B-cell-dominant infiltrates.<sup>114</sup> The greater destructiveness of Marburg's MS compared to typical MS is not understood. Some individuals with Marburg's MS may be intrinsically predisposed to more aggressive MS because they express a less cationic, and possibly less compact, isoform of myelin basic protein (MBP).<sup>116,117</sup>

Historically, Marburg's MS was reported to be fatal within 1 year of onset with death due usually to direct brainstem involvement or brainstem herniation related to raised ICP.<sup>114,118</sup> Advances in the treatment of acute demyelination and supportive care have substantially improved prognosis. Intravenous corticosteroids, often followed by PLEX is the usual first-line treatment.<sup>114</sup> Mitoxantrone and high-dose cyclophosphamide have also been used successfully in individual cases.<sup>119,120</sup> Whether MS DMTs influence prognosis is unknown.



## **CONCLUSIONS AND FUTURE DIRECTIONS**

The literature on AD syndromes is confusing and occasionally contradictory, partly due to their rarity, and the potential for overlapping clinical, serological, radiological and pathological findings. Case definitions are incomplete, and only a limited number of syndromes, such as NMOSD and ADEM, have diagnostic criteria that are well accepted. Changing ascertainment enabled by neuroimaging and biopsy that permit ante-mortem diagnosis, have and continue to change, the spectrum of these diseases.

The current classification of inflammatory demyelinating syndromes is based on clinical features, MRI characteristics, pathology and more recently a limited number of serologic tests. It is unclear whether the radiological and pathological differences between TD, Marburg's MS and BCS are sufficient to define them as separate diseases. They may be different manifestations of demyelination of a variety of causes. While both TD and BCS are most closely associated with prototypic MS, both can occur in NMOSD, a clinically, immunologically, pathologically and therapeutically distinct disease from MS. TD and BCS lesions are also encountered as isolated or recurrent events in an individual with Marburg's MS or as a manifestation of ADEM. TD and BCS lesions might therefore reflect different mechanisms of local tissue injury, and therefore be manifestations shared between demyelinating lesions. Typical periventricular MS lesions may be seen in NMOSD, BCS, TD, Marburg's MS and ADEM. Clinicians, therefore, should be cautious about making a syndromic diagnosis based on a single event or lesion type.

SD lacks distinctive clinical or pathological features and, in most cases can be given an alternative diagnosis, such as adrenoleukodystrophy, Marburg's MS or ADEM. ADEM itself is still a heterogeneous disease despite improvements in diagnostic criteria. An important

question is whether ADEM is best diagnosed clinically, radiologically and serologically, or clinicopathologically, appreciating that most patients will not have a brain biopsy. The emerging role of MOG-IgG may require reclassification of some patients. Although ADEM as we currently understand it as a post-infectious or post-vaccination related syndrome appears to be a distinct disease from MS, ADEM heralds MS in almost 10% of children affected<sup>62</sup> indicating current definitions are still imprecise.

The difficulties in categorising the demyelinating diseases force clinicians to consider whether an AD event in a patient represents characteristics of that event only, predicts that an individual has a tendency to experience atypical manifestations of prototypic demyelinating disease, or indicates the characteristics of a unique but uncommon disease such as NMOSD (Table 1).<sup>121</sup> The dilemmas of clinical diagnosis highlight the importance of discovering and implementing novel and highly specific biomarkers to distinguish amongst inflammatory demyelinating disease subtypes. The discovery of aquaporin-4 antibodies in some forms of NMOSD helped to reinvigorate the diagnosis of NMOSD and led to a paradigm shift in treatment, and serves as an example of how distinguishing amongst atypical forms of demyelination can be rewarding. The emergence of MOG-IgG as a potential discriminator of yet further subtypes of NMOSD, has been a promising recent development that may further solidify the importance of antibody markers for AD disease. Increasingly, AQP4-IgG testing is performed in all cases of atypical demyelination, irrespective of the MRI features, due to the immediate treatment implications of a positive test and considering the wider spectrum of the manifestations now attributed to NMOSD.

When faced with an AD lesion or syndrome, clinicians must successively decide on appropriate short-term therapies to facilitate remission and subsequently the indications for

and the nature of chronic immunotherapy. Although acute therapies in general are similar for all AD subtypes, the need for and the nature of long term immunotherapy varies considerably for different diagnoses. ADEM may not require long term immunotherapy, and the treatments for MS and NMOSD differ.

Rare disease registries avoiding bias and preconception of disease phenotype that document detailed clinical, radiologic and pathologic data, and relevant long term outcomes, will advance understanding of AD disease. Other potential avenues for advancement include developments in MR imaging, pathology, immunogenetics and through observing the successes or failures of different immunotherapies in treating these conditions.

## **DECLARATION OF INTERESTS**

TAH: Has received honoraria for talks and advisory boards and support for scientific meetings from Novartis, Biogen Idec, Merck-Serono, Alexion and Genzyme. MHB: Has received institutional support from Biogen, Genzyme, Novartis and Teva; and travel support from Novartis and Biogen. SWR: Has received honoraria for talks and advisory boards and support for scientific meetings from Bayer-Schering, Novartis, Biogen Idec, Merck-Serono, and Genzyme and is a director of Medical Safety Systems Pty Ltd that provides services to Genzyme. JP is partly funded by highly specialised services to run a National congenital myasthenia service and a neuromyelitis service. She has received support for scientific meetings and honorariums for advisory work from Merck Serono, Biogen Idec, Novartis, Teva, Chugai Pharma, MedImmune, Alexion and Bayer Schering, and unrestricted grants from Merck Serono, Novartis, Biogen Idec, Teva, Genzyme and MS Society. Her hospital trust receives funds for her role as clinical lead for the RSS, and she has received grants from the MS Society and Guthrie Jackson Foundation for unrelated research studies. She is a board

member for the charitable European MS foundation 'The Charcot Foundation' and on the steering committee for a European collaborative MS imaging group 'MAGNIMS'. CFL has a special project agreement to support some of her research with Biogen and Novartis. BGW receives royalties from RSR and Oxford University for technology license for aquaporin-4 autoantibodies used for diagnosis of neuromyelitis optica. He serves on data safety monitoring committees for Novartis, Biogen-Idec and Mitsubishi pharmaceutical companies, and serves on an adjudication panel for Medimmune Pharmaceuticals. He served as a consultant for GlaxoSmithKline, Elan, Ono, Chugai Alexion, Chord and Novartis pharmaceutical companies.

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## **CONTRIBUTORSHIP STATEMENT**

TAH conceived the idea for the article and TAH and BGW drafted the manuscript. All authors revised the manuscript critically for important intellectual content, and gave final approval of the version to be published.

## **SELECTION SEARCH STRATEGY AND CRITERIA**

References for this Review were identified through searches of PubMed with the search terms “Multiple sclerosis”, “atypical demyelination”, “neuromyelitis optica spectrum disorder”, “neuromyelitis optica”, “NMO”, “NMOSD”, “Aquaporin-4”, “myelin oligodendrocyte glycoprotein”, “MOG”, “tumefactive demyelination”, "Balo", “Balo’s”, "Baló", "Concentric", “Schilder”, “Schilder’s”, “Marburg” and "Marburg’s" from January, 2011, until December, 2015. Articles were also identified through searches of the reference lists of the articles found with the above cited search terms and of Google Scholar and the authors' own files. There were no language restrictions. The final reference list was generated on the basis of originality and relevance to the scope of this Review.

**Table 1** Characteristics informing classification of the atypical demyelinating (AD)

conditions

Syndrome or disease	Characteristic of an attack within a patient	Characteristic of a patient but not distinctive of a disease	Characteristic of a disease
Typical multiple sclerosis (MS)			++ (although there may be unrecognized heterogeneity)
Neuromyelitis optica spectrum disorder (NMOSD)			+++ (further stratification based on serology likely; e.g. AQP4+, MOG+)
Acute disseminated encephalomyelitis (ADEM)	+ (minority who present with an ADEM-like relapse as initial presentation of MS or NMOSD)		+ (majority)
Tumefactive demyelination (TD)	+++	+ (occasional relapsing TD)	
Balós concentric sclerosis (BCS)	+++	+ (rare relapsing BCS)	
Marburg's multiple sclerosis	++	+ (occasional relapsing Marburg's MS)	+/- (possibly in patients with deficiencies in compact myelin) (Wood et al., 1996; Beniac et al., 1999)

**Figure 1** Neuromyelitis optica spectrum disorder (NMOSD). (A) Sagittal FLAIR sequence showing typical hyperintense lesion in dorsomedial medulla (arrow) in an AQP4-IgG seropositive patient (B) Sagittal T2 MRI of the cervical spinal cord in an AQP4-IgG seropositive patient showing a hyperintense, longitudinally extensive cord lesion from C2 to C6 with associated cord swelling and oedema (C) The same cervical cord lesion on T1 sequence diffusely enhances with gadolinium, most markedly at C2 (D) High T2 signal on axial image in the cervical cord in the same patient with a “bright spotty lesion” of more intense T2 signal within the lesion to the left of the midline (arrow) (E) Coronal T2 sequence showing increased T2 signal and swelling in the right optic nerve (thick arrow) compared to the normal left optic nerve (thin arrow) in a patient seropositive for MOG-IgG. (F) A patient with seronegative NMOSD with increased FLAIR signal in the right frontal lobe and ex-vacuo dilatation of the adjacent lateral ventricle consistent with a chronic tumefactive demyelinating lesion.

**Figure 2** Acute disseminated encephalomyelitis. (A-B) Axial FLAIR images from a patient with brain biopsy-confirmed ADEM showing hyperintensities in the deep and juxtacortical white matter with relative sparing of periventricular regions and (C) involvement of the cerebellum and bilateral cerebellar peduncles. None of these lesions were gadolinium-enhancing. An MRI brain one month earlier was normal (not shown) indicating the lesions are all of the same or similar ages. The patient was MOG-IgG seropositive. In the same patient (D) a sagittal FLAIR image showing a lesion in the central cervical cord spanning almost 3 vertebral segments. (E) Axial FLAIR image from another patient showing bilateral patchy, ill-defined thalamic hyperintensities (arrows) (F) T1 post-gadolinium image demonstrating a lack of clear enhancement. (G) Axial FLAIR images showing a better

defined deep white matter ovoid hyperintensity in the left frontal lobe (arrow) with (H) T1 post-gadolinium image showing faint enhancement.

**Figure 3** Tumefactive demyelination. (A) Axial and (B) sagittal FLAIR image showing a tumefactive demyelinating lesion in the right parietal periventricular white matter with surrounding oedema (C) Diffusion-weighted image (DWI) showing ring-shaped diffusion restriction at the periphery of the lesion around an area of central hypointensity with (D) corresponding changes on the apparent diffusion coefficient (ADC) sequence. (E) The post-gadolinium T1 image demonstrates “open ring” enhancement.

**Figure 4** Baló’s concentric sclerosis. (A) Sagittal FLAIR image showing simultaneous Baló’s concentric sclerosis lesions affecting the right parietal lobe and (B) left frontal lobe. (C) and (D) The parietal and frontal lesions seen on axial T2 sequences. The lesions are associated with peripheral restricted diffusion on DWI (E) and open ring enhancement on the post-gadolinium T1 sequence (F).

**Figure 5** Marburg’s MS. (A) and (B) Axial FLAIR images showing large demyelinating lesions in the left frontal and left parieto-occipital white matter involving the corpus callosum with local oedema, mass effect and midline shift. (C) DWI and (D) ADC images showing peripheral diffusion restriction. (E) The post-gadolinium T1 image shows diffuse heterogeneous enhancement of the lesions. (F) Axial FLAIR and T1 sequences 21 months later showing resolution of the earlier acute changes with residual hypodense areas of cavitation at the lesional sites.



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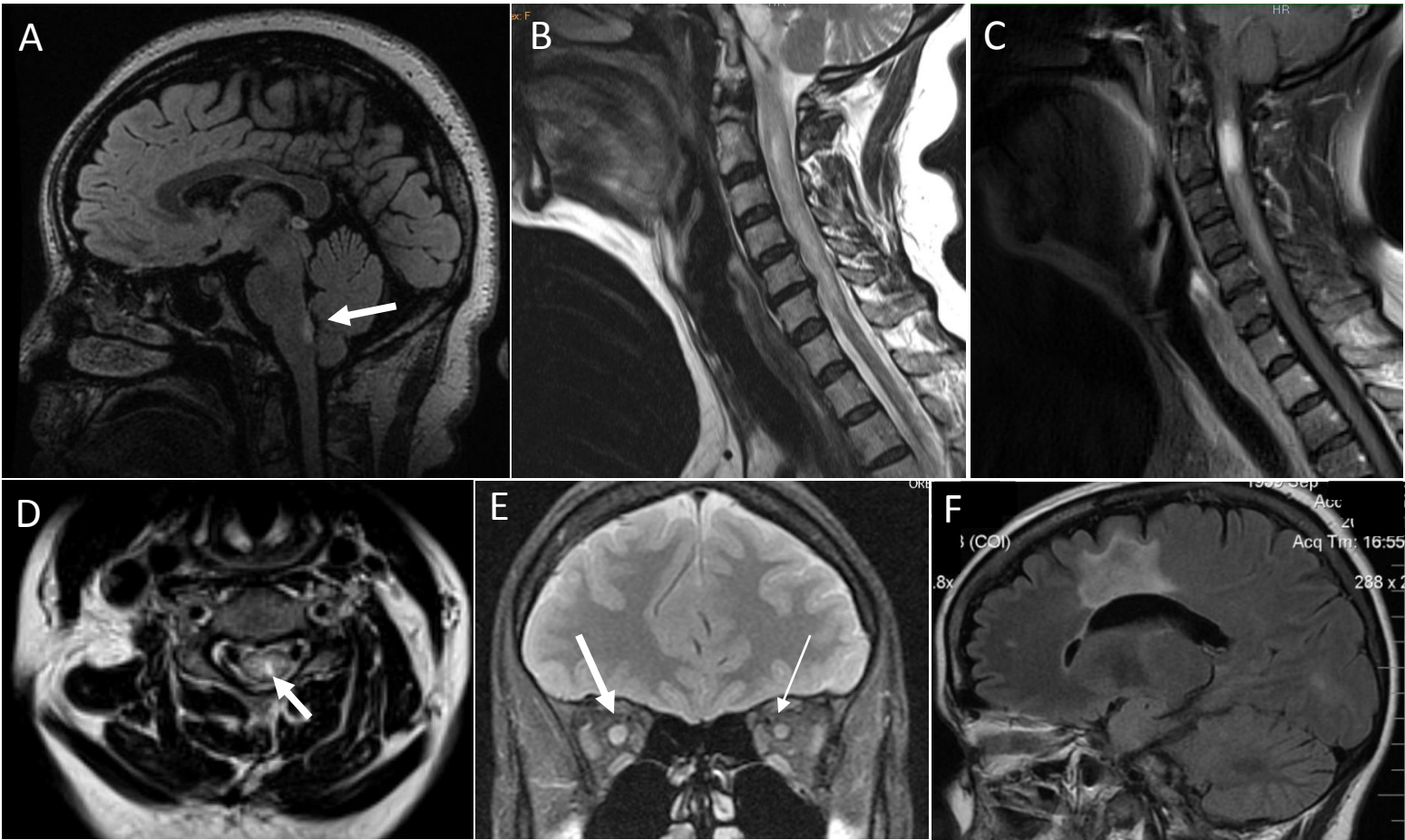


Figure 2  
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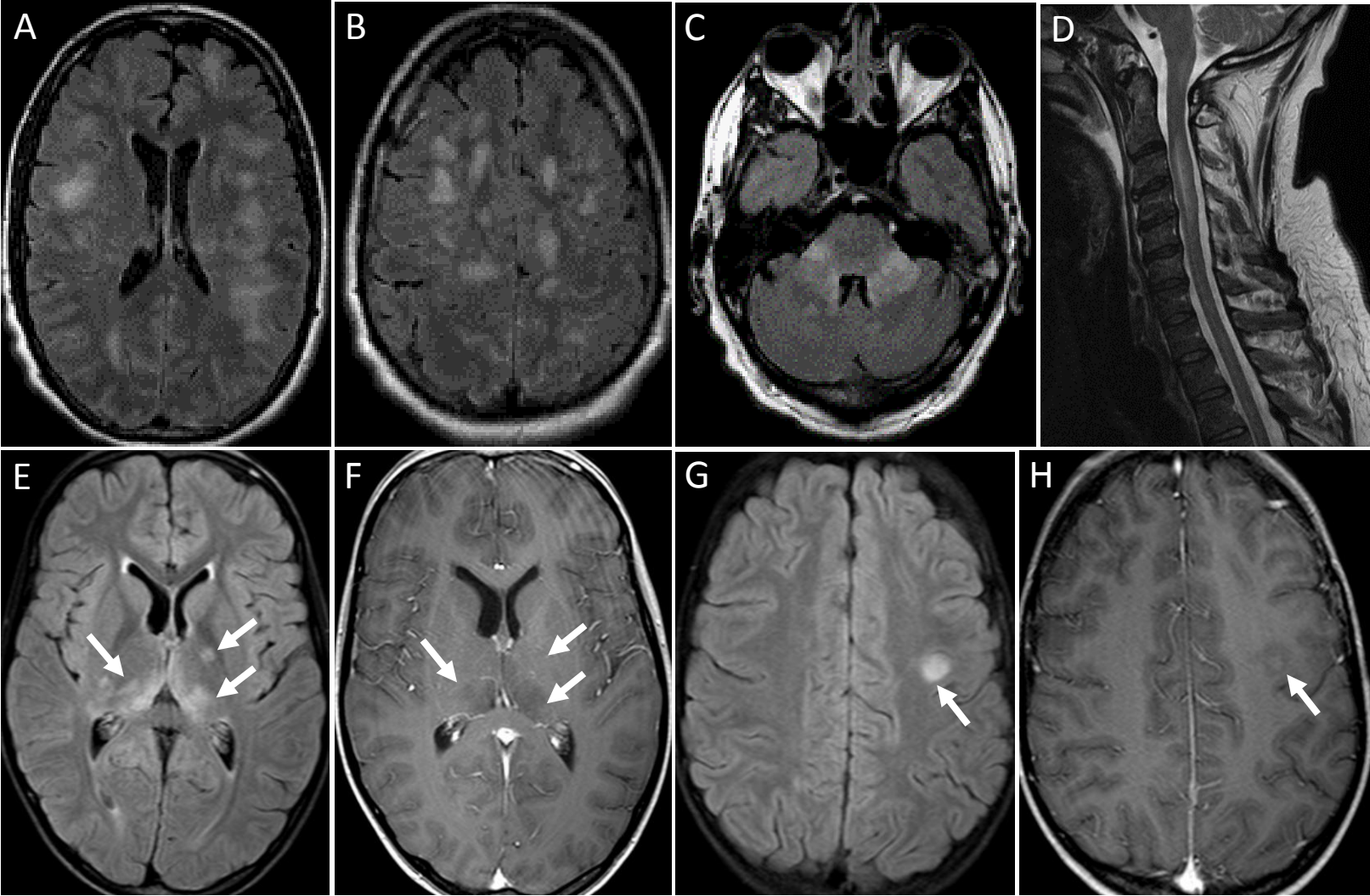
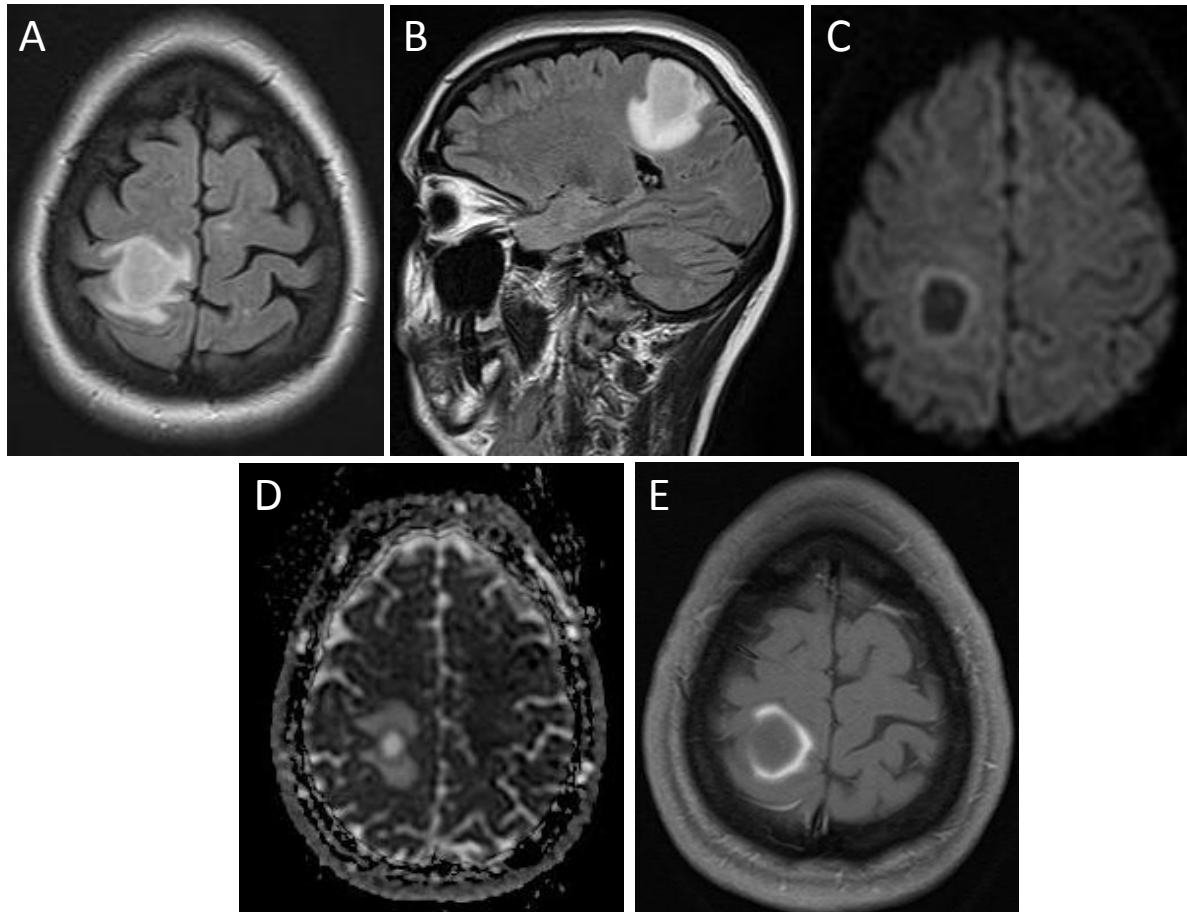


Figure 3

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**Figure 4**

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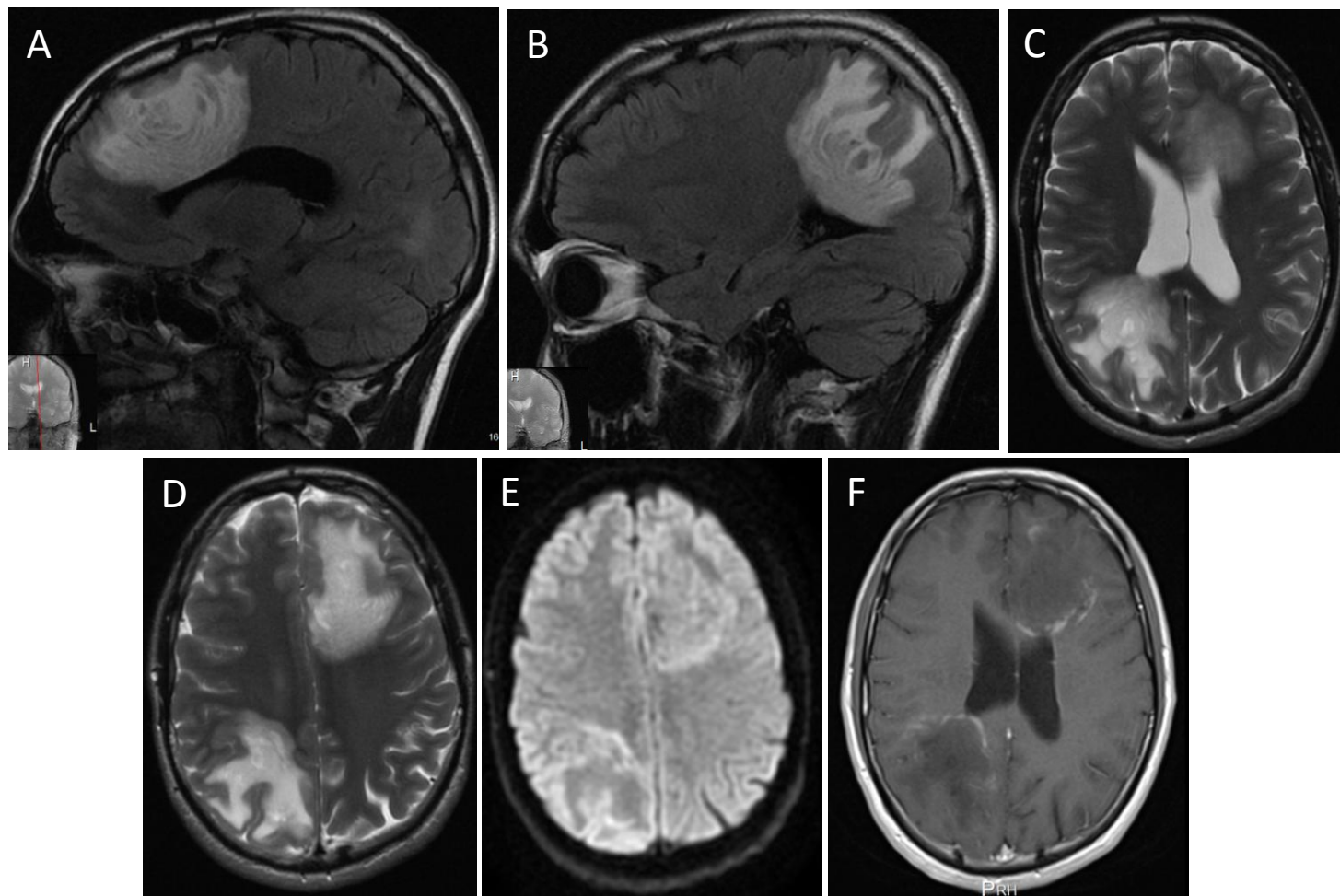


Figure 5

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