Central nervous system (CNS) demyelinating diseases are typically chronic disorders. Episodic relapses, a hallmark of the early phase of the disease, are usually mild and remit spontaneously or following a brief course of corticosteroids. Attacks of CNS demyelinating disease occasionally present with serious and emergent neurologic complications, either directly because of inflammation and destruction of brain or spinal cord tissue or because of secondary complications; these complications may result from brain edema that leads to mass effect and occasional brain herniation syndromes, or from systemic disturbances attributable to the function of the specific structures affected by the lesions, including pulmonary edema and respiratory failure. These complications may occur in the context of prototypic MS but are even more likely in the setting of alternative demyelinating disease contexts (eg, acute disseminated encephalomyelitis [ADEM], or neuromyelitis optica [NMO], tumefactive forms of MS, including Baló concentric sclerosis, and Marburg variant).

This article reviews the spectrum of acute emergent presentations of demyelinating disease and the importance of identification of the demyelinating disease context in which they occur to evaluate prognosis and institute effective long-term management. With emergency presentations, which are unusual in CNS demyelinating disease, consideration of other conditions that may mimic demyelinating disease is
critical. Clinicians should be aware of the myriad of mimics and the “red flags” that suggest a diagnosis other than demyelinating disease that may require specific treatment. Investigation should be individualized based on the index of suspicion for specific diagnoses suggested by these “red flags.” Guided by the index of suspicion, investigations, including cerebrospinal fluid (CSF) analysis, magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and, occasionally, brain/spinal cord biopsy, are helpful in excluding neoplasms (gliomatosis, lymphoma), vasculitis, sarcoidosis, and infections, such as progressive multifocal leukoencephalopathy, among other disease entities.

Treatment options for acute demyelinating disease (corticosteroids, plasmapheresis, intravenous immunoglobulin [IVIG], and immunosuppression) are reviewed, largely in the context of acute management. Potential neurologic and medical complications that may occasionally occur in the context of demyelinating disease, including brain herniation, posterior reversible encephalopathy syndrome (PRES), respiratory failure, neurogenic pulmonary edema, and acute heart failure are summarized, along with their management.

OVERVIEW OF INFLAMMATORY DEMYELINATING DISEASE

The spectrum of CNS inflammatory demyelinating diseases (CNS IDDs) is broad. The commonest variant is prototypic multiple sclerosis (MS), but other variants are relatively more likely to present with severe clinical deficits and emergency complications, including ADEM, NMO, and less common variants such as Baló concentric sclerosis, the Marburg variant of MS, and tumefactive MS.1 The boundaries between some of these entities are becoming better defined, in particular those that distinguish NMO from MS; however, some of these entities are much less well distinguished and intermediate phenotypes may defy accurate classification. Clinicopathological differences among these various conditions lead to different emergent presentations; however, the treatment of these emergency conditions is often the same regardless of phenotype, although the prognosis and long-term management may vary.

Dissemination in space coupled with dissemination in time is a time-honored concept in the field of MS; however, at initial presentation, these criteria may not be satisfied. It is often necessary to establish a working diagnosis of demyelinating disease at the first presentation, especially when it presents with severe disability or some other emergency complication. The inflammatory demyelinating lesions are pathologically heterogeneous. Although biopsy is not a commonly applied investigation when making a diagnosis, biopsy may be indicated for patients who present atypically (eg, with a large lesion with mass effect, or with atypical multifocal disease simulating vasculitis, gliomatosis cerebri, or other CNS pathologies). ADEM and NMO are usually pathologically distinguishable from prototypic MS and from one another.2,3 Prototypic MS has been classified immunopathologically into 4 separate patterns of demyelination.4 Patterns I and II suggest an immune-mediated attack, either cellular (pattern I) or antibody-mediated (pattern II), whereas patterns III and IV suggest a primary oligodendrogliopathy. The specific pattern may dictate responsiveness to certain immunotherapies. For example, patients with pattern II pathology, characterized by immunoglobulin deposition and terminal membrane attack complement activation, respond favorably to therapeutic plasma exchange.5

Acute Disseminated Encephalomyelitis

ADEM has classically been described as a monophasic illness most common in children who have had an antecedent viral illness or immunization.6–9 Recurrent or
relapsing forms have been described, although how these are distinguished from MS remains controversial.\textsuperscript{10,11} Patients with ADEM commonly report a preceding nonspecific upper respiratory infection.\textsuperscript{1} Specific infections that have been associated with ADEM include herpes virus infections (Epstein-Barr virus, cytomegalovirus, herpes simplex virus, and varicella zoster virus), influenza A and B, rubella, mumps, and HIV. Immunizations for varicella, influenza, diphtheria-tetanus, polio, and rabies occasionally precede ADEM.\textsuperscript{12} Perivenous distribution of inflammation and demyelination are usually present in ADEM, whereas confluent demyelination occurs in acute MS, including tumefactive forms. Hemorrhagic variants (acute hemorrhagic leukoencephalitis, Hurst disease) are thought to be severe variants of ADEM.\textsuperscript{13} Fig. 1 shows an example of MRI findings in ADEM. Oligoclonal bands are less likely to be present in the CSF of patients with ADEM than in patients with MS.\textsuperscript{8}

The proposed consensus definitions by the International Pediatric MS Study Group for monophasic ADEM require encephalopathy as part of a polysymptomatic presentation, in large part because its presence discriminates between MS and ADEM; however, encephalopathy may be seen in acute variants of MS and should not be considered as diagnostic of ADEM.\textsuperscript{11} Encephalopathy may present as behavioral changes, including confusion, irritability, and restlessness. Alternatively, ADEM may result in altered consciousness producing lethargy and drowsiness, or in more severe cases, obtundation, stupor, and coma that may require airway protection and can be fatal directly owing to cerebral herniation or to a supervening medical complication in some instances. The development of fever, headaches, seizures, and meningeal signs may reflect a meningoencephalitis and is more common in pediatric cases. Manifestations of ADEM may include optic neuritis or transverse myelitis.

High-dose intravenous corticosteroids are widely used as initial treatment for ADEM. The typical dose is intravenous methylprednisolone 30 mg/kg per day (maximum of 1000 mg/d) in children and 1000 mg per day in adult patients.\textsuperscript{9} Infusions are typically given for 3 to 5 consecutive days followed by an optional oral steroid taper over 2 to 3 weeks. Management in corticosteroid-refractory cases is not well established; based on its proven efficacy in a randomized clinical trial of acute, severe demyelinating disease (class I evidence), we recommend plasma exchange 1.0 to 1.5 plasma volumes per exchange, 7 treatments over 2-weeks.\textsuperscript{14,15} The use of plasma exchange has recently been systematically reviewed by the American Academy of Neurology and the American Society for Apheresis and found to be appropriate for the treatment of acute fulminant demyelinating CNS disease.\textsuperscript{16,17} IVIG, 1 to 2 g/kg given in 1 dose or divided over 3 to 5 days has also been reported as an effective treatment.\textsuperscript{18}

**Neuromyelitis Optica**

NMO (or Devic disease) was historically diagnosed in patients who experienced severe bilateral optic neuritis and transverse myelitis that developed concurrently or occurred sequentially within weeks of one another. In Asia, optic-spinal MS (OSMS) was recognized as a relapsing variant with special predilection for optic nerves and spinal cord, distinct from classical MS. A potential relationship of OSMS to NMO was recognized, but that relationship remained unclear. In the early twenty-first century, a pathogenic antibody (NMO–immunoglobulin G [NMO-IgG]) specifically reactive to aquaporin-4, a water channel protein on astrocyte foot processes, was found to distinguish NMO and many cases of OSMS from prototypic MS.\textsuperscript{19} The revised diagnostic criteria by Wingerchuk and colleagues\textsuperscript{20} in 2006 incorporate serum NMO-IgG antibody seropositivity as 1 of 3 supportive criteria in addition to requiring optic neuritis and myelitis to have occurred. NMO spectrum disorders (NMOSDs),
such as recurrent optic neuritis or recurrent longitudinally extensive transverse myelitis (LETM) in patients seropositive for NMO-IgG who do not satisfy the full NMO criteria, are increasingly being recognized and studied, as are patients with NMOSD with characteristic brain lesions for NMO, such as hypothalamic lesions associated with a symptomatic form of narcolepsy.

The vast majority of patients with NMO diagnosed by contemporary diagnostic criteria have a relapsing course. Relapses are often, although not invariably, more severe and are associated with more severe visual and sensorimotor deficits than

Fig. 1. Acute disseminated encephalomyelitis. (A) Axial fluid-attenuated inversion recovery (FLAIR) image showing multiple large indistinct homogeneous T2 signal abnormalities. (B) Axial T1 postcontrast image showing multiple enhancing lesions. (C–D) Same as (A) and (B) but at a more rostral level. (Courtesy of Dr Moses Rodriguez, Mayo Clinic, Rochester, MN.)
MS relapses; typically, myelitis is accompanied by a longitudinally extensive lesion on MRI of the spinal cord that spans 3 or more vertebral segments; patients often have a complete transverse myelitis with severe, and sometimes symmetric motor and sensory findings below the highest involved spinal level. However, the NMO spectrum includes a variety of brain and brainstem lesions, the most common and characteristic of which is intractable nausea with vomiting or hiccups associated with lesions in the area postrema in the floor of the fourth ventricle. Emergencies occurring in the setting of NMO exacerbations include neurogenic respiratory failure owing to upper cervical cord and brainstem involvement, as discussed later in this article. Hypothalamic involvement that has been documented in NMO may cause hypothermia and a symptomatic form of narcolepsy associated with profound somnolence. PRES has been identified in a series of patients with NMOSD that may be caused by vasogenic edema secondary to impairment of water flux as a result of aquaporin-4 autoimmunity and may present a self-limiting, reversible coma or cortical blindness.

Acute NMO exacerbations are routinely treated with high-dose intravenous corticosteroids. A typical course of treatment is methylprednisolone 1000 mg intravenously daily for 5 days with an optional oral prednisone taper. Patients failing to respond to corticosteroids benefit from plasma exchange, as reviewed in several articles including the recently released management guidelines by the European Federation of Neurologic Societies.

Traditional MS treatments, such as β-interferon drugs, have generally been ineffective and, according to some publications, actually deleterious in patients with NMO and are not usually recommended. In 2 Japanese studies that involved interferon β-1b subcutaneous injections given every other day, one showed no significant reduction in relapse rates whereas the other found an increase in severe attacks of optic neuritis and transverse myelitis. Long-term treatment options include azathioprine (2–3 mg/kg/d) in conjunction with prednisone (1 mg/kg/d for 6 months and then tapered), mycophenolate mofetil (2000 mg daily) combined with prednisone for 6 months, and rituximab (1000 mg intravenously administered twice 2 weeks apart, repeated every 6 months).

Acute Multiple Sclerosis (Marburg Variant)

A fulminant case of MS was described by Otto Marburg in 1906 that is now considered to be an example of a variant form of MS. Marburg described a 30-year-old woman who died 26 days after presenting with headaches, vomiting, confusion, left hemiparesis, gait unsteadiness, and a left extensor plantar response. This eponymously named variant is a monophasic illness with rapid progression that may lead to death from rapidly destructive brain pathology within a few weeks of onset.

The Marburg variant of MS is distinguished from ADEM, despite its overlapping clinical presentation, by the greater asymmetry of lesions, greater tendency to produce focal neurologic findings (eg, hemiparesis, aphasia), and lesser tendency to cause encephalopathy; it is most definitively distinguished pathologically, however. Lesions associated with the Marburg variant lack perivenous demyelination characteristic of ADEM. The large demyelinating lesions are also more destructive than those seen with ADEM or classical MS in terms of myelin loss and axonal injury.

Brainstem involvement with attendant quadriplegia, ophthalmoplegia, ataxia, dysarthria, and dysphagia may prove fatal. Aspiration pneumonia with potentially life-threatening consequences may result from impaired control of secretions; however, much of the morbidity in survivors reflects the severe destructive nature of the supratentorial lesions that predominate in this condition. Hemiparesis and seizures may result from cerebral hemispheric lesions. A decompressive hemicraniectomy was
recently performed in a patient with the Marburg variant who developed subfalcine and uncal herniation in the setting of increased intracranial pressure secondary to the presence of large, active supratentorial lesions.37

Treatments recommended for this rare condition are high-dose intravenous corticosteroids and immunosuppressants, such as cyclophosphamide.36 We recommend plasma exchange based on its favorable results in other fulminant cases of MS.

Baló Concentric Sclerosis

Baló concentric sclerosis is a tumefactive type of demyelinating disease characterized pathologically or radiologically based on a whorled pattern of demyelination of varying degrees; typically, it results in a solitary tumorlike lesion, and cerebral and brainstem locations have been reported. Similar to the Marburg variant of MS, Baló concentric sclerosis is usually characterized by a monophasic rapidly progressive course that can result in death within months.38 **Fig. 2** shows a characteristic Baló lesion with concentric rings. Causes of mortality include cerebral herniation and pneumonia often secondary to aspiration in the setting of bulbar dysfunction. Brainstem lesions may cause diplopia, dysarthria, dysphagia, ophthalmoplegia, and ataxia. A patient with cerebral hemispheric lesions may present with hemiparesis and hypoesthesia reminiscent of cerebral infarction.39

Young adults are most commonly affected, with the upper age range of published cases approaching the sixth decade of life. The distinctive onion bulblike concentric rings of demyelination and myelination that are best seen by MRI have also been found in patients with prototypic MS and ADEM, and the boundaries between MS and Baló disease are not entirely clear.40

**Fig. 2.** Baló concentric sclerosis. Axial FLAIR image showing a lesion with a concentric ring pattern in the right centrum semiovale. (*Courtesy of Dr John Corboy, University of Colorado, Denver, CO.*)
Intravenous methylprednisolone in one antemortem case was followed by clinical improvement. In another case, a 16-year-old boy with a biopsy suggestive of Baló concentric sclerosis was treated with adrenocorticotropic hormone and intravenous cyclophosphamide. Improvement was observed after 2 weeks, although the investigators questioned whether the patient may have had ADEM. The patient was later treated with azathioprine. Although optimal management is unclear, treatments used for acute attacks of MS seem to be most appropriate.

**Tumefactive Multiple Sclerosis**

MS lesions with atypical radiological features bearing a tumorlike appearance are labeled as having tumefactive MS. These radiological features include diameter greater than 2.0 cm, vasogenic edema, mass effect, and partially open ring enhancement (Fig. 3). Other diagnoses should be carefully considered before making a diagnosis of tumefactive MS, including high-grade glioma, metastasis, or primary CNS lymphoma. Magnetic resonance spectroscopy or a stereotactic brain biopsy may be helpful (see Demyelinating Disease Mimics and Investigations section). An opening sign (incomplete ring of gadolinium enhancement with the nonenhancing section of the ring typically abutting the deep gray matter or cortical ribbon), when present, may distinguish demyelinating disease from a neoplasm; the sensitivity and specificity of this sign are imperfect. An accurate histopathological determination of the MRI abnormality in question can be challenging, but is critical. A highly cellular lesion with atypical astrocytes, some with nuclear debris mimicking mitotic figures (Creutzfeldt cells), as seen in acute demyelinating disease, may lead to misdiagnosis in inexperienced hands as glioblastoma; inappropriate irradiation of an MS lesion may exacerbate demyelinating disease.

Tumefactive cerebral hemispheric lesions may produce mass effect, resulting in midline shift and transtentorial herniation. Cerebral herniation may lead to a decreased level of consciousness with eventual progression to stupor, coma, and then death. Such lesions may result in apraxia, aphasia, and cortical blindness. Seizures and

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**Fig. 3.** Tumefactive MS. (A) Axial FLAIR image showing a large right frontal lesion with T2 signal abnormality including a small resolving focus of hemorrhage at a biopsy site. (B) Axial T1 postcontrast image showing incomplete ring enhancement. (Courtesy of Dr Istvan Pirko, Mayo Clinic, Rochester, MN.)
encephalopathy less commonly occur. Brainstem lesions can cause quadriplegia, ophthalmoplegia, and bulbar dysfunction in the form of dysarthria or dysphagia.

A large retrospective study of biopsy-confirmed CNS IDD included 168 patients.\textsuperscript{43} Table 1 summarizes symptoms at disease onset; most had polysymptomatic presentation. All but 13 (7.7\%) of the patients had a prebiopsy MRI lesion greater than 2.0 cm in diameter. The median age at onset was 37 years, and the median time to the second attack was nearly 5 years. Half of patients ultimately had recurrent attacks leading to a diagnosis of relapsing-remitting MS, whereas a quarter remained monophasic. Compared with a population-based MS cohort matched for disease duration, the average Expanded Disability Status Scale score in those longer than 10 years from onset in the tumefactive MS group (1.5) was better than the population-based MS group (3.5), justifying aggressive rescue therapy even in critically ill patients.

High-dose intravenous corticosteroids are normally used for the initial treatment of tumefactive MS. In refractory cases, plasmapheresis may be effective.\textsuperscript{48,49}

**DEMYELINATING DISEASE MIMICS AND INVESTIGATIONS**

The differential diagnosis of suspect demyelinating disease is usually of “acute leukoencephalopathies” that are acute or subacute diseases that affect the white matter of the CNS that preferentially, but not exclusively, target the brain.\textsuperscript{1} Acute demyelinating disease may also present primarily as acute myelopathy, the differential diagnosis of which will be discussed separately later in this article. Leukoencephalopathy and myelopathy may occur simultaneously, and when this occurs, a diagnosis of demyelinating disease is more likely, although it does not exclude other diseases. Typically, clinicians consider a diagnosis of demyelinating disease when there is prominent involvement of long-fiber tracts and/or optic nerves; however, patients with acute leukoencephalopathies can present primarily or exclusively with symptoms often associated with diseases affecting gray matter, such as coma, cognitive impairment, or seizures. MRI has revolutionized the recognition of acute leukoencephalopathies that present with atypical symptoms by revealing pathology that is confined to or principally affects white matter. Radiologically, brain involvement in demyelinating disease can be unifocal, multifocal, or diffuse. In this section, situations where white matter disease is both the predominant and the causative lesion for the clinical state is considered and not situations wherein extensive

| Table 1 |
|-----------------|-----------------|
| **Neurologic symptoms at presentation of tumefactive MS** | |
| **Motor** | 50\% |
| **Cognitive** | 43\% |
| **Sensory** | 36\% |
| **Cerebellar** | 31\% |
| **Brainstem** | 24\% |
| **Visual field defect** | 10\% |
| **Seizure** | 6\% |
| **Optic neuritis** | \textsuperscript{~5\%}\textsuperscript{a} |
| **Bowel/bladder/sexual dysfunction** | \textsuperscript{~5\%}\textsuperscript{a} |

\textsuperscript{a} Estimated from bar graph.

ischemic, degenerative white matter changes are detected on MRI scan and thought to be incidental to the clinical presentation. Furthermore, situations where white matter changes are a result of extensive vasogenic cerebral edema reflecting an underlying focal cerebral lesion (eg, cerebral edema in a patient with a meningioma) are not considered.

The differential diagnosis of an acute leukoencephalopathy often focuses on acute inflammatory demyelinating diseases of the CNS; however, a large variety of other conditions in a variety of categories may mimic idiopathic inflammatory disease of the CNS, which may also be unifocal, and some multifocal or diffuse. Box 1 shows the major conditions to be considered in the differential diagnosis are ischemic vascular conditions, including vasculitis and other noninflammatory vasculopathies, tumors (lymphoma and glioma), infectious disorders, toxic exposures, and other inflammatory disorders including paraneoplastic disorders and autoimmune encephalopathies.

Although a detailed discussion of all of the entities summarized in Box 1 is beyond the scope of this article, we focus on the general approach, concentrating on recognizing “red flags” that suggest a diagnosis other than inflammatory demyelinating disease. These red flags are broadly classified into 4 groups:

1. Demographic and other risk factors: for example, cardiovascular risk factors (consider embolic strokes); preexisting cancer (consider metastases, coagulopathy or paraneoplastic disorder); known systemic autoimmune disease (consider vasculitis or other direct complication of autoimmune disease; note, however, that NMO frequently coexists with other autoimmune disease; coexisting systemic lupus erythematosus or Sjögren syndrome does not “rule out” NMO); phenotypic features of mitochondrial disorder (short stature, hearing loss, retinitis pigmentosa, migrainelike headaches, seizures)

2. Specific neurologic symptoms, especially ones atypical for demyelinating disease: for example, hearing loss (suggests Susac syndrome, the MRI of which is characteristic but frequently leads to misdiagnosis as ADEM because of the presentation with encephalopathy and multifocal nature of lesions with predilection for the corpus callosum); coexisting migraine (suggests cerebral autosomal dominant arteriopathy with subcortical ischemic leukoencephalopathy [CADASIL], antiphospholipid antibody syndrome or mitochondrial encephalomyopathy)

3. Specific non-CNS syndrome: for example, mucocutaneous ulcers (suggests Behçet syndrome); livedo reticularis (suggests antiphospholipid antibody syndrome); peripheral neuropathy (suggests B12 deficiency, sarcoidosis, or systemic vasculitis)

4. Imaging features. Acute demyelinating lesions are usually not single lesions, they exert relatively little mass effect, and they often manifest an “open ring” pattern of enhancement (discontinuity of a ring of gadolinium enhancement along the “trailing edge” of a tumefactive lesion, which, when present, is helpful in suggesting that demyelinating disease is the pathology). Red flags include prominent mass effect (suggests tumor, infection); homogeneous pattern of enhancement in some/most lesions (suggests neurosarcoidosis or lymphoma); lack of enhancement in an acute lesion (suggests progressive multifocal leukoencephalopathy, ischemia, paraneoplastic disorder, although can be seen occasionally in ADEM and does not rule out demyelinating disease).

A general approach to the differential diagnosis is shown in Fig. 4. As illustrated, the index of suspicion for an alternative diagnosis and the entity suspected based on the 4 categories of “red flags” outlined previously is a critical first step. Often, it is necessary
### Box 1
Differential diagnosis of acute leukoencephalopathy

1. **Inflammatory**
   a. Idiopathic inflammatory demyelinating disease
   b. Drug-induced inflammatory demyelinating disease (- 5FU/levamisolea; TNFα scavengers)
   c. Behçet syndrome
   d. Hashimoto (autoimmune) encephalopathy
   e. Other (eg, SLE, Sjogren syndrome)
   f. Neurosarcoidosis

2. **Ischemic/Vascular**
   a. Thromboembolic (cardiac, arterial, paradoxic)
   b. Vasculopathy
      i. Moyamoya
      ii. Retinocochlear vasculopathy of Susac
      iii. CADASIL
   c. Vasculitis
      i. Systemic
      ii. Primary CNS
      iii. Drug-induced
      iv. Infection-associated
   d. Venous infarction owing to venous sinus thrombosis
   e. Other
      i. Degos disease

3. **Metabolic/Nutritional**
   a. Mitochondrial encephalomyopathy
   b. Vitamin B12 deficiency
   c. Central pontine myelinolysis

4. **Infectious**
   a. Cerebritis/abscess
   b. Viral encephalitis
   c. Progressive multifocal leukoencephalopathy
   d. Whipple disease
   e. HIV
      i. Primary infection
      ii. Opportunistic infection
   f. SSPE and other slow viral illnesses
   g. Neurosyphilis

5. **Postinfectious**
6. **Radiation induced**
to begin treatment before alternative diagnoses can be excluded with certainty. There are relatively few contraindications to brief courses of high-dose corticosteroids, which may also benefit neoplasms, systemic autoimmune disorders, and other potential mimics, although they could potentially exacerbate some entities, such as progressive multifocal leukoencephalopathy. Conversely, response to corticosteroids should be interpreted conservatively and not considered as diagnostic of inflammatory demyelinating disease. Many disease entities, including lymphoma, cerebral edema of any cause, and even cord compression, may benefit from corticosteroids. Rapid and dramatic benefit with remission is suggestive of demyelinating disease in a clinically suspicious context, however. Identification of red flags and targeted investigation

### Toxic
- a. Chemotherapy
  - i. Methotrexate
  - ii. Nitrous oxide (produces acute B12 deficiency)
- b. Solvents
- c. Carbon monoxide
- d. Clioquinol*
- e. Lead

### Genetic
- a. Mitochondrial encephalopathy
- b. CADASIL*

### Oncologic
- a. Neoplastic
  - i. CNS glioma
  - ii. Gliomatosis cerebri
  - iii. Primary CNS lymphoma
  - iv. Intravascular lymphoma (neoplastic angioendotheliomatosis)
- b. Paraneoplastic-limbic encephalitis
  - i. Progressive spasticity and dementia associated with anti-amphiphysin antibodies*
  - ii. Brainstem encephalitis

### Miscellaneous
- a. Posterior reversible leukoencephalopathy
- b. CLIPPERS (Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids)*

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*Abbreviations: 5FU, 5 fluorouracil; CADASIL, cerebral autosomal dominant arteriopathy with subcortical ischemic leukoencephalopathy; CNS, central nervous system; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus; SSPE, subacute sclerosis panencephalitis; TNF, tumor necrosis factor.

*Entities currently thought to be rare, although some are recently recognized and accurate estimates of their occurrence are unavailable.

with relatively noninvasive tests based on high index of suspicion of a given diagnosis is preferred; however, when a patient is rapidly deteriorating or when corticosteroids fail and a patient has severe neurologic disability, a brain biopsy is often the most definitive way to establish a diagnosis of demyelinating disease when an adequate biopsy can be safely obtained (difficult or impossible for some brainstem and spinal cord lesions or deep cerebral lesions) of an acute, typically gadolinium-enhancing lesion. When the situation is less acute, a variety of ancillary investigations shown in Table 2 may be informative, although when the index of suspicion is low, these investigations often do not yield a diagnosis when ordered as a broad panel to rule out a variety of potential mimics.

Neuroimaging has acquired recent interest as a tool to distinguish neoplasms from tumefactive demyelinating disease.\textsuperscript{50–53} Indeed, in some pediatric metabolic disorders and mitochondrial disorders, the findings on MRS may be diagnostic.\textsuperscript{52} The findings in demyelinating disease evolve over the course of the lesion\textsuperscript{54} and are nonspecific.\textsuperscript{55} In general, there is an increase in choline, lipids, and myoinositol, reflecting myelin breakdown, an increase in lactate reflecting inflammation, and a decrease in N-acetylaspartate reflecting neuronal injury.\textsuperscript{52} The findings overlap with those seen in ischemic and neoplastic disorders, however. A persistent reduction in N-acetylaspartate accompanied by sustained reduction in magnetization transfer ratio, reflecting myelin loss, is suggestive of demyelination, but acute decreases in N-acetylaspartate may be transient and recovery may occur as a result of resolution of edema.\textsuperscript{54} Recently, increased levels of glutamate and glutamine have also been reported in demyelinating lesions.\textsuperscript{50,51} Another recently observed imaging characteristic of demyelinating disease, although perhaps not entirely specific, has been peripheral lesion restriction on diffusion-weighted imaging.\textsuperscript{51} These techniques should be used in the context of a multimodal approach of MR that includes conventional MRI (including analysis of gadolinium enhancement and diffusion-weighted imaging) and advanced MR techniques, including magnetization transfer, diffusion tensor imaging, and spectroscopy.

Brain biopsy may be diagnostic of acute demyelinating disease, but may be misinterpreted. Acute demyelinating lesions are typically hypercellular, and therefore may be misdiagnosed as brain tumors. The key features are the typical presence of large numbers of foamy macrophages with myelin debris, perivascular inflammatory cells,
and an intimate admixture of histiocytes with reactive astrocytes, occasionally with Creutzfeldt cells, which are prominent astrocytes with nuclear debris that may be mistaken for mitotic figures (see previous discussion of tumefactive demyelinating disease). Neuromyelitis optica lesions have some overlapping characteristics but are notable for the prominence of neutrophils and eosinophils in these lesions, prominent gray matter involvement, prominent perivascular complement and immunoglobulin,3 and selective loss of immunoreactive aquaporin-4 in acute lesions.56 As long-term treatment of NMO differs from MS, it is important to differentiate NMO from MS. ADEM lesions typically lack confluent demyelination but have prominent perivascular mononuclear inflammation; demyelination is typically mild and surrounds the zones of perivascular inflammation.2 Although acute disseminated encephalomyelitis may be associated with severe encephalopathy or coma, it typically causes less necrosis and the long-term outcome in survivors is favorable. Approximately 30% of cases are misdiagnosed, however, based on current clinical criteria, as ADEM is ultimately diagnosed with a fulminant form of MS, and it is precisely in such cases that an

| Table 2 |
| Non-MRI diagnostic evaluation of leukoencephalopathy of unknown cause |
| **Source** | **Test** | **Reason** |
| CSF | IgG index | Inflammatory demyelinating (MS) |
| | Oligoclonal bands | SSPE |
| | Measles antibody titer | HIV |
| | PCR | Other Infection |
| | *Tropheryma whippelii* | SSPE |
| | JC virus | Whipple disease |
| | Other (HSV, CMV, VZV) | PML |
| | Lactate/Pyruvate | Viral encephalitis |
| | **Echocardiogram** | Mitochondrial encephalopathy |
| | **Ophthalmologic examination, including fluorescein angiography** | Endocarditis |
| | **Evidence of retinal vasculitis?** | Cardioembolic source |
| | **Evidence of uveitis/pan planitis?** | Potential for paradoxical embolism |
| | **Cerebral angiography** | Susac syndrome |
| | | Other vasculitis (e.g., Eale disease) |
| | | MS |
| | | Sarcoidosis |
| | | Lymphoma |
| | **Other biopsies** | Vasculitis |
| | **Conjunctiva** | Vasculopathy (e.g., moyamoya disease) |
| | **Small bowel** | Atheroembolic disease |
| | **Skin** | Venous sinus thrombosis |
| | **Abbreviations:** CADASIL, cerebral autosomal dominant arteriopathy with subcortical ischemic leukoencephalopathy; CMV, cytomegalovirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; IgG, immunoglobulin G; JC, initials of patients in whom causative virus for PML first discovered; MRI, magnetic resonance imaging; MS, multiple sclerosis; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy; SSPE, subacute sclerosing panencephalitis; VZV, varicella zoster virus. |
early diagnosis and aggressive early immunosuppression may be most needed. Brain biopsy may show specific abnormalities leading to alternative diagnoses, either with standard staining techniques (eg, granulomas, vasculitis, neoplasms) or with special immunopathological stains, such as staining for light chain immunoglobulin fragments to detect lymphoma, or with other special pathologic techniques, such as in situ hybridization for JC virus for progressive multifocal leukoencephalopathy.

Inflammatory demyelinating disease may present with an acute myelitis leading to paraplegia or quadriplegia, urinary retention, and occasionally respiratory failure. The most important item in the evaluation is to rule out structural causes of myelopathy with MRI. The presence of a symptomatic intrinsic spinal cord lesion still has a broad differential diagnosis, which includes infectious myelitis as may occur with certain herpes viruses, such as varicella zoster; other inflammatory disorders, such as sarcoidosis; vascular disorders (vasculitis, embolic infarction, including cholesterol embolism, hypoperfusion syndromes, hemorrhage, and venous hypertension in association with arteriovenous fistula); neoplasms (glioma and ependymoma are the most frequent); paraneoplastic disorders often presenting as progressive “tractopathy”; structural disorders, such as syringomyelia; and occasionally metabolic disorders, such as B12 or copper deficiency. Differential diagnosis, as is true for leukoencephalopathies, depends on index of suspicion. Often corticosteroid treatment is urgently necessary for presumptive inflammatory demyelinating transverse myelitis before a final diagnosis. In addition to MRI, helpful investigations include CSF analysis (IgG index, oligoclonal bands, cell count, polymerase chain reaction [PCR] when viral infection suspected); serology (NMO-IgG for NMO spectrum disorder; SSA/Ro and SSB/La, which are also associated with NMO-associated myelopathy and increase risk of recurrent myelitis; antinuclear antibody; antiphospholipid antibody); B12 and methylmalonic acid and copper in patients with posterior column sensory syndrome suggestive of subacute combined degeneration of the cord; chest CT scan is indicated when neurosarcoidosis is suspected.

MANAGEMENT OF CNS INFLAMMATORY DEMYELINATING DISEASE EMERGENCIES

Management of patients’ CNS IDD emergencies can be divided into 3 categories: supportive care, acute remission-inducing therapy, and therapy of associated complication.

Supportive Care

Patients with severe attacks of CNS IDD may deteriorate rapidly, requiring airway support or mechanical ventilation. Although a detailed discussion of respiratory and other supportive care is beyond the scope of this article, it is appropriate to emphasize that aggressive supportive care is recommended because of the high frequency of reversibility of acute neurologic deficits experienced by patients with IDD. Critically ill patients are at risk of pressure ulcers, deep venous thrombosis, or respiratory or urinary tract infections; management requires a multidisciplinary team.

Acute Remission-Inducing Treatment

Therapy for the severe attack of CNS IDD generally consists of corticosteroids and plasma exchange. Intravenous corticosteroids are indicated for patients with a suspected severe or catastrophic demyelinating event even before defining the specific type of underlying CNS IDD, such as distinguishing between ADEM from acute severe MS or a severe attack of MS or between MS or NMO. High-dose methylprednisolone, typically 1 g daily intravenously for 3 to 5 days, is recommended for acute MS
attacks. There are no controlled studies that specifically aimed at studying the efficacy of corticosteroids in catastrophic CNS IDD. It is widely thought that patients with acute severe MS (Marburg variant) usually die of their illness based on the literature, but this is likely the result of reporting biases of fatal cases. This impression has led to therapeutic nihilism; however, we have treated patients who have survived and experience prolonged quiescent periods if they survive their acute or subacute illness. Corticosteroids have rapid onset of action. They reduce inflammatory edema by reducing capillary permeability as early as 8 hours after administration. The radiological accompaniment is a reduction in gadolinium enhancement on MRI. Corticosteroids induce monocytopenia, and reduce the number of CD4 lymphocytes and B cells. In addition, they reduce proinflammatory cytokines. Animal models show that glucocorticoids may prevent axonal injury when administered early in the disease.

Plasma exchange (PLEX) is now widely accepted to be an effective treatment of severe attacks of CNS IDD, and perhaps the treatment of choice. Its efficacy in this context is supported by one randomized controlled trial (class I evidence) for effectiveness of PLEX in severe acute demyelinating attacks of MS, ADEM, transverse myelitis, and NMO. Plasma exchange is achieved by separation of plasma from the cellular blood elements, discarding plasma, and replacing it with colloid fluid. In the United States, the process is accomplished typically with a centrifuge device, although a variety of filtration devices, occasionally followed by a second selective form of filtration or immunoadsorption, are used outside of the United States to accomplish similar or more complete Ig removal; PLEX may require placement of a double-lumen central venous catheter, although it can be accomplished via large-bore peripheral venous catheters if venous access is satisfactory. Evidence for efficacy of PLEX in severe CNS IDD was robustly demonstrated by Weinshenker and colleagues in a randomized controlled crossover study of 22 patients with severe attacks of CNS IDD who failed to respond to intravenous corticosteroids, including those with transverse myelitis, ADEM, NMO, and MS. Patients were randomized to 7 sessions of true versus sham exchanges over 14 days. Nine patients experienced moderate to marked improvement, 8 of whom received true PLEX and 1 sham therapy. After crossover, 3 of 8 who had received sham exchange in the first treatment period and had not improved, experienced moderate to marked improvement after receiving active treatment in the second treatment period, whereas none of the 6 patients who failed active plasma exchange improved after crossing over to sham treatment. Several subsequent uncontrolled prospective or retrospective studies that followed this one confirmed this finding in patients with severe attacks of CNS IDD, including transverse myelitis, MS, and NMO. Keegan and colleagues retrospectively studied patients treated with PLEX and found 59 patients with severe episodes of CNS IDD, including 22 patients with MS, 10 with NMO, and 10 with ADEM. The investigators found that 44.1% of patients showed moderate or marked response and that early therapy (within 20 days of symptom onset), male sex, and preservation of tendon reflexes predicted a positive response. Llufriu and colleagues conducted a retrospective study of 41 patients with CNS IDD episodes treated with PLEX. Thirty-nine percent of patients showed improvement at hospital discharge and 63% at 6-month follow-up. The mechanism of action of PLEX is suspected to be the result of removal of humoral circulating factors, although alterations in T-cell behavior following PLEX have also been documented. In NMO, antibodies to the dominant CNS water channel AQP-4 (NMO IgG) have been shown to be pathogenic in the disease. Therefore, removal of this antibody and complement might explain its therapeutic efficacy in NMO. In addition, other humoral factors, including proinflammatory cytokines and chemokines,
likely have an important role. On the other hand, MS is associated with cellular and humoral mechanisms and the exact mechanism of PLEX efficacy in acute MS attacks is uncertain, although the presence of antibody and complement in biopsies from patients undergoing plasma exchange showed strong concordance with favorable response. Complications of PLEX in general relate to the venous access (risk of sepsis or accidental arterial puncture), hypotension, or citrate toxicity; angiotensin-converting inhibitor medications may cause systemic reactions, such as flushing, hypotension, and dyspnea owing to impaired bradykinin metabolism in patients treated with immunoabsorption. There are no PLEX-related complications that are unique to patients with CNS IDD.

The role of cyclophosphamide in treatment of severe attacks of CNS IDD has not been studied systematically. A retrospective study of patients with transverse myelitis showed improvement in outcome. The study, however, was limited by the retrospective nature, variability in baseline patient characteristics, and nonstratification of patients based on specific underlying cause of transverse myelitis (MS, NMO, isolated transverse myelitis). Cyclophosphamide may have a role in chronic therapy once patients recover the severe attack in patients at risk of relapse.

Pradhan and colleagues reported a series of 4 children (ages 1, 4, 12, and 14 years) with ADEM who did not respond to intravenous corticosteroids and subsequently following treatment with IVIG improved markedly. All 4 patients were in critical care units with encephalopathy and quadriplegia and showed response to therapy within 2 to 3 days of IVIG therapy and were able to ambulate over 10 to 14 days.

The need for and choice of a chronic immunotherapy of CNS IDD is determined by the underlying demyelinating disease context; for example, immunomodulatory therapies effective for MS are not effective for NMO. A detailed discussion of chronic maintenance immunotherapy is beyond the scope of this article.

**Emergency Complications**

The potential medical complications of CNS IDD are diverse, as shown in Box 2. They may result from unique functions related to the site of the lesion (eg, neurogenic pulmonary edema with certain brainstem lesions), may result from particularly severe inflammation (eg, mass effect and cerebral herniation), or may reflect a unique pathophysiology of a specific inflammatory demyelinating disease (eg, posterior reversible encephalopathy in the context of NMO owing to disruption of brain water channel function). Management of these complications is generally the same as for that of the same complications in other settings, but also involves management of the underlying inflammatory demyelination, as described in the previous section on management of demyelinating emergencies.

**Box 2**

**Emergency complications of CNS IDD**

- Raised intracranial pressure and cerebral herniation
- Neurogenic pulmonary edema
- Myocardial dysfunction
- Hypothermia
- Posterior reversible encephalopathy syndrome
- Aspiration pneumonia
Large CNS inflammatory demyelinating lesions may result in cerebral edema and consequently raised intracranial pressure (ICP) in the setting of tumefactive multiple sclerosis or acute severe multiple sclerosis (Marburg variant), or in diffuse CNS IDD (ADEM). This complication should be treated aggressively with measures to reduce ICP, including elevation of head of the bed, fluid restriction, blood pressure control, hyperventilation (to a target pCO2 28–32 mm Hg), intravenous mannitol (1.0–1.5 g/kg of 20% solution rapid infusion), and, when necessary, with phenobarbital coma and/or hypothermia.

**Table 3** summarizes several reported cases with resistant focal cerebral edema treated with hemicraniectomy that include focal tumefactive lesions that occurred in the context of different types of CNS IDD. The development of raised ICP occurred at different tempos and the management of raised ICP and of the primary CNS IDD differed in these cases. Mass effect is uncommon in CNS IDD, but may occur with tumefactive demyelinating lesions, acute severe MS, or ADEM. The reasons why certain patients with CNS IDD experience mass effect is unknown. The clinical outcome relates to the degree of injury and is a combined effect of the cerebral edema and raised ICP and primary pathologic process of the demyelinating disease. Hemicraniectomy should be considered in patients with tumefactive lesions with refractory raised ICP as a life-saving measure.

Respiratory failure may occur in patients with inflammatory demyelinating disease. Patients with NMO or MS with lesions involving the brainstem and cervical cord may develop neurogenic respiratory failure. Respiratory failure in the context of an acute attack is less common in patients with multiple sclerosis, who typically develop respiratory failure in the setting of severe chronic preexisting disability. Mechanical ventilation is indicated in these patients with catastrophic brainstem attacks, while aggressive treatment for underlying inflammatory demyelinating disease is administered. Respiratory failure in patients with MS is often caused by aspiration pneumonia in patients with chronic progressive disease; mechanical ventilation and tracheostomy in these patients is associated with overall improved survival.

Neurogenic pulmonary edema may occur in patients with head and/or neck injury, subarachnoid hemorrhage, seizures, brain tumors, and Reye syndrome. The most well recognized lesion in the setting of IDD associated with neurogenic pulmonary edema is a lesion of the nucleus tractus solitarius located in the medulla oblongata accompanied by neurologic signs of medullary involvement, such as rotary nystagmus, dysphonia, unilateral paralysis of the soft palate, mental status changes, diplopia, or hemifacial numbness. It may, however, occur as a solitary manifestation of a lesion in this location. A single patient with MS is reported to have developed unilateral neurogenic pulmonary edema responsive to intravenous steroid therapy. Animal models show that lesions of the nucleus of the tractus solitarius cause increased pulmonary arterial pressure and pulmonary lymph flow resulting in pulmonary edema. The pathophysiology underlying this rare complication is likely multifactorial and includes altered vascular permeability and abnormal myocardial function owing to alteration in central sympathetic output. Other possible causes include proinflammatory cytokines and chemokines (tumor necrosis factor α, interleukin-1β, and interleukin-6) that may be induced by acute neurologic disorders. Focal structural lesions have been implicated in neurogenic pulmonary edema, such as lesions of the preoptic chiasm that are believed to cause pulmonary edema as a release phenomenon as a result of loss of the inhibitory effect of the preoptic chiasm. Acute heart failure is another rare complication of MS that may result in pulmonary edema or cardiogenic shock. It is attributed to variation in sympathetic tone as has been invoked as a potential explanation of pulmonary edema. One reported patient
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Age, y/ Gender</th>
<th>Interval (Onset-Craniecotomy)</th>
<th>Symptom Onset</th>
<th>MRI Findings</th>
<th>Therapy Before Hemicraniectomy</th>
<th>Therapy Following Hemicraniectomy</th>
<th>Outcome/Interval from Hemicraniectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed et al, 2010</td>
<td>38 F</td>
<td>2 d</td>
<td>Ataxia, hemiparesis, coma</td>
<td>Monofocal</td>
<td>Mannitol, dexamethasone</td>
<td>Intravenous methylprednisolone pulse therapy</td>
<td>Minimal deficit (Interval NS)</td>
</tr>
<tr>
<td>Von Stuckrad-Barre et al, 2003</td>
<td>34 F</td>
<td>6 d</td>
<td>Hemiplegia</td>
<td>Monofocal</td>
<td>Intravenous methylprednisolone, midazolam, mannitol</td>
<td>Intravenous immunoglobulin</td>
<td>Minimal deficit (3 mo)</td>
</tr>
<tr>
<td>Nilsson et al, 2009</td>
<td>50 F</td>
<td>2 wk</td>
<td>Seizures, dysphasia, hemiparesis</td>
<td>Multifocal</td>
<td>Betamethasone</td>
<td>High-dose intravenous corticosteroids pulse therapy</td>
<td>Minimal deficit (6 wk)</td>
</tr>
<tr>
<td>González Sánchez et al, 2010</td>
<td>31 F</td>
<td>NS</td>
<td>Coma</td>
<td>Monofocal</td>
<td>PLEX, IVIG, barbiturate coma</td>
<td>No further treatment</td>
<td>Minimal deficit (3 mo)</td>
</tr>
</tbody>
</table>

*Abbreviations: IVIG, intravenous immunoglobulin; NS, not specified; PLEX, Plasma exchange.*
had myocardial impairment in addition to unilateral pulmonary edema associated with severe left ventricular dysfunction on transthoracic echocardiography. She was treated with aggressive diuresis in addition to intravenous steroid therapy and improved within 24 hours. Another study reported acute heart failure in a 19-year-old woman with a 3-week history of progressive bulbar symptoms and MRI evidence of multiple T2 hyperintensities. She developed acute cardiac failure and cardiogenic shock with signs of multiorgan failure. The patient was treated with implantation of a left ventricular assist device. Myocardial function recovered spontaneously after 2.5 months and the device was successfully explanted. There was no histopathological evidence of myocarditis. Eight weeks later, the patient had a clinical relapse of MS. Whether this is complication is similar in pathogenesis to stress cardiomyopathy (Takotsubo cardiomyopathy) is unclear.

Hypothermia is an uncommon and easily unrecognized complication that typically occurs in patients with advanced MS and manifests as episodic encephalopathy (Box 3). Typically, hypothermia occurs in patients with advanced disability in the setting of chronic demyelinating disease and not in the setting of an acute inflammatory attack. Body temperature may decline to as low as 29°C and thus a thermometer capable of reliably recording hypothermia is essential to make the diagnosis. Lower temperatures are often associated with other systemic symptoms, such as thrombocytopenia, coagulopathy, or neurologic symptoms, such as delusions, dysarthria, bradycardia, and/or miosis. Patients with hypothermia demonstrated MRI abnormalities in the hypothalamic region. Severe episodes may lead to death. Subacute onset of neurologic decline is typical. Patients respond to rewarming within 48 hours. Recurrent episodes were reported to respond to steroid therapy, perhaps suggesting an underlying inflammatory etiology.

PRES is a clinical-radiographic condition of multiple symptoms, including seizures, encephalopathy, headache, and visual symptoms, such as cortical blindness, associated with reversible areas of subcortical brain edema on MRI. Lesions occur preferentially in the posterior areas of the brain. It occurs in hypertensive emergencies and is associated with eclampsia. It was reported in a recent series of 5 patients with NMO, which likely reflects excess occurrence in this subtype of IDD. The postulated pathophysiology in this context is thought to relate to depletion of aquaporin-4 (AQP4) water channels, which is known to occur when cells are exposed to NMO-IgG in the absence of complement. Autopsy samples show extensive loss of AQP4 regardless of lesion stage in the spinal cord lesions of patients with NMO. AQP4 knock out mice are prone to vasogenic edema. PRES is treated with supportive care and corticosteroids to reduce inflammatory activity of NMO; most lesions resolve within 7 days.

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**Box 3**

**Vignette: hypothermia presenting as encephalopathy in a patient with secondary progressive MS**

A 60-year-old man with MS for more than 20 years with a secondary progressive course presented with slowness of thinking and speech that progressed to coma. He had a persistent core body temperature of 32°C. After improving upon rewarming, he experienced recurrence of symptoms with subsequent drops in core body temperature. His optimal body temperature was 35°C and once the temperature dropped below 33°C, he developed slowness of speech and thinking. Neurologic examination revealed mild cognitive impairment. He had bilateral internuclear ophthalmoplegia, mild cerebellar dysarthria, cerebellar incoordination in the upper extremities, and paraplegia. Head MRI showed chronic MS lesions with no evidence of contrast enhancement.
REFERENCES