Immune Mediated Diseases and Immune Modulation in the Neurocritical Care Unit

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Abstract This chapter will review the spectrum of immune-mediated diseases that affect the nervous system and may result in an admission to the neurological intensive care unit. Immunomodulatory strategies to treat acute exacerbations of neurological diseases caused by aberrant immune responses are discussed, but strategies for long-term immunosuppression are not presented. The recommendations for therapeutic intervention are based on a synthesis of the literature, and include recommendations by the Cochrane Collaborative, the American Academy of Neurology, and other key organizations. References from recent publications are provided for the disorders and therapies in which randomized clinical trials and large evidenced-based reviews do not exist. The chapter concludes with a brief review of the mechanisms of action, dosing, and side effects of commonly used immunosuppressive strategies in the neurocritical care unit.

Keywords Immunomodulation · Autoimmune · Plasmapheresis · Corticosteroids · Intravenous immunoglobulin · Cyclophosphamide · Rituximab

Immune-mediated Diseases That Affect the Nervous System

Demyelinating Diseases

Multiple Sclerosis

Multiple sclerosis (MS) is the most common immune-mediated disease of the central nervous system (CNS) and the leading cause of nontraumatic disability among young adults in Western countries [1]. The course may be relapsing and remitting or chronic and progressive. The incidence of MS in Europe and North America is between 50 and 70 per million of the population [1]. Patients with MS have a threefold increase in mortality and a shorter life expectancy than the general population (by 6–12 years), and half of the deaths that occur are related to MS itself [2–6].

Autoimmune responses to myelin-associated peptides, including myelin basic protein, proteolipid protein, and myelin oligodendrocytes glycoprotein are seen in patients with MS [7, 8]. The immune responses to these antigens may be either cellular or humoral, and the described pathology is quite varied [9]. The effect of immune-modulating treatments on disease activity would thus be expected to vary depending on the predominant pathophysiology, although in general practice the underlying immunopathology for a given individual is not known.

A full discussion of MS, its diagnosis, and the approaches to chronic immunosuppression are beyond the scope of this chapter; therefore, readers are referred to several recent reviews for additional information [10–12]. Comments regarding the treatment of MS will be restricted to those atypical presentations that may necessitate intensive care unit (ICU) admission, which primarily occurs with the rare tumefactive

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variants of MS and include Schilder's disease, Marburg disease, and Balo's concentric sclerosis. Magnetic resonance imaging (MRI) generally shows a single large demyelinating lesion associated with marked edema and mass effect [13]. Symptoms include focal neurological deficits and seizures. For patients with larger lesions, decreased level of consciousness can occur due to elevated intracranial pressure and incipient herniation. MRI, including magnetic resonance spectroscopy, can be helpful in distinguishing tumefactive lesions from true tumors, but biopsy may be necessary for definitive diagnosis [14–16]. Tumefactive lesions can also be mistaken for severe acute disseminated encephalomyelitis (ADEM), and ADEM should be considered in the differential, especially in patients with fever, recent illness, or recent vaccine. Tumefactive lesions are also reported in patients with neuromyelitis optica (NMO) spectrum disorders [17–20].

High-dose parenteral corticosteroids are the primary therapy for the treatment of acute MS exacerbations, including tumefactive MS [21, 22]. Based on a single randomized clinical trial (RCT), plasmapheresis may also have some benefit for treating exacerbations in patients with relapsing-remitting disease [23]. Intravenous immune globulin (IVIG) does not appear have any benefit as an adjunct therapy to methylprednisolone in the treatment of MS exacerbations, and generally it is also not recommended [24]. Because the mass effect associated with tumefactive lesions can potentially lead to herniation, osmotic therapy is often instituted concomitant with corticosteroids, and decompressive hemicraniectomy has been reported in the treatment of tumefactive MS [25].

Neuromyelitis Optica

NMO is an inflammatory demyelinating disorder of the CNS that primarily affects the optic nerves (optic neuritis) and the spinal cord (myelitis). NMO is rare and accounts for only 1% of all demyelinating diseases [26–28]. The incidence of NMO is estimated to be approximately 4 per million of the population and the prevalence is somewhere between 3 and 44 per million, depending on ethnicity and geographic location [26–29]. Disease onset is usually in the fourth decade of life; women are affected more commonly than men (approximately 3:1); and non-Caucasians (especially Japanese) are affected more commonly than Caucasians [29–32]. Most patients with NMO (60–90%) have autoantibodies directed toward the aquaporin 4 (AQP4) channel, and these antibodies are thought to be pathogenic [29, 33]. AQP4 is the most common water channel in the brain and is expressed on astrocytes of the glia limitans. NMO immunoglobulin (Ig) G antibodies can induce breakdown of the blood–brain barrier and cause destruction of the astrocytes that express AQP4 [34–36].

Patients with NMO can present with a monophasic illness, but more commonly have a relapsing-remitting course.

The visual loss in NMO tends to be more severe than in MS and can affect both eyes simultaneously or in rapid succession [30, 37, 38]. Spinal cord involvement is longitudinally extensive (≥ 3 vertebral segments) in patients with NMO in contrast to the spinal lesions seen in patients with MS, which are much more limited in extent [39]. Respiratory function can be affected by spinal lesions that extend into the brainstem, but isolated brainstem lesions leading to respiratory compromise have also been described [29, 40]. The prognosis appears to be particularly poor in patients who require mechanical ventilatory support [40]. The 5-year mortality in NMO is reported to be as high as 32%, with most deaths occurring due to respiratory failure [41, 42]. Because NMO can present with tumefactive lesions, brain death due to herniation has also been described [20].

The diagnosis of NMO requires the appropriate constellation of clinical symptoms (optic neuritis and transverse myelitis) plus 2 of the following: MRI imaging demonstrating extensive longitudinal involvement of the spinal cord; MRI imaging of the brain not meeting diagnostic criteria for MS; identification of AQP4 antibodies in the serum or cerebrospinal fluid (CSF) [43]. The AQP4 antibodies are fairly specific for NMO but have limited sensitivity, and thus seronegative patients can be diagnosed with NMO [44]. CSF analysis may show pleocytosis and elevated protein, and oligoclonal bands (OCBs) may be seen, but are much less common than in MS [29, 38, 45].

There are no RCTs addressing the best approach to immunomodulation in patients with NMO. The standard approach for treating acute attacks is similar to that for the treatment of MS exacerbations and consists of high-dose parenteral corticosteroids followed by a gradual oral corticosteroid taper [45]. Most literature suggests that plasmapheresis is of benefit, and plasmapheresis is generally recommended when corticosteroids are not effective [23, 45–47]. The utility of IVIG in the treatment of acute NMO has not been adequately studied. A variety of immunosuppressive drugs, including rituximab, mitoxantrone, mycophenolate mofetil (MMF), and azathioprine have been used to prevent relapses of NMO, but their effectiveness in the treatment of acute exacerbations is unknown [48–52].

ADEM

ADEM is a monophasic disorder characterized by acute inflammation of the brain and spinal cord. ADEM is most common in children, with an incidence of approximately 4 per million of the population who are <20 years of age (and even higher among younger children) [53]. Adults can develop ADEM, but it is uncommon. Symptom onset usually occurs within days to weeks after a trivial infection or a vaccination, but ADEM can also occur without a clear precipitant [54, 55]. Pathogens associated with ADEM include a

number of different viruses, β -hemolytic streptococci, and intracellular bacteria, such as *Mycoplasma pneumonia* [56]. Symptoms vary, but may include diffuse encephalopathy, focal neurological signs, and seizures [55]. Maximal neurological deficits usually occur within hours to a few days after symptom onset. There are no specific diagnostic criteria for ADEM, and the diagnosis generally relies on the exclusion of other disorders (such as MS). MRI shows multifocal T2 and fluid attenuation inversion recovery (FLAIR) FLAIR-weighted lesions, which may faintly enhance, and the spinal cord is involved in most cases [55, 57]. The lesions can show restricted diffusion in the acute phase [58]. CSF analysis shows elevated protein and/or pleocytosis in most patients [54]. In distinction from MS, OCBs are rare in ADEM [59]. Acute hemorrhagic leukoencephalitis (AHLE), or Hurst's Disease, is considered to be a more severe type of ADEM by some and a distinct clinical entity by others. The clinical characteristics of AHLE are quite similar to those for ADEM, but AHLE may preferentially affect the brainstem, and as the name suggests, the lesions are hemorrhagic. Red blood cells, as well as polymorphonuclear cells, are generally present in the CSF of patients with AHLE, whereas OCBs are rare [60–62].

The pathophysiology of ADEM and AHLE is thought to be related to either molecular mimicry, with the immune response to the pathogen cross reacting to components of myelin, or to direct pathogen-mediated injury of the brain, with altered antigens exposed to the immune system precipitating an immune response. A high proportion of patients with ADEM, especially children, are found to have antibodies directed toward myelin oligodendrocytes glycoprotein [63–66]. AHLE has been reported to occur in the context of several different viral infections, including cytomegalovirus, Epstein Barr virus, herpes simplex virus, the mumps virus, and the H1N1 virus [67–71].

There are no RCTs addressing appropriate therapy for ADEM; recommendations regarding therapeutic interventions are therefore limited and based on anecdotes and case series. Prior to institution of immune modulating therapy, the possibility of infectious encephalitis should be excluded. Treatment with high-dose parental corticosteroids (followed by an oral taper) is considered to be the standard of care. Plasmapheresis and/or IVIG may be of benefit for patients who fail to respond to corticosteroids [23]. Finally, in both ADEM and AHLE, the brain lesions can be associated with significant edema. The mass effect associated with these lesions can be life-threatening, and measures to reduce brain swelling, including hypothermia and craniectomy, may be needed [72–75]. In addition to demyelination, pathology in AHLE shows fibrinoid necrosis of small vessels [62]. Outcome is poor in patients who have AHLE, with mortality approaching 70% [62]. Patients with ADEM have a much better outcome, but approximately one third of them will go on to develop MS [76].

Acute Transverse Myelitis

Acute transverse myelitis (ATM) describes the involvement of the spinal cord by any inflammatory process that leads to sensory, motor, or autonomic dysfunction. Demyelinating disorders, such as MS and NMO, are probably the most common causes of ATM. Absent MS and NMO, most cases of ATM appear to follow an infection or vaccination, although the etiology of ATM is not determined in up to 30% of cases [77]. Rarely, systemic autoimmune disorders, such as systemic lupus erythematosus (SLE) and Sjögren's Syndrome can affect the spinal cord [77]. The reported incidence of ATM depends on whether or not patients with MS and NMO are included in the estimate. Overall, there are approximately 25 cases of ATM per million of the population each year; if patients with MS and NMO are excluded, the annual incidence of ATM is somewhere between 1 and 8 per million, with a peak incidence between the ages of 10 and 19 and 30 and 39 [77–79].

The onset of symptoms in ATM can be either acute or subacute, and symptoms usually peak within 4 hours to 21 days of onset (median time to maximum deficit is 3 days) [80]. Clinical examination generally reveals a clear sensory level. The cord involvement, by definition, is bilateral, but not necessarily symmetric. The diagnostic criteria suggest that there be evidence of spinal cord inflammation, either by MRI imaging (gadolinium enhancement of the cord) or by CSF analysis (pleocytosis and/or an elevated IgG index), but in reality, many patients with ATM have neither [78, 79]. The differential diagnosis of longitudinally extensive cord lesions (≥ 3 vertebral levels) also includes NMO, SLE, sarcoidosis, Sjögren's Syndrome, and spinal ischemia [81–83]. Extrinsic compression of the cord, neoplastic and vascular etiologies, and radiation-induced changes of the cord must be excluded before the diagnosis of ATM can be made. MS should also be considered in the differential of ATM, although the cord involvement in MS is generally more discrete and spans < 2 vertebral levels [80]. Furthermore, MRI of the brain should be normal in patients with ATM, whereas patients with MS will often have evidence demyelination [78].

There are no RCTs to define the optimal treatment for ATM, but high-dose parenteral corticosteroids are the standard of care [84]. Limited data suggest that plasmapheresis may be of benefit for patients with ATM that fail to respond to high-dose treatment with corticosteroids [23, 85, 86]. Outcome from ATM can be predicted by the severity of symptoms at presentation. Patients with a very rapid onset of symptoms and features of spinal shock are especially prone to poor outcome [78, 80].

Guillain-Barré Syndrome

Acute inflammatory demyelinating polyneuropathy (AIDP) or Guillain-Barré syndrome (GBS) is perhaps the prototypical

immunologically mediated neurological illness prompting admission to the ICU. The incidence of AIDP/GBS is roughly 12 to 19 per million of the population per year, and males are more commonly affected than females [87]. The diagnosis of AIDP/GBS depends on the appropriate clinical presentation with ascending weakness and the finding of areflexia. By definition, patients should present within 4 weeks of symptom onset, although the mean time from symptom onset to maximal symptoms is approximately 10 days [88]. CSF analysis usually reveals elevated protein and few cells (cytoalbuminemic dissociation). Electrical studies show absent F waves. The differential diagnosis for acute onset of flaccid paralysis is fairly extensive, but it is important to note the recent addition of west Nile virus to the differential [89].

Patients with AIDP/GBS often require mechanical ventilation and AIDP/GBS is one of the most common causes of neuromuscular respiratory failure [90]. Autonomic instability is also very common, with dramatic fluctuations in blood pressure and heart rate. Symptomatic bradycardia has also led to the need for pacemaker implantation in some patients [91–96].

The clinical trials in AIDP/GBS have largely been performed in patients with moderate-to-severe disease (unable to walk) early after symptom onset (within 2 weeks). Plasmapheresis is the only therapy shown to be superior to supportive care alone [97]. Administration of IVIG is as effective as plasmapheresis, but the combination of plasmapheresis and IVIG offers no benefit over plasmapheresis alone [98]. Importantly, corticosteroids are ineffective in the treatment of GBS [99]. The usefulness of plasmapheresis and IVIG in patients with milder symptoms at presentation and in those who have had more than 2 weeks of symptoms is unknown. That plasmapheresis may be of benefit in patients without severe disease, however, was suggested by a large multicenter study that found 2 sessions of plasmapheresis to be better than none in mildly affected patients and that 4 sessions of plasmapheresis were better than 2 in moderately affected patients, indicating a dose response [100].

Current recommendations are that plasmapheresis should be offered to patients with AIDP/GBS who are unable to walk independently or who require mechanical ventilation. For patients with milder presentations of AIDP/GBS, plasmapheresis should also be considered, but the data to support this recommendation are not as robust. IVIG is a reasonable alternative to plasmapheresis, and the data do not support the superiority of one treatment over another [23, 98]. Despite improvement in ICU care and advances in immunotherapy, the mortality in patients with AIDP/GBS are still at least 2 to 3%, and may even approach 10% [88, 101–103]. Advanced age and the presence of medical comorbidities are the most potent predictors of poor outcome [104–106].

Miller-Fisher Syndrome

Miller-Fisher Syndrome (MFS) is a variant of GBS and is characterized by impaired eye movements (ophthalmoplegia), incoordination (ataxia), and loss of tendon reflexes (areflexia). Bickerstaff's Brainstem Encephalitis (BBE) is similar to MFS, but patients with BBE have upper motor neuron signs and impaired consciousness. Diplopia and gait impairment are the most common presenting symptoms for both disorders, and these symptoms often develop on the same day [107]. The annual incidence for MFS is approximately 1 per million of the population; BBE is much less common. Men appear to be affected more commonly than women, especially with BBE [107].

MFS and BBE are considered to be a single autoimmune disease with variable involvement of the CNS and peripheral nervous system (PNS). The suggestion that MFS and BBE have a common pathogenesis is based on the fact that anti-GQ1b IgG antibodies and antecedent *Campylobacter jejuni* or *Haemophilus influenza* infections may be seen in both disorders [107–109]. The classic CSF finding of cytoalbuminemic dissociation is a bit more common in MFS, whereas pleocytosis is a bit more common in BBE, but these differences do not discriminate between the 2 disorders [107]. And given that impaired consciousness is necessary to diagnose BBE, it is not surprising that patients with BBE are more likely to have MRI evidence of brainstem involvement than patients with MFS [107, 110]. The neurophysiological findings (absent soleus H-reflex) are also common in both conditions [107].

There are no RCTs assessing therapeutic options in either MFS or BBE, but case series describe successful use of plasmapheresis and high-dose parenteral corticosteroids [111]. The usefulness of IVIG is unclear [112].

Primary CNS Vasculitides

Primary Angiitis of the Central Nervous System

Primary angiitis of the central nervous system (PACNS) is a rare disorder associated with significant morbidity and mortality. The annual incidence is approximately 2 per million of the population, and it occurs more commonly in men, with the onset usually in the fifth decade of life [113, 114]. Patients generally present with headache and encephalopathy; strokes may also occur. MRI is almost always abnormal, but the imaging findings are nonspecific. CSF may show evidence of mild inflammation, with pleocytosis, and an elevated protein level, but the CSF may also be normal. Systemic markers of inflammation, such as plasma high sensitivity C-reactive protein and the erythrocyte sedimentation rate are generally normal. Angiography may reveal typical findings of beading, with arterial narrowing followed

by arterial dilation. The differential diagnosis of PACNS includes the reversible cerebral vasoconstriction syndrome, which is a self-limited disorder that occurs in individuals following exposure to vasoactive substances [115, 116].

Brain biopsy is the gold standard for diagnosis of PACNS, but false negative biopsies do occur [117]. Biopsy yield may be better if it is directed to an area of enhancement on MRI [118]. PACNS affects both medium and small arteries of the meninges and cortex. Typical histological findings include lymphocytic cellular infiltrates with a variable number of plasma cells, histiocytes, neutrophils, and eosinophils. In some cases, the inflammatory infiltrate may be granulomatous or necrotizing [118]. Patients with granulomatous angiitis of the CNS tend to do more poorly than those with PACNS and often require more aggressive immunosuppressive therapy [119].

There are no RCTs to address appropriate therapy for PACNS. Treatment is generally initiated with high-dose corticosteroids and is often followed by cyclophosphamide [119]. Relapse is common and occurs in up to 25% of patients [113]. Successful therapy with tumor necrosis factor (TNF)- α inhibitors, rituximab, and MMF has been described [120–122]. Recent reports suggest that mortality and severe morbidity is seen in at least 14% of patients 1 year after diagnosis [118].

Cerebral Amyloid Angiopathy-Related Inflammation

Some patients with cerebral amyloid angiopathy (CAA) develop a marked CNS inflammatory response resulting in cerebral edema and mass effect. These individuals present with the acute or subacute onset of headaches, cognitive and behavioral changes, seizures, and focal neurological deficits. CAA with inflammation is rare and is thought to be due to an inflammatory response to β amyloid ($A\beta$) in the walls of blood vessels [123, 124]. This hypothesis is supported by the observation that a subset of patients with Alzheimer's disease undergoing experimental therapy with an antibody directed toward $A\beta$ developed a syndrome closely resembling spontaneous CAA-related inflammation [125]. Further, recent reports indicate that patients with CCA-related inflammation have antibodies directed toward $A\beta$, suggesting that an aberrant immunological response is responsible for the inflammation [126, 127].

Patients with CAA-related inflammation tend to be younger (seventh decade of life) than patients with CAA and no inflammation (eighth decade of life) and are more likely to be men [128]. In cases in which genotyping has been performed, most patients have the apoe $\epsilon 4/\epsilon 4$ genotype [129]. CSF analysis may show elevated protein and/or pleocytosis [129]. An MRI typically shows asymmetric white matter hyperintensities on T2 or FLAIR-weighted sequences, and in some cases, resembles a tumor [128]. Patchy contrast enhancement may be seen in both the leptomeninges and in the parenchymal

lesions [130]. Susceptibility weighted imaging sequences show evidence of prior hemorrhage (usually microhemorrhages) [129]. Cerebral angiography is generally normal, despite the fact that the pathology is due to vascular inflammation [129].

Definitive diagnosis of CAA-related inflammation requires biopsy, although empiric immunomodulatory therapy can be used once the possibility of infection has been eliminated. First line therapy is usually parenteral corticosteroids, and the response to corticosteroids is generally good [128, 129, 131, 132]. In some cases, additional immunosuppressive agents, primarily cyclophosphamide, have been used [128]. Most patients have a monophasic illness without recurrent symptoms [128].

Giant Cell Arteritis

Giant cell arteritis (GCA) should be included in the differential of CNS vasculitis. This disorder typically affects the medium and large extracranial vessels. Involvement of the central retinal, posterior ciliary, and ophthalmic arteries can lead to visual loss. Patients with GCA are generally older (>50 years of age), women are affected more commonly than men, and Caucasians are affected more commonly than non-Caucasians. The incidence in Europe and North America is 200 to 300 per million of this population [133]. Typical presenting symptoms include visual disturbance, jaw claudication, and tenderness of the superficial temporal arteries (STAs). The erythrocyte sedimentation rate is generally elevated (>50 mm/h), as is the high sensitivity C-reactive protein, but both can also be normal. Examination should reveal scalp tenderness or decreased STA pulses. There is frequent overlap of GCA with polymyalgia rheumatica, and a history of diffuse aches, pains, arthralgias, and myalgias is often elicited. The diagnosis relies on clinical suspicion and STA biopsy demonstrating granulomas with giant cells on histopathology. It is important to realize, however, that GCA can also affect the intracranial vessels (granulomatous angiitis of the CNS). Granulomatous involvement of the intracranial vessels is most often seen in the extradural space, and the inflammation can be severe enough to cause profound vessel narrowing and strokes. Most GCA-related strokes occur within the vertebral-basilar system [134, 135].

If giant cell arteritis is considered in the differential, treatment with high-dose corticosteroids should commence immediately and not be delayed until after the STA biopsy is performed, as the biopsy will remain positive for days after institution of corticosteroids. The survival rate for giant cell arteritis is said to be equivalent to the age-matched population [136]. There are case reports, however, of fulminant GCA and death, despite aggressive therapy with corticosteroids and other immune-modifying agents [137].

Systemic Vasculitides that Affect the CNS

Wegener's Granulomatosis (WG), Churg-Strauss Syndrome (CSS), and microscopic polyangiitis (MPA) are associated with the presence of anti-neutrophil cytoplasmic autoantibodies (ANCA) and are collectively referred to as ANCA-associated vasculitides (AAVs). ANCAs are IgG antibodies directed against antigenic constituents of the azurophilic granules in neutrophils and the lysosomes of monocytes. When these antibodies are fluorescently tagged, cells may stain in either a predominantly cytoplasmic ANCA pattern or a perinuclear ANCA pattern. Most cases of cytoplasmic ANCA staining are due to antibodies directed toward proteinase 3 (PR3) and most cases of perinuclear ANCA staining are due to antibodies directed toward myeloperoxidase (MPO) [138].

AAVs are rare, with WG being the most common and CSS the least common. These disorders occur most commonly in Caucasians with the mean age of presentation being approximately 55 years of age [139]. The AAVs are systemic vasculitides that predominantly affect the lungs and the kidney, but involvement of the nervous system, including the brain, can be seen. A brief discussion of the AAVs thus follows.

Wegener's Granulomatosis

WG is a systemic granulomatous necrotizing vasculitis that primarily involves small blood vessels, but medium-sized vessels may also be involved. Although WG can affect almost any organ system, the respiratory tract (both upper and lower) and kidneys are most commonly involved. Most patients (80 to 90%) with WG have ANCAs, and most of these ANCAs are directed toward PR3 [140]. The PR3 ANCAs are believed to be pathological and mediate the disease.

The incidence of WG is approximately 8 per million of the population and the prevalence 160 per million [139, 141, 142]. Caucasians are more frequently affected than other race/ethnicities, and men are affected more often than women. Common symptoms are related to granulomatous involvement of the airway, and include bloody rhinorrhea, and rhinosinusitis. Cavitory and nodular lesions of the lungs may occur, and granulomatous invasion of the respiratory tract can lead to pulmonary hemorrhage. The PNS is affected more commonly than the CNS, and usually manifests as polyneuropathy or mononeuritis multiplex due to inflammation of the vaso nervorum. CNS involvement generally takes the form of vasculitis and meningitis; it is rare and occurs in approximately 4% of patients [143]. Granulomatous invasion of the orbit with involvement of the cranial nerves, however, is much more common [144].

To diagnosis WG, patients need to have at least 2 of the following symptoms or signs: nasal or oral inflammation, an

abnormal chest radiograph (with nodules, fixed infiltrates, or cavities), an active urine sediment (with microhematuria or red cell casts), granulomatous inflammation and/or necrotizing vasculitis on tissue biopsy, and a positive enzyme immunoassay for antibodies to PR3 [145]. Once diagnosed, induction therapy for treatment of WG usually consists of parenteral corticosteroids and cyclophosphamide [146]. In a recent study in which all patients were treated with high-dose corticosteroids to induce remission, rituximab was shown to be as good as cyclophosphamide for treating ANCA-associated vasculitides and better than cyclophosphamide for patients with relapsing-remitting disease [147, 148]. There are insufficient data to recommend IVIG for treating WG [149]. Long-term maintenance therapy may be achieved with a variety of immunomodulatory drugs, including methotrexate and azathioprine [150]. The survival rate for patients with WG is estimated to be 74 to 91% at 5 years [136, 151].

Microscopic Polyangiitis

Necrotizing and crescentic glomerulonephritis and pulmonary capillaritis are common features of MPA. Because of the capillary inflammation, lung involvement usually manifests as diffuse pulmonary hemorrhage leading to respiratory insufficiency [152]. The ANCAs in MPA are usually directed toward MPO [140]. The incidence of MPA is approximately 4 per million of the population and the prevalence is 94 per million [139, 142]. As in WG, neurological involvement in MPA usually manifests as peripheral neuropathy and mononeuritis multiplex [153]. Involvement of the CNS is quite rare, but both ischemic and hemorrhagic strokes are reported [154–158].

For active disease, induction therapy with corticosteroids and cyclophosphamide is standard care, although methotrexate and azathioprine are reasonable alternatives for long-term maintenance therapy [146, 150]. In a recent study in which all patients were treated with high-dose corticosteroids to induce remission, rituximab was shown to be as good as cyclophosphamide for treating AAVs and better than cyclophosphamide for patients with relapsing-remitting disease [147, 148]. The survival rate for MPA is reported to be 45 to 76% at 5 years [136, 151].

CSS

CSS is the rarest of the necrotizing small-vessel vasculitides, with an incidence of roughly 2 per million of the population with a prevalence 14 per million [139, 142]. CSS is characterized by asthma, lung infiltrates, extravascular necrotizing granulomas, and hypereosinophilia. Similar to WG, granulomatous involvement of the respiratory tract is seen, but in CSS the inflammatory process is characterized by eosinophils.

ANCA positivity is seen in approximately 40% of patients with CSS and MPO antibodies predominate [140, 159].

As for the other AAVs, the most common neurological manifestation of CSS are neuropathy and mononeuritis multiplex with the peroneal nerve most commonly being involved [160, 161]. CNS involvement is seen in approximately 6 to 8% of patients with CSS and cerebral infarction, as well as intracerebral and subarachnoid hemorrhage being reported [160–162]. Patients with active disease, especially with neurological involvement, should undergo induction therapy with corticosteroids and cyclophosphamide [146]. Rituximab has also been reported to improve outcome in both patients with and without CNS involvement [163, 164]. The survival rate for CSS is reported to be 60 to 97% at 5 years [136, 151].

Venous Vasculitides

Behçet's Disease

Behçet's is a chronic relapsing-remitting disorder that tends to affect individuals of Eastern, Middle Eastern, and Mediterranean descent. The prevalence in Turkey ranges from 200 to 4,210 per million, whereas the prevalence in other European countries is only 24 per million [165]. Onset is generally in the third to fifth decades of life; men are affected more often than women and tend to have a worse outcome [166, 167]. The vascular inflammation in Behçet's primarily affects the venous system. The classic presentation of Behçet's is that of recurrent oral ulcers. Other characteristic findings include genital ulcers, uveitis, skin lesions (erythema nodosum, pseudofolliculitis, papulopustular lesions, acneiform nodules), and pathergy (development of skin lesions with minor trauma) [168]. The diagnosis of Behçet's is made entirely on clinical grounds, as there are no blood tests, imaging studies, or pathological studies that are pathognomonic.

Behçet's is a presumed autoimmune disease that is triggered by an environmental or infectious agent in immunologically predisposed individuals. Neurological complications of Behçet's occur in approximately 10% of patients, which are more commonly seen in men and tend to occur after several years of having the disease [166, 167]. Most patients have parenchymal involvement of the brain due to inflammation of the small veins [166]. The brainstem is commonly involved, but other brain regions, as well as the spinal cord, may also be involved [169–171]. Aseptic meningitis also occurs [172]. In addition to inflammatory pathology in the brain, patients with Behçet's are prone to the development of cerebral vein thrombosis (CVT). The reported incidence of CVT in patients with Behçet's varies, but is roughly 3 per 1,000 person years [173].

The consensus among physicians who commonly treat Behçet's is that therapy should start with parenteral corticosteroids followed by a slow taper of oral corticosteroids.

However, there are an accumulating number of publications reporting successful therapy with infliximab (monoclonal antibody directed against TNF- α) and other biologics [174, 175]. For patients who develop CVT, anticoagulation is required, even in patients with hemorrhagic infarction [176]. The mortality in Behçet's occurs almost exclusively in men and is nearly 3 times that of age-matched controls [177]. Extracranial large vessel involvement is the leading cause of death in Behçet's, although CNS involvement is also a common causes of death [177].

Nonvasculitic Systemic Inflammatory Disorders that Affect the Nervous System

Sarcoidosis

Sarcoidosis is a systemic disorder that can affect multiple different organ systems. The etiology of sarcoid is unknown, but it is presumed to be related to an immune response toward an unidentified antigen. Sarcoid affects African-Americans more commonly than Caucasians with the incidence in North America estimated to be and 350 to 800 per 1 million African Americans and 30 to 100 per 1 million Caucasians of the population [178]. Females are affected more often than males [178].

Sarcoid is often referred to as the great imitator as it can masquerade as a number of other diseases. Tuberculosis should always be in the differential for sarcoid and must always be considered prior to institution of immunomodulatory therapy. Somewhere between 5% and 15% of patients with sarcoid will develop neurological complications, and the estimated incidence of neurosarcoid is approximately 10 per million of the population [179, 180]. In most patients with neurosarcoid, the neurological disease is the presenting manifestation of sarcoid [179–181]. The neurological involvement can take the form of distal symmetric neuropathy and mononeuritis multiplex to basilar meningitis, granulomatous mass lesions, seizures, and endocrine dysfunction. Headaches and visual complaints are the most common presenting symptoms [180]. Cranial neuropathies occur in up to 75% of patients and most commonly involve the optic nerve, although involvement of the facial nerve is considered classic [179, 180, 182]. Endocrine abnormalities are common in sarcoid and are related to the fact that it tends to involve the hypothalamus and pituitary [183]. Typical findings include diabetes insipidus, adrenal insufficiency, and amenorrhea-galactorrhea syndrome [183]. Myelopathy may occur due to transverse myelitis or granulomatous invasion of the spinal cord itself or of the intradural or extradural space [83, 184]. Cases of a GBS-like illness associated with sarcoid have also been reported [185].

Because of the wide range of neurological problems that can occur with neurosarcoid, it is likely that some of these

problems at some point in time in the patients with sarcoid will be seen in the neurological ICU. Neuromuscular weakness resembling GBS may necessitate ventilatory assistance, whereas patients with intrinsic lung disease from their sarcoid may require respiratory assistance while being evaluated for less severe neurological problems. Emergent neurosurgical intervention may also be needed for obstructive hydrocephalus, due to space-occupying granulomas and communicating hydrocephalus due to involvement of the arachnoid granulations [186, 187]. Sarcoid also affects the heart in up to 25% of patients with sarcoidosis and may manifest as left ventricular dysfunction with congestive heart failure, as well as potentially life-threatening arrhythmias due to granulomatous involvement of the conduction system [188].

Magnetic resonance Imaging in patients with neurosarcoid may show enhancement of the meninges and cranial nerves, enhancing brain lesions, nonspecific white matter changes, and hydrocephalus [180, 189]. The presence of an enhancing suprasellar mass should always raise the suspicion of sarcoidosis. CSF analysis may show elevated protein, pleocytosis, and OCBs [180]. Elevated CSF angiotensin-converting enzyme levels appear to be specific, but not very sensitive for sarcoid [190]. Biopsy is a mainstay of the diagnostic evaluation, and the pathologic hallmark of sarcoidosis is a noncaseating granuloma, which consists of a collection of centrally organized macrophages and epithelioid cells encircled by lymphocytes.

Standard induction therapy for active sarcoid is high-dose parenteral corticosteroids [180]. A variety of immunosuppressive agents have been used for long-term maintenance therapy, including cyclophosphamide and azathioprine [180, 182]. Successful treatment with infliximab, MMF, and rituximab has been reported [191–194]. Hydroxychloroquine has been reported to stabilize symptoms [195]. The prognosis in neurosarcoid is unclear, given the rarity of the condition and the lack of good epidemiological data. Overall, the mortality from sarcoid appears to be increasing with the duration of time, but much of this appears to be related to pulmonary involvement [196]. Myelopathy portends a poor outcome [180].

Sjögren's Syndrome

Sjögren's syndrome is clinically characterized by keratoconjunctivitis sicca (dry eyes) and symptomatic xerostomia (dry mouth). These symptoms result from involvement of the lacrimal and salivary glands. Pulmonary involvement is also common, affecting $\leq 50\%$ of patients, but it is generally mild [197]. Sjögren's syndrome affects women up to 9 times more often than men [198, 199]. The incidence is estimated to be 40 to 50 per million of the population in Europe, with a prevalence of 2000 to 30,000 per million [200]. Sjögren's syndrome can affect both the PNS and the CNS, and $\leq 60\%$

or more patients with Sjögren's syndrome will develop neurological symptoms, although it is largely due to cryoglobulins and anti-nuclear antibodies (anti-SSA and anti-SSB) [198]. PNS involvement is characterized by sensory polyneuropathy and mononeuritis multiplex [198]. CNS manifestations occur in 6% to 25% of patients with Sjögren's syndrome, depending on the study and the definitions used, and these include encephalopathy, aseptic meningitis, optic neuritis, and MS-like disease [198, 201, 202]. Involvement of the CNS is more likely in patients with lung involvement [201]. Although most of the neurological manifestations of Sjögren's syndrome are not severe enough to warrant ICU admission, acute myelopathy can occur and potentially necessitate ventilatory support [203, 204]. Tumefactive brain lesions are also reported in Sjögren's syndrome [205, 206].

The diagnosis of Sjögren's is made in the appropriate clinical setting (dry eyes, dry mouth) in patients who have anti-SSA (Ro) and anti-SSB (La) antibodies, although seronegative Sjögren's is frequently described in patients with CNS involvement [207–209]. Salivary gland scintigraphy or biopsy of the salivary glands may also aid in the diagnosis [210]. The preferred treatment for Sjögren's syndrome who have neurological involvement is high-dose pulse corticosteroids [211]. Other immunosuppressants, such as cyclophosphamide, may be considered in patients who fail to respond to corticosteroids, as an adjunct to corticosteroids or as a long-term alternative to corticosteroids. Rituximab has also been used with success [212]. There are also reports of plasmapheresis and IVIG use for the treatment of Sjögren's-related neuropathy [213, 214]. Despite the female predominance in the occurrence of Sjögren's syndrome, death is more common in men [214]. Patients with Sjögren's syndrome are at increased risk of developing malignancies, especially lymphoma [215, 216].

Neuropsychiatric Systemic Lupus Erythematosus

Neuropsychiatric systemic lupus erythematosus (NPSLE) tends to occur at the time of diagnosis with SLE or within the first year after diagnosis with SLE. Patients with NPSLE generally have anti-nuclear antibodies, as well as antibodies to extractable nuclear antigens and double-stranded DNA. Anti-phospholipid antibodies are also common in SLE. NPSLE may present with an array of behavioral abnormalities, as well as with headache, seizures, chorea, aseptic meningitis, transverse myelitis, neuropathy (both cranial and peripheral), and strokes [217]. Transverse myelitis occurs in about 2% of patients with SLE [81, 218].

It is important to realize that vasculitis is rare in SLE and that most vascular complications are related to thrombosis [219, 220]. The absence of vasculitic changes is particularly striking in NPSLE [221]. The management of NPSLE depends on whether the symptoms are believed to be a

manifestation of the underlying autoimmune disorder or whether they are believed to be ischemic, resulting from the thrombotic manifestations associated with anti phospholipid antibodies. When the symptoms are believed to be secondary to inflammation, corticosteroids and other immunosuppressive therapies, including cyclophosphamide, are indicated [222–224].

Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (APS) is an acquired thrombophilia associated with a heterogeneous group of antibodies to a variety of phospholipids. APS is defined by the occurrence of venous or arterial thrombosis and recurrent fetal losses in the presence of antiphospholipid antibodies. Catastrophic APS is a potentially life-threatening condition, in which patients evidence multi-organ involvement for a very short time period (less than 1 week), and there is histological evidence of multiple small vessel occlusions, as well as laboratory confirmation of antiphospholipid antibodies (usually in high titer) [225]. Mortality approaches 50% [225], and although <1% of patients with APS develop this complication, its high mortality rate demands that clinicians be able to recognize the syndrome and treat it appropriately. Precipitating factors for catastrophic APS include surgery, infections, and withdrawal of anticoagulation [226].

Strokes (both hemorrhagic and ischemic) are a common manifestation of APS and the most frequent cause of death, followed by cardiac issues and infection [226, 227]. Analysis of prognostic variables show that patients with SLE have higher mortality with catastrophic APS than those without [226]. Anticoagulation of patients with catastrophic APS is imperative. Aggressive immune modulating therapies are also advocated and include parenteral corticosteroids, along with adjunctive therapy-like plasmapheresis or IVIG [228, 229]. With early recognition of catastrophic APS and institution of these therapies, reports suggest that mortality has decreased by approximately 20% to 30% [226].

Autoimmune Encephalopathies

A number of autoimmune encephalopathies have been described along the years. In some instances there is a clear association between the immune response to a given antigen and the encephalopathy, whereas in other cases the antigens identified as the target of the autoimmune response may merely reflect the propensity for autoimmunity and are not responsible for the symptoms. It is very clear that malignancies can trigger an immune response that cross reacts with self-antigens, but in many instances, patients do not have evidence of malignancy and the triggers are unknown.

Limbic Encephalitis

Limbic encephalitis was originally identified as a paraneoplastic disorder related to antibodies directed against onconeural targets (including Hu, Ma2, CV2/CRMP5, amphiphysin). More recently, however, limbic encephalitis has been recognized to occur in patients without cancer and a variety of pathologic antigenic targets have been identified. Antibodies to voltage-gated potassium channels (VGKCs) were identified in a number of patients with non-paraneoplastic limbic encephalitis, but further studies have shown that the real antigens in these patients are leucine-rich glioma inactivated 1, contactin-associated protein-like 2, and contactin-2, all of which are associated with VGKCs [230, 231]. The spectrum of autoantigens associated with in limbic encephalitis, however, continues to expand, and now includes the N-methyl-D-aspartate receptor (NMDAR), the AMPA receptor, the GABA = gamma-aminobutyric acid receptor, and glutamic acid decarboxylase [232–235]. It is quite likely that many other pathologic autoantigens will be identified.

Symptom onset in limbic encephalitis is generally subacute and characterized by behavioral changes and seizures. Imaging should show involvement of the limbic system and the CSF evidence of inflammation. Idiopathic limbic encephalitis may be suggested by the presence of high titers of VGKC antibodies, although this finding is not specific as patients with paraneoplastic limbic encephalitis may occasionally have high serum titers of VGKCs as well [236]. Patients with a clinical diagnosis of limbic encephalitis should be screened for potential malignancies [237].

For patients with paraneoplastic limbic encephalitis, treatment should be directed at removal of the tumor. For noncancer-related limbic encephalitides, immunomodulatory therapies, such as corticosteroids, plasmapheresis, and IVIG have all been used with success [234, 238]. As opposed to NMDAR antibody encephalitis, outcome in limbic encephalitis is generally better in patients without an identified tumor [239].

NMDAR Antibody Associated Encephalitis

NMDAR antibody associated encephalitis is one of the more common autoimmune encephalitides. Similar to the other limbic encephalitides, it was first described to occur in association with tumors, specifically in young women with ovarian teratomas [240, 241]. NMDAR antibody associated encephalitis is now known to occur in patients without tumors as well. The antibodies are directed against the NR1 subunit of the NMDA receptor [242]. The clinical spectrum of NMDAR antibody associated encephalitis ranges from memory disturbances and movement disorders to seizures (including status epilepticus), catatonia, and

coma [243, 244]. Hypoventilation may necessitate mechanical ventilation [245]. Dysautonomia is common and can be severe enough to require cardiac pacing [245, 246]. The MRI is often abnormal and the electroencephalography is almost uniformly abnormal in patients with NMDAR antibody associated encephalitis. CSF analysis usually reveals a mild lymphocytic pleocytosis and occasionally shows increased protein and OCBs. Definitive diagnosis depends on identifying the pathologic NMDAR antibodies [245].

Immunomodulatory therapies, such as corticosteroids, plasmapheresis, and IVIG have all been used with success in the treatment of NMDAR antibody associated encephalitis, and outcome appears to be better in patients in whom teratomas are found and removed [245]. A combination of rituximab and cyclophosphamide is typically used when treatment with plasmapheresis or IVIG do not result in sufficient improvement [243].

Steroid Responsive Encephalopathy Associated with Autoimmune Thyroiditis

Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT), also known as Hashimoto's encephalopathy, is rare, poorly understood, and likely underdiagnosed. The literature is comprised solely of case reports. Neuropsychiatric symptoms are common and memory loss is nearly universal in patients with SREAT. Seizures may occur as can strokes or stroke-like episodes [247–249]. Tremor and myoclonus are frequently seen on clinical examination [250, 251]. Hypersomnolence is also seen and can progress to coma [252]. Thyroid hormone concentrations (T3, T4, thyroid-stimulating hormone) may be normal [253]. Antibodies to thyroperoxidase and thyroglobulin are suggestive of SREAT in the appropriate clinical setting [254]. These antibodies, however, are not believed to be pathogenic. The exact mechanism of disease is unknown, but is speculated to be by either vasculitis or direct neuronal/glial recognition by autoantibodies (but not anti-thyroperoxidase or anti-thyroglobulin antibodies) [254, 255]. The CSF may show a slight pleocytosis and mild-moderate elevation of protein. Approximately half of the patients with SREAT have focal or diffuse nonenhancing abnormalities on MRI. The MRI can also reveal acute infarcts, raising the specter of vasculitis [256]. The differential for SREAT includes viral encephalitis, Creutzfeldt-Jakob disease, and other forms of dementia [251, 257–261].

As the name suggests, SREAT is generally steroid responsive, yet review of the literature suggests that approximately only 50% of patients respond to corticosteroids. Plasmapheresis has been used in some patients and there are reports of successful treatment with IVIG and rituximab [262–266].

Rasmussen's Encephalitis

Rasmussen's encephalitis (RE) is a rare inflammatory disorder that affects primarily children, but can also affect adults [267–271]. The clinical presentation is that of refractory seizures with cognitive decline, hemispheric atrophy, and progressive hemiparesis; young children tend to progress much more rapidly than young adults. A serendipitous finding that rabbits immunized with the glutamate receptor GluR3 developed a syndrome similar to RE, which led to the identification of antibodies to GluR3 in the serum of many patients with RE [272]. Despite the presence of GluR3 antibodies in the serum, histology suggests that RE may be a T-cell mediated disease [273]. The diagnosis of RE is a clinical one, as the imaging and EEG findings are not specific, and the presence of GluR3 antibodies is neither specific nor sensitive [274]. Pathology generally shows changes consistent with chronic encephalitis (in various stages of active inflammation), findings which are also nonspecific.

Symptomatic treatment of RE includes the use of anti-convulsants. Given the presumed contribution of the immune system to the pathogenesis of RE, a number of immunomodulatory therapies, including plasmapheresis, IVIG, and corticosteroids have been used to treat the disorder; plasmapheresis or IVIG are usually recommended [275, 276]. These treatments appear to reduce the frequency of seizures, but are seldom curative. Definitive treatment is still considered to be hemispherectomy [277, 278].

Disorders of the Neuromuscular Transmission (Including Channelopathies)

Myasthenia Gravis

Myasthenia gravis (MG) is perhaps the best characterized autoimmune disease that affects the nervous system. Patients present with fatigable muscle weakness. MG is most commonly related to antibodies to the acetylcholine receptor (AChR), although other pathologies have also been described. Approximately 70 to 95% of patients with MG will have detectable AChR antibodies [279]. The annual incidence of MG is estimated to be 5 per million persons of the population with a prevalence of 78 per million person years [280]. The incidence of MG is much higher in women during the first 5 decades of life, but then it becomes higher in men during the subsequent 3 decades [281]. Of the patients with AChR seronegative MG, many have antibodies to muscle specific tyrosine kinase (MuSK) [282, 283]. The patients with anti-MuSK antibodies tend to be predominantly female and present in their 40s with ocular and bulbar symptoms [284].

The diagnosis of MG is based on appropriate history and examination (fatigable muscle weakness) and diagnostic

studies, including assays for AChR or MuSK antibodies. Electrical studies are also valuable in making the diagnosis of MG. With repetitive nerve stimulation (at 2 to 3 Hz) there is a progressive decrement in the amplitude of the compound muscle action potential. The decremental response is most reliably found in clinically weak muscles and may not be seen at all in patients with predominantly oculobulbar weakness. Single fiber electromyography (EMG) is more sensitive than repetitive nerve stimulation, and abnormalities are seen in virtually all patients with MG in whom the weak muscles can be studied.

Myasthenic crisis is defined as acute weakness with inability to breathe or swallow; approximately 15% to 20% of patients with MG will suffer a crisis at some point during their illness [285, 286]. Myasthenic crisis is the one of most common causes of neuromuscular respiratory failure seen in the ICU [90]. Therapeutic management relies on the combination of acetylcholinesterase inhibitors and immunomodulation. The acetylcholinesterase inhibitors can improve strength quickly, whereas immunomodulation takes time. Corticosteroids are often avoided in MG as they can potentially exacerbate weakness following initial administration. For patients admitted to an ICU in crisis, however, transient mild worsening of weakness is a minor concern. Most guidelines, therefore, suggest that high-dose parenteral corticosteroids be given to patients in crisis along with another form of therapy, such as plasmapheresis or IVIG. There are no adequate RCTs evaluating the role of plasmapheresis *versus* conservative therapy in patients with MG, but there are several case series which seem to suggest that plasmapheresis does have a short-term benefit in patients with myasthenic crisis [23, 287]. For exacerbations of MG, there is a single RCT showing benefit to treatment with IVIG and another study that showed IVIG and plasmapheresis to be of similar efficacy [288]. A review of the Nationwide Inpatient Sample database for the years 2000 to 2005 shows that the use of IVIG has been steadily increasing and that adjusted mortality and complication rates were similar for patients treated with plasmapheresis and IVIG [289]. For patients with anti-MuSK antibodies, plasmapheresis may be superior to IVIG [284]. A discussion regarding ventilator management in patients with neuromuscular disorders is beyond the scope of this chapter, but the general consensus is that during the acute crisis for which immunomodulatory therapy (i.e., plasmapheresis or IVIG) is being given, patients should be allowed to “rest” on full ventilatory support.

Mortality for patients with MG is 0.1 to 0.9 per million per year [280]. As might be expected, the mortality rate in patients with crisis is much higher, and approximately 4% of patients will die during hospitalization for myasthenic crisis [289]. Both older age and respiratory failure are associated with increased mortality [281, 289].

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton Myasthenic Syndrome (LEMS) was first described as a paraneoplastic syndrome associated with small cell lung cancer. It is now known to occur as a primary autoimmune disease, independent of cancer. Patients with LEMS have antibodies to the P/Q-type voltage-gated calcium channels that attack the presynaptic nerve terminal. Patients present with muscle weakness, fatigue, and autonomic dysfunction (especially dry mouth). LEMS is rare, with an incidence of 0.4 per million of the population and a prevalence of 2.5 per million [290]. Electrical studies are important for diagnosis of LEMS and show facilitation of compound motor action potentials after high frequency (20–50 Hz) stimulation. Clinically, patients are weak and may be either hyporeflexic or areflexic; both the weakness and hyporeflexia improve after exercise.

Patients with LEMS can present with respiratory failure [291–298]. The mainstay of treatment for LEMS is 3,4-diamino pyridine, which increases the amount of acetylcholine released at the neuromuscular junction [299]. There is at least some evidence, albeit from a very small trial, that treatment with IVIG may be of benefit in patients with LEMS [299]. The usefulness of corticosteroids and plasmapheresis for the treatment of LEMS has not been assessed in RCTs.

Stiff-Person Syndrome

Antibodies to glutamic acid decarboxylase are found in the majority (60–80%) of patients with stiff-person syndrome (SPS) [300–302]. Other autoantibodies associated with SPS include those to the GABA-A receptor, amphiphysin, and gephyrin [303–306]. Patients with progressive encephalopathy associated with limb rigidity are said to have progressive encephalomyelitis with rigidity and myoclonus (PERM) or stiff-person plus syndrome. Antibodies to the glycine receptor have been identified in patients with PERM [307, 308]. Patients with SPS, and especially PERM, may develop respiratory failure and are at risk for sudden cardiac death [309].

SPS is rare, but there has been a single RCT demonstrating a benefit to IVIG therapy; IVIG is thus the therapy with the best available evidence [310, 311]. Because SPS is an antibody mediated disorder, it would be expected that plasmapheresis and rituximab would be reasonable treatments, and both have been used with reports of success [309, 312].

Neuromyotonia

Neuromyotonia (or Issac’s syndrome) is associated with antibodies to VGKCs and result in hyperexcitability of the peripheral motor nerve. Patients with neuromyotonia complain

of muscle cramps and have evidence of muscle twitching (myokymia and neuromyotonia), muscle hypertrophy, muscle weakness, and hyperhidrosis on examination. If central features are present (anxiety, memory problems, personality changes, sleep disturbance), the disorder is referred to as Morvan's syndrome. Patients with Morvan's syndrome may develop agrypnia excitata, which is characterized by autonomic activation, persistent insomnia, and generalized overactivity with inability to generate slow wave sleep [313, 314]. Agrypnia excitata is extremely rare and can be life-threatening.

EMG shows spontaneous and continuous motor unit discharges, fasciculations, and myokymic discharges. The phenotype of the disorder caused by VGKC's appears to be related to the component of the K^+ channel to which the antibody is directed. For instance, antibodies to contactin-associated protein-2 tend to be associated with limbic encephalitis, Morvan's syndrome, and Isaac's syndrome, and are seen in patients with thymomas [231, 239, 315, 316]. Antibodies directed toward leucine-rich glioma inactivated 1 are associated with epilepsy and limbic encephalitis, and are seen in patients without tumors [239, 315].

The mainstay of therapy for patients with neuromyotonia is the use of anti-epileptic drugs that decrease nerve excitability. In addition, high-dose parenteral corticosteroids are commonly used for treating patients with acute presentations; IVIG and plasmapheresis have also been used with reports of benefit [311, 317–319].

Immunomodulatory Therapies

There is an ever increasing armamentarium of drugs and antibodies available to modulate the immune response. Most of these therapies are used for chronic immunosuppression, and many take weeks to months before their biological effect is realized. We will focus only on those interventions that are commonly used in the ICU for the acute treatment of the immune-mediated neurological diseases previously described. The indications and levels of evidence for each of these interventions are summarized in Table 1 using the guidelines adopted by the American Academy of Neurology [320].

Plasmapheresis

Therapeutic plasma exchange (plasmapheresis) is an extracorporeal blood purification technique designed to remove large molecular weight particles from plasma. Blood is removed from the patient, plasma is separated from the blood's cellular elements, and is exchanged with colloid replacements (usually fresh-frozen plasma or albumin solution); the cellular blood components are returned to the patient. The principle mechanism of action in plasmapheresis is thought to be the removal of pathogenic autoantibodies, as well as macromolecular

immune complexes, inflammatory cytokines, and other mediators from the intravascular space. Reduction of serum immunoglobulin levels and pathogenic antibodies to gangliosides in GBS and to the acetylcholine receptor and muscle specific kinase in patients with MG is documented [321, 322]. The mechanism of action of plasmapheresis, however, is likely more complex than simple physical removal of antibodies from the blood. Multiple effects on the cellular components of the immune system have also been described. Plasmapheresis induces the proliferation of lymphocytes in patients with both MS and GBS, perhaps due to removal of an unknown lymphocyte suppression factor [323, 324]. It is felt that the enhanced proliferation could augment the action of immunosuppressive drugs that target actively dividing lymphocytes. A variety of other effects of plasmapheresis on immune function have been postulated [325–327].

For the treatment of acute exacerbations of most autoimmune neurological conditions, a series of plasma exchanges (50 mL/kg or 1.0–1.5 plasma volumes per procedure per day) for a 1- to 2-week period of time is recommended [328]. The optimal number of plasmapheresis treatments for most disorders is unclear, but the usual practice is approximately 5 treatments over approximately 10 days. Treatments every other day (as opposed to daily) are probably more effective in reducing the antibody levels, as it allows for redistribution of extravascular immunoglobulins into the intravascular space. The effects of plasmapheresis are of limited duration as the autoantibodies removed by plasmapheresis are quickly replaced by synthesis of new autoantibodies in the face of ongoing antigenic stimulation. Repeated plasmapheresis treatments are thus required to achieve the desired effects [329].

As previously outlined and summarized by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, plasmapheresis is of proven benefit for the treatment of AIDP/GBS and may also be of value for the treatment of MS relapses [23]. Data to support the use of plasmapheresis for the treatment of MG, NMO, and other fulminant demyelinating disorders are insufficient, although it is commonly used [23].

Plasmapheresis is only available in specialized centers and is associated with risks. Adverse reactions can occur due to the need for central venous access (infection, thrombosis, and pneumothorax). Hypotension may occur in up to 20% of patients undergoing plasmapheresis, and certain filtration techniques can cause hemolysis [330]. Unstable hemodynamics, coagulopathy, sepsis, and problems with vascular access can preclude the use of plasmapheresis. Repeated treatments with albumin replacement may lead to depletion of coagulation factors and immunoglobulins, increasing the risk of bleeding and infections. If fresh-frozen plasma is used as replacement fluid, there is a risk (albeit very low) of transmission of viruses, such as hepatitis C virus or

Table 1 Important immunological treatments in the neurological ICU

Treatment	Plasmapheresis	IV Corticosteroids	IVIG	Rituximab	Cyclophosphamide
Main indications (class of evidence and level of recommendation)	AIDP/GBS (IA)	Acute CNS demyelination (IB)	AIDP/GBS (IA)	WG (FDA-approved)	Acute CNS demyelination (IIaC)
	CIDP (IB)	myasthenia gravis (IIbC)	myasthenic crisis (IA)	MPA (FDA-approved)	primary CNS vasculitis (IIbC)
	acute CNS demyelination (IB)	primary CNS vasculitis (IIbC)	acute CNS demyelination (IIB)	MS (IIB)	NMDAR encephalitis (IIIU)
	myasthenic crisis (IIIU)	Hashimoto encephalopathy/ SREAT (IaB)	limbic encephalitis (IIA)	NMO (IIIU)	Hashimoto encephalopathy/ SREAT (IIBC)
Typical dosing	5 Treatments every other day with 1–1.5×plasma volume each	Methylprednisolone 1 g i.v. × 3–5 days	0.4 g/kg i.v. Daily × 5 days (i.e., 2 g/kg total)	375 mg/m ² i.v. Once weekly for 4 weeks	15 mg/kg i.v. Every 2–3 weeks
Main side effects in acute treatment	Risks associated with central line; hypocalcemia, hypotension, coagulopathy risk of FFP	Gastric ulcers, hyperglycemia, hypokalemia, mood instability, insomnia	Acute renal failure, thrombotic events, anaphylaxis infection (HIV, HCV)	Anaphylaxis infusion reaction, risk of PML	Leukopenia hemorrhagic cystitis, bladder cancer, nausea, vomiting, teratogenicity

AIDP=acute inflammatory demyelinating polyneuropathy; CIDP=chronic inflammatory demyelinating polyneuropathy; CNS=central nervous system; FDA=Food and Drug Administration; FFP=fresh frozen plasma; GBS=Guillain-Barré syndrome; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICU=intensive care unit; IV=intravenous; IVIG=intravenous immune globulin; MPA=microscopic polyangiitis; MS=multiple sclerosis; NMDAR=N-methyl-D-aspartate receptor; NMO=neuromyelitis optica; PML=progressive multifocal leukoencephalopathy; RCT=randomized clinical trial; SREAT=steroid responsive encephalopathy; WG=Wegener's granulomatosis

Levels of evidence are adopted from the American Academy of Neurology guidelines [320]. Briefly, class I evidence is derived from a high-quality RCT, class II evidence is derived from a lesser quality RCT, class III evidence is derived from trials using historical controls or crossover designs, and class IV evidence is all evidence that does not meet the criteria for class I, II, or III evidence (and includes consensus, as well as expert opinion). The recommendations are categorized as level A (established to be effective, ineffective, or harmful by at least 2 class I studies), level B (probably effective, ineffective, or harmful based on 1 class I study or 2 consistent class II studies), C level (possibly effective, ineffective, or harmful, based on 1 class II study or 2 consistent class III studies), or U level (inadequate or conflicting data)

human immunodeficiency virus (HIV). Citrate infused for anticoagulation or as part of fresh-frozen plasma may lead to hypocalcemia or metabolic acidosis. Symptoms of hypocalcemia occur in 1.5 to 9% of plasmapheresis treatments and include paresthesias, muscle cramps, and, in severe cases, cardiac arrhythmias [331].

Pharmaceuticals

Corticosteroids

The anti-inflammatory effects of corticosteroids are mediated by a number of different mechanisms, including both genomic and nongenomic actions. With activation of the cytoplasmic glucocorticoid receptor, the receptor translocates to the nucleus and binds to glucocorticoid response elements in the promoter region of target genes and activates transcription (transactivation) or inhibits the transactivating function of transcription factors (transrepression), such as

nuclear factor kappa-B, which is responsible for the transcription of proinflammatory genes [332]. These genomic changes require at least several hours before taking effect. More immediate effects of corticosteroids (seconds to minutes) can be seen due to multiple nongenomic mechanisms of action, although these effects are less well-understood. Some of the nongenomic effects include inhibition of inflammatory cytokine secretion due to decreased stability of mRNA for genes of inflammatory proteins and impairment of leukocyte adhesion, extravasation, and entry into inflamed tissue [333]. Furthermore, corticosteroids cause T-cell apoptosis and lead to a transient rise in circulating neutrophils due to accelerated release from the bone marrow and reduced migration out of the blood into inflammatory sites [334, 335].

Methylprednisolone is the most commonly used parenteral corticosteroid in the United States and the usual dose for treating acute neurological diseases is 500 mg to 1,000 mg per day for 3 to 5 days. Methylprednisolone has some

mineralocorticoid effect, so electrolytes (particularly K^+) need to be monitored daily during therapy. Dexamethasone is less commonly used than methylprednisolone for the treatment of inflammatory neurological diseases. The relative anti-inflammatory potency of dexamethasone, however, is 6 times higher than that of methylprednisolone [336]. Dexamethasone is typically given at a dose of 4 mg IV every 6 hours. Unlike methylprednisolone, dexamethasone has purely glucocorticoid actions.

Side effects associated with high-dose parenteral corticosteroids, even short courses of therapy, include gastrointestinal ulcers, and prophylaxis with an H_2 blocker or a proton pump inhibitor is recommended. Many patients will require insulin administration during treatment with corticosteroids due to hyperglycemia. The risk of deep venous thrombosis may also be increased with high-dose parenteral corticosteroids. In the ICU setting, and especially in patients requiring neuromuscular blockade, steroid-induced myopathy may occur. Finally, important neuropsychiatric side effects of high-dose corticosteroids include insomnia, mood instability (hypomania or irritability), and psychosis [337].

Chronic corticosteroid use is associated with multiple side effects; initiation of “steroid-sparing drugs” is thus considered concomitant with the use of parenteral corticosteroids as these “steroid-sparing drugs” often take weeks to months until the therapeutic effects become apparent. The side effects seen with corticosteroid therapy include obesity, diabetes, skin atrophy, disturbed wound healing, cataracts, glaucoma, and bone loss [338]. The risk of osteoporosis is dose-related and can be reduced by vitamin D and calcium supplementation [339]. Patients treated with chronic corticosteroids are at increased risk for infection with *Pneumocystis carinii* pneumonia, and prophylaxis with trimethoprim/sulfamethoxazole is often recommended [340]. Importantly, hypothalamic-pituitary-adrenal axis suppression necessitates a slow taper instead of abrupt discontinuation of corticosteroids to avoid adrenal insufficiency. For patients treated with long-term corticosteroids, adrenal insufficiency should be considered in the setting of acute illness.

Cyclophosphamide

Cyclophosphamide was originally developed for the treatment of malignancies. Although cyclophosphamide is not approved by the Food and Drug Administration (FDA) for the treatment of autoimmune diseases of the nervous system, it is nonetheless used for the treatment of a number of these diseases. Cyclophosphamide is transformed in the liver into its active form, an alkylating drug that binds to DNA and interferes with cell mitosis and replication. Some of the immunosuppressive effects of this drug are likely due to the reduction in lymphocyte numbers, both B-cells and T-cells, which interfere with both cell-mediated and humoral immune responses.

Cyclophosphamide also appears to selectively suppress the activity of Th1 helper cells and enhance Th2 helper responses [341]. Furthermore, it has been shown to lead to suppression of interleukin-12 production by monocytes and dose-dependent alterations in the number and function of $CD4^+CD25^+$ regulatory T-lymphocytes [342].

As a steroid-sparing agent in chronic therapy, cyclophosphamide may be given as a daily oral medication or as an intravenous infusion every few weeks. A typical dose of oral cyclophosphamide for the treatment of vasculitis is 2 mg/kg with a maximum of 150 mg/day (adjusted dose in renal insufficiency) daily for 4 weeks [147]. Typical dosing of intravenous cyclophosphamide for the treatment of primary CNS vasculitis is 15 mg/kg every 2 to 3 weeks [343]. Data suggest that pulse doses of cyclophosphamide may be safer and better tolerated than daily oral doses [343–345]. MS is usually treated with monthly infusions of up to 1500 mg/m² (with dose reductions depending on the white blood cell nadir) [342]. High-dose cyclophosphamide, at 200 mg/kg divided into 4 daily doses of 50 mg/kg followed by granulocyte colony-stimulating factor, has also been used in therapy-refractory myasthenia gravis, NMO, and rapidly progressive MS [346–349].

Important side effects of cyclophosphamide include leukopenia and hemorrhagic cystitis. The latter is thought to be caused by acrolein, a byproduct of cyclophosphamide, and hemorrhagic cystitis occurs more commonly in patients with prior dysfunction of the urinary tract system. Sodium 2-mercaptoethane sulfonate (mesna) is given along with cyclophosphamide to prevent bladder injury. An increased risk of bladder cancer has been observed in patients with prolonged cyclophosphamide use, and regular screening of urine cytology is recommended [350]. The incidence of other cancers, including secondary acute leukemia and skin cancers, is also increased by cyclophosphamide use [351]. High-dose cyclophosphamide can cause acute cardiac toxicity and premature gonadal failure, especially in women. As with most anti-neoplastic agents, cyclophosphamide is teratogenic and should not be given to women who can become pregnant or to nursing mothers, because it is excreted in breast milk. Other side effects include mild alopecia, nausea, and vomiting; these side effects are dose-dependent, transient, and reversible.

Biologics

Intravenous Immunoglobulin

IVIG is a fractionated blood product from pooled plasma of several thousand donors. The main component of IVIG is IgG, although smaller amounts of IgA and IgM antibodies, as well as other molecules such as cytokines, may also be present in IVIG and contribute to its therapeutic effects. The

mechanisms by which IVIG exerts its therapeutic effects, however, are not fully understood. A detailed exploration of the numerous hypotheses explaining the mechanism of IVIG in autoimmune diseases is beyond the scope of this review, but can be found in previous reviews [352, 353]. One of the main effects of IVIG, however, is thought to be its inhibition of autoantibody mediated injury by increased catabolism of pathologic antibodies, interference of pathologic antibodies from binding to their targets, and prevention of complement activation [329, 354–358]. IVIG may also affect the cellular immune response by altering the interaction of T-cells with antigen presenting cells and by hastening apoptosis of autoreactive T-cells [352]. Additionally, IVIG may interfere with the differentiation, activation, and proliferation of B cells, enhance their apoptosis, and block the activity of cells that release autoantibodies [359–362]. Additional mechanisms of action for IVIG have also been postulated, but by and large, the mechanism of action of IVIG remains unclear [363–365].

The only neurological disease with an FDA-approved indication for IVIG is chronic inflammatory demyelinating polyneuropathy, a disorder that rarely requires ICU admission and is not discussed in this chapter. Off-label use of IVIG, however, is widespread [366, 367]. In practice, IVIG is considered to be an alternative to plasmapheresis. The usefulness of IVIG is best proved for GBS, in which several RCTs find IVIG and plasmapheresis to be equally efficacious [368]. IVIG is also beneficial in the treatment of myasthenic crisis, an approach that is supported by a single randomized trial [369]. Results from randomized trials comparing the efficacy of IVIG and plasmapheresis in myasthenia exacerbations are equivocal [288]. In addition to the treatment of chronic inflammatory demyelinating polyneuropathy, AIDP/GBS, and MG, IVIG is often considered for the treatment of acute exacerbations of demyelinating CNS disease, such as MS, NMO, and ADEM, although no RCTs have confirmed the benefit of IVIG in any of these conditions [45, 370–375].

The dose of IVIG for the acute treatment of neurological autoimmune diseases is generally 0.4 g/kg i.v. daily for 5 days (for a total dose of 2 g/kg) [328]. IVIG is usually well-tolerated, with adverse reactions occurring in <5% of patients. Common reactions include headache, chills, fever, myalgias, and noncardiac chest discomfort.[353] Self-limited aseptic meningitis is rare and typically occurs within 72 h of the first dose [367]. Fluid overload and hyponatremia can be seen with IVIG treatment. More serious reactions include thrombotic events, acute renal dysfunction, and anaphylactic reactions. Venous and arterial thrombotic events due to transient hyperviscosity are reported in up to 1% of patients; the risk may be limited by slower infusion rates [376, 377]. Acute renal dysfunction is rare and more likely to occur in products stabilized with sucrose [378]. Patients with IgA deficiency appear to be at higher risk of hypersensitivity and anaphylactic reactions to

IVIG, and some centers will rule out IgA deficiency prior to initiation of therapy [379]. Finally, because IVIG is isolated from pooled human plasma, infection with HIV, hepatitis B virus, or hepatitis C virus is a theoretical concern.

Rituximab

Rituximab is a genetically engineered human/murine chimeric monoclonal antibody that is directed against the transmembrane protein CD20, which is expressed on pre-B-cells in the bone marrow as well as mature B-cells, but not antibody secreting plasma cells. Treatment with rituximab thus selectively depletes B-lymphocytes, but not plasma cells [380]. The depletion of B-cells occurs through a combination of antibody dependent cell-mediated toxicity and complement-mediated cytotoxicity, and lasts for approximately 6 months [381].

Despite the fact that CD20 is not present on antibody-producing plasma cells, a reduction of autoantibodies is seen following treatment with rituximab likely due to the depletion of CD27⁺ memory B-cells, the precursors of the short-lived plasma cells [381, 382]. In addition to reduced antibody production, rituximab has been shown to reduce TNF- α production by macrophages and increase the frequency of regulatory CD4⁺CD25(high) T-cells and CD56(bright) NK cells [383, 384].

Rituximab is approved by the FDA for the treatment of malignancies (non-Hodgkin's B-cell lymphoma and chronic lymphocytic leukemia), as well as autoimmune disorders, including rheumatoid arthritis (as an adjunct to methotrexate), and WG and MPA (as an adjunct to corticosteroids). In addition, rituximab is increasingly being used “off-label” to treat a variety of immunologically mediated neurological diseases, particularly those thought to be secondary to the production of autoantibodies. In relapsing-remitting MS, a placebo-controlled blinded study of 104 patients showed a reduction in relapse rate in patients treated with rituximab, and in a subgroup of patients with primary-progressive MS <51 years of age and with active gadolinium-enhancing lesions on MRI, treatment with rituximab led to slowing of disease progression compared to placebo [385, 386]. Smaller noncontrolled trials or case reports exist for NMO, MG, Sjögren's syndrome, NMDAR encephalitis, and other antibody mediated neurological diseases.

The dose of rituximab approved for the treatment of WG and MPA is 375 mg/m² once weekly for 4 weeks. For rheumatoid arthritis, the dosing regimen is 2 doses of 1000 mg IV each separated by 2 weeks and repeated every 6 months. The side effect profile of rituximab is relatively favorable, although mild-to-moderate infusion-related reactions can be observed. Infusion reactions may consist of flu-like symptoms, such as fever, rigors, and headache. Hypotension has also been described and antihypertensive

medications are usually held on the day of infusion. Rashes and anaphylactic reactions may also seen, but can be prevented by premedication with antihistamines (and occasionally methylprednisolone). These reactions typically occur with the first infusion [387].

A potentially more serious concern related to the use of rituximab is the occurrence of progressive multifocal leukoencephalopathy (PML), a devastating infectious disease that results in demyelination of the brain. PML is caused by reactivation of JC virus, which is found in a large proportion of the healthy population. In patients with a compromised immune system due to malignancy, HIV infection or certain immunomodulatory drugs, most notably in natalizumab (a monoclonal antibody used in the treatment of MS and Crohn's disease), the JC virus becomes active and demyelinate the brain. Recent case reports suggest that therapy with rituximab is also associated with an increased risk of PML [388, 389].

Conclusions

In this chapter, we attempted to summarize the most common inflammatory diseases that affect the nervous system. It is impossible in the space provided to discuss all such diseases that could affect either the CNS or PNS. The theme that emerges for most of the disease entities discussed in this article is that treatment of acute presentations should use drugs/interventions that have an immediate onset of action, such as corticosteroids, plasmapheresis, and IVIG. Another theme that emerges is that diseases for which antibodies are thought to be pathologic, plasmapheresis and treatment with rituximab appear to be logical therapeutic strategies. Because many of the disorders discussed are quite rare, RCTs would be nearly impossible to perform, so recommendations for therapy are based on case series and anecdotal reports.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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