J Neurol (2012) 259:801–816
DOI 10.1007/s00415-011-6240-5

REVIEW

A differential diagnosis of central nervous system demyelination: beyond multiple sclerosis

Christopher Eckstein · Shiv Saidha · Michael Levy

Received: 15 June 2011 / Revised: 28 August 2011 / Accepted: 30 August 2011 / Published online: 20 September 2011

Abstract Although multiple sclerosis (MS) is the most common demyelinating disorder of the central nervous system (CNS), it lacks any definitive diagnostic test. Instead, diagnosis of MS primarily depends upon clinical criteria, supported by abnormalities characteristic of MS on para-clinical investigations including magnetic resonance imaging of the brain and spine, in the absence of an alternative explanation for underlying neurologic symptoms. While many of the potential disorders that may mimic MS in routine clinical practice are either extremely rare, or associated with specific and characteristic distinguishing diagnostic features, some inflammatory demyelinating disorders of the CNS may be particularly challenging to distinguish from MS, especially during initial presentation. In particular, acute disseminated encephalomyelitis, neuromyelitis optica, and idiopathic transverse myelitis may closely resemble MS, impeding prompt and accurate diagnosis. In this review, we describe the clinical features, diagnosis, pathology, and treatment of these other CNS demyelinating disorders. In addition, we review relevant features of other CNS inflammatory disorders that may mimic MS, including Sjögren's syndrome, systemic lupus erythematosus, Behçet's disease, and primary CNS vasculitis.

Keywords Multiple sclerosis · Neuromyelitis optica · Transverse myelitis · Acute disseminated encephalomyelitis · Demyelination

Introduction

Multiple sclerosis (MS), the most common demyelinating disorder of the central nervous system (CNS), characterized by multifocal areas of CNS demyelination disseminated in time and space, is diagnosed primarily on clinical grounds in accordance with the revised McDonald criteria [1]. Para-clinical investigations in MS, including magnetic resonance imaging (MRI) of the brain and spinal cord, serve as useful identifiers of abnormalities consistent with and supportive of MS, rather than for definitive diagnostic purposes, due to insufficient sensitivity and specificity alone. An important component of diagnostic clinical criteria for MS is the exclusion of alternative disorders that may be responsible for underlying neurologic symptoms.

The differential diagnosis for MS includes an exhaustive list of potential mimickers, encompassing infectious, inflammatory, rheumatologic, metabolic, nutritional, and degenerative entities. Notably, the majority of MS differentials exhibiting dissemination in space, time, or both, are either extremely rare and seldom encountered in routine clinical practice, or are associated with specific and characteristic distinguishing diagnostic features. As such, the scope of this review will predominantly focus on other neuro-inflammatory demyelinating conditions, which can particularly confound the diagnosis of MS, namely acute disseminated encephalomyelitis (ADEM), neuromyelitis

Christopher Eckstein and Shiv Saidha contributed equally to this work.

C. Eckstein
Department of Neurology, University of South Alabama College of Medicine, Mobile, AL, USA

S. Saidha · M. Levy (✉)
Department of Neurology, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Pathology 515, Baltimore, MD 21287, USA
e-mail: mlevy@jhmi.edu

optica (NMO), and idiopathic transverse myelitis (ITM). Additional inflammatory differential diagnoses of MS, including Sjögren's syndrome, systemic lupus erythematosus (SLE), Behçet's disease (BD), and vasculitis will also be briefly overviewed.

ADEM

ADEM is an uncommon disease lacking well-defined or widely accepted diagnostic criteria. Conventionally, ADEM is regarded as a monophasic illness, which occurs in the post-infectious or post-vaccination setting and is associated with multifocal demyelinating symptoms, notably including encephalopathy or coma, as well as seizures [2, 3]. Diagnosis, however, is not without a certain degree of fallibility. There is sufficient clinical overlap between ADEM and MS, such that ADEM and an initial MS attack may be virtually indistinguishable. This is especially the case when there is a lack of a clearly defined and temporally associated infection (typically a viral infection, often exanthematous and associated with a prodrome) or vaccination history.

While ADEM may occur at any age, it occurs most frequently in younger patients, with a peak incidence in children (mean age of onset 5.7 years), and consequently, the majority of ADEM studies are conducted in the pediatric setting. Annual incidence for patients less than 15 years of age is reported to be 0.64/100,000, with those older than 10 years of age displaying lower rates of encephalopathy [4]. Post-vaccination incidence varies, ranging from 1:1,000 to 1:20,000, dependent upon the vaccine administered, with measles vaccination being associated with the greatest risk [5]. Precise incidence in adults is more difficult to establish, but clinically adults tend to experience fever, encephalopathy, and seizures less frequently than children do.

Diagnosis

The proposed diagnostic criteria primarily aim to differentiate ADEM and MS. Conventionally, ADEM is considered a clinically distinct entity from MS, as it is typically monophasic and associated with symptoms not typical of MS including encephalopathy or coma and seizures, in addition to multiple other neurologic symptoms common to both disorders. It is proposed that an initial attack consistent with a demyelinating event with acute or subacute onset, a stable to stuttering course, and concomitant encephalopathy should constitute a diagnosis of ADEM (Table 1). The traditional monophasic course of ADEM is now less rigorously emphasized, although new symptoms occurring more than 1 month following a remission of initial symptoms is considered more suggestive of MS. Without occurrence of remission, new symptoms may continue to emerge over a 3-month period following initial onset and continue to constitute a diagnosis of ADEM [2, 6]. While these clinical criteria may be useful for most cases, there may still be some difficulty in clinically distinguishing ADEM from conditions such as Marburg variant MS, a fulminant monophasic demyelinating disorder with large lesions and associated edema often resulting in death months after onset.

Table 1 Proposed diagnostic criteria for acute disseminated encephalomyelitis

Subacute encephalopathy
Evolution over 1 week to 3 months
Accompanied by improvement or recovery (may have residual deficits)
MRI with white matter lesions that:
Are acute (remote lesions with encephalomalacia cast doubt on diagnosis)
Are typically multiple
Include at least one large lesion (1–2 cm in diameter)
Are supra- and/or infra-tentorial
May have gadolinium enhancement (not required)
May have basal ganglia lesions (not required)

Miller et al. [2]

There is considerable debate regarding recurrent or multiphasic ADEM. A recurrence of the same symptoms following resolution of the initial acute phase of the disease is often termed "recurrent ADEM." Previously existing lesions may even enlarge or re-enhance with gadolinium during this [6, 7]. However, multiphasic disease, characterized by new or different symptoms beyond a 3-month period from the initial event, typically results in ultimate diagnosis of MS, regardless of the specific clinical symptoms. There are more recent suggestions that such patients may have multiphasic ADEM, although the controversy regarding this remains unresolved. These cases are perhaps less confounding when the disease course is preceded by recurrence of infectious signs, such as fever, or repeated vaccination [6–8]. Clinically, multiphasic ADEM represents a potential major dilemma in the diagnosis of MS, as one may expect a high degree of misdiagnosis between the two groups, with unknown implications for long-term management of both diseases.

MRI may be helpful in distinguishing ADEM and MS. ADEM is classically associated with large, confluent, and symmetric white-matter lesions (Fig. 1), whereas in MS, lesions are more often sharply demarcated, round-edged, and oval in shape [9]. Periventricular lesions are less frequently seen in ADEM than MS, and there is more homogeneous contrast enhancement in ADEM lesions

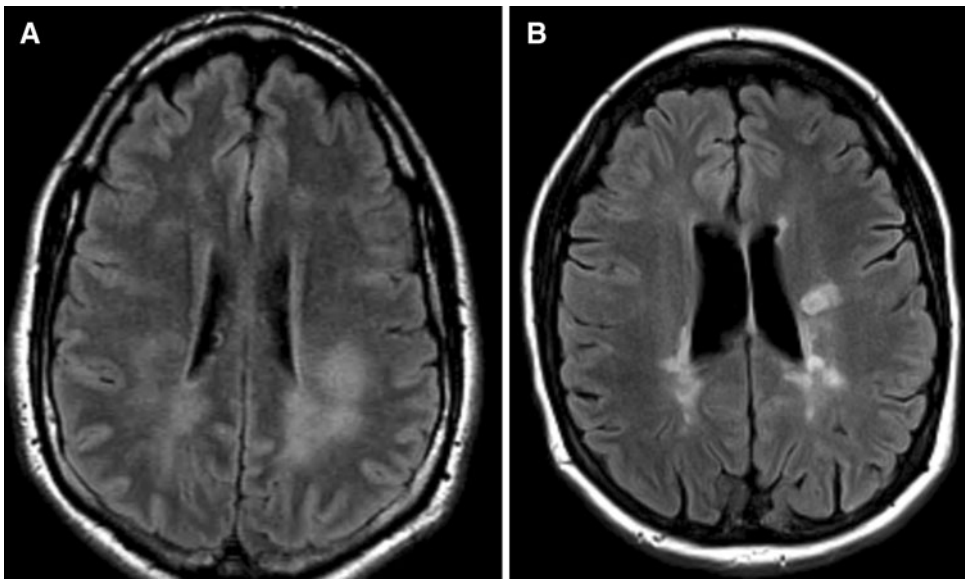

Fig. 1 Cerebral lesions in ADEM versus MS. FLAIR sequence MRI in a patient with ADEM (**a**) compared to a patient with MS (**b**). Lesions associated with ADEM are typically larger, more confluent, with less distinct borders than those seen in MS, which are often smaller and more sharply demarcated

[10]. More advanced imaging techniques, such as magnetic resonance spectroscopy, have demonstrated elevation of lipids and reduction of the myo-inositol:creatinine ratio during the acute phase, followed by reduction in lipids and increased myo-inositol:creatinine ratios in the chronic setting [11].

Cerebrospinal fluid (CSF) findings are nonspecific in ADEM, often with an elevated white cell count, protein <100 mg/dl, and absence of oligoclonal bands [12, 13]. These findings may be similar to those seen in MS and are less helpful in differentiating the two disorders. Notably, CSF-specific oligoclonal bands are less frequently detected very early in the course of MS than later.

In pediatric patients, anti-myelin oligodendrocyte glycoprotein (MOG) antibodies may assist in the diagnosis of ADEM. While anti-MOG antibodies are not specific for demyelination in adult patients, and have also been identified in healthy controls, anti-MOG antibodies are thought to be specific for demyelination in the pediatric population, with high reactivity being more suggestive of ADEM. However, anti-MOG antibodies are considered insensitive in both adults and children [14, 15].

Pathology

Differentiating ADEM and MS histologically can be tenuous, but there are some differences in the pathological patterns between the two disorders [16]. The lesions in ADEM typically spread radially outward from cerebral vessels, with macrophages concentrated around the vessels, whereas the plaques of MS are more discontinuous, with macrophages more prominently seen at the plaque border. Additionally, MS lesions have sharp, distinct borders while those of ADEM are not as clearly delineated. With regards to outcome, following the acute phase of ADEM there is sparse, nonspecific gliosis without myelin loss, whereas MS lesions remain present, even if they were not especially active [17].

Treatment

With regards to therapy, there is limited controlled data, but treatment is primarily limited to high-dose intravenous steroids or plasmapheresis [18, 19]. Steroids are also helpful in cases where there is cerebral edema, helping to reduce inflammation and blood–brain barrier permeability. For unknown reasons, a proportion of ADEM patients do not respond to steroids, however. In these patients, plasmapheresis is often instituted with benefit. Intravenous immunoglobulin (IVIg) is of questionable use [20–22].

Prognostically, there is limited controlled data available. There is some evidence that patients with a history of ADEM may subsequently develop deficits in attention and executive function [23]. More diffuse lesions, especially with cortical involvement, may indicate a worse prognosis [24]. Additionally, some studies indicate that approximately 30% of patients diagnosed with ADEM will eventually progress to a diagnosis of MS [3, 25, 26].

Neuromyelitis optica

NMO is a relatively homogeneous disorder characterized by demyelination of the optic nerves and spinal cord and may be the most common non-MS demyelinating disease of the CNS [27–29]. Although previously considered to be a predominantly monophasic disease, it is now recognized that the majority of NMO cases are relapsing [30, 31].

Table 2 Proposed Wingerchuk diagnostic criteria for definite NMO

1: Optic neuritis
AND
2: Acute myelitis
AND
3: At least two of the following:
(a) Contiguous spinal cord MRI lesion extending three or more vertebral segments
(b) Brain MRI not meeting diagnostic criteria for MS
(c) NMO IgG seropositive status

Wingerchuk et al. [27]

NMO is more common in females, with a female-to-male ratio of 9:1. It has an overall prevalence as high as 4.4/100,000 [30, 32].

Diagnosis

The diagnosis of NMO is made using clinical criteria, in conjunction with radiologic and serologic testing, as previously proposed by Wingerchuk et al. (Table 2) [27]. NMO can be difficult to distinguish from MS, especially at initial onset, as it can present with acute optic neuritis, acute myelitis, or both. Additionally, brain lesions may be seen on MRI in NMO. These lesions, however, are typically distinct from those seen in MS, frequently being more linear and having a more limited distribution than MS lesions, often restricted to the periventricular region [33]. Perhaps the most helpful tool for distinguishing NMO from MS is the anti aquaporin-4 autoantibody, also referred to as the NMO IgG antibody, which has a sensitivity of 50–75% and a specificity of 90% for NMO [34, 35].

The myelitis seen in NMO (Fig. 2) is also typically distinct from that of MS. It commonly manifests as a complete transverse myelitis, often with incomplete recovery, as compared to the myelitis of MS (Fig. 3), which is most commonly a partial TM. Spinal imaging often reveals longitudinally extensive transverse myelitis (LETM) extending three or more vertebral segments in length in NMO, although this has an extensive differential in itself [27, 36]. The spinal lesions seen in MS are usually two or less vertebral segments in length.

It is worth noting that LETM is commonly encountered in Asians with the optico-spinal variant of MS (OSMS), in which up to 59% of patients have extensive spinal cord lesions during acute relapses [37]. OSMS accounts for 15–40% of MS cases in Japan and may closely resemble NMO both clinically and radiologically [38]. Further confounding differentiation between NMO and OSMS, NMO IgG antibody may be positive in up to 60% of OSMS patients [39, 40]. While the similarities and potential differences between NMO and OSMS require further clarification, OSMS should be considered in appropriate patient populations, as it may have therapeutic management implications [41].

Pathology

Pathologically, the lesions of NMO exhibit an antibody-mediated inflammatory reaction, which may involve both gray and white matter. They display marked edema, perivascular and parenchymal infiltrates, necrosis, cavitation, and perivascular immunoglobulin deposition [42, 43]. Aquaporin 4 antibody immunoreactivity is reduced or lost in both spinal cord and brain lesions [44].

Treatment

Generally, NMO carries a poorer prognosis than MS. Treatment of NMO should be aggressive and aimed at

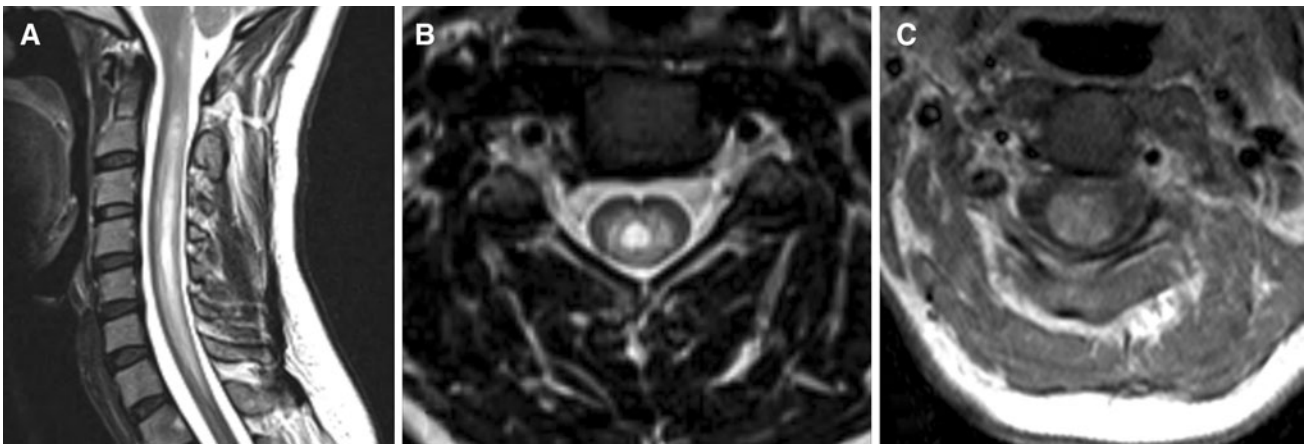

Fig. 2 MRI of NMO-associated myelitis. Sagittal T2-weighted MRI of the cervical spinal cord demonstrates a longitudinally extensive high signal intensity extending from C2 to T1 (**a**). Axial T2-weight MRI through the cervical lesion demonstrating a complete myelitis (**b**). Axial post-gadolinium T1-weighted MRI with enhancement involving the entire cross-sectional area of the spinal cord (**c**)

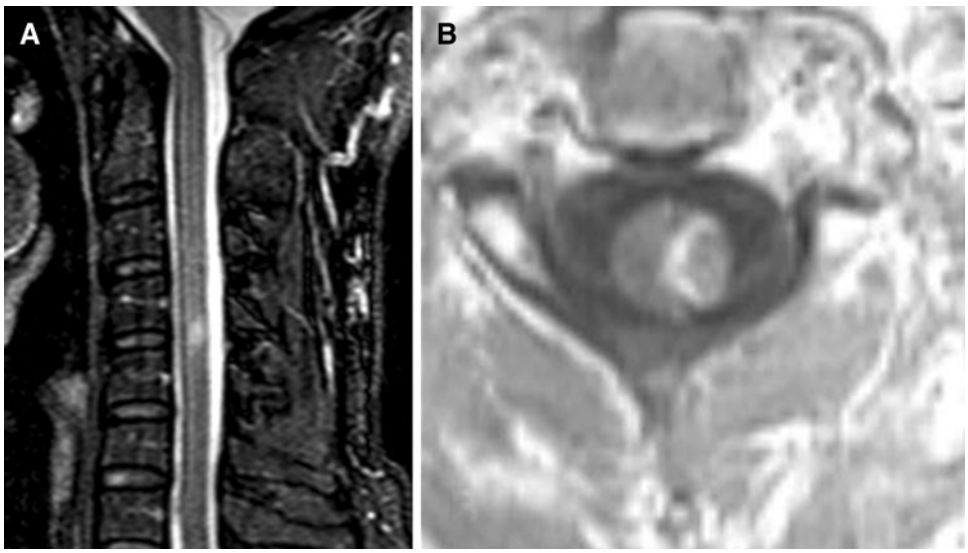

Fig. 3 MRI of idiopathic transverse myelitis. Sagittal T2-weighted MRI of the cervical spinal cord demonstrating myelitis, which is less than two spinal segments in length (**a**). Axial post-gadolinium T1-weighted MRI through the cervical lesion demonstrating enhancement in the left lateral cord (**b**), more consistent with partial myelitis

preventing additional relapses and subsequent disability. Acutely, high-dose IV steroids are the standard treatment. Long-term, systemic immunosuppression, such as azathioprine or mycophenolate mofetil is the standard therapy [45]. Rituximab, a targeted B cell depletion therapy, is also being used with promising results [46, 47]. It has been demonstrated to be well tolerated with repeated dosing, resulting in a reduction in relapses of up to 88% and a relapse-free rate of up to 70% after 2 years [48, 49]. Mitoxantrone, though a general immunosuppressant, may preferentially target CD19+ B cells, and thus, has also been investigated as a potential NMO treatment [50–52]. It has been shown to achieve a 75% reduction in annualized relapse rate with 50% of patients remaining relapse free [53]. In contrast to MS, interferon-beta therapy is not effective in NMO and may actually exacerbate the disease [45, 54].

NMO spectrum disorder

It is becoming increasingly common to encounter patients afflicted with either recurrent optic neuritis or myelitis in the setting of a positive NMO IgG. These patients do not meet criteria for a diagnosis of definite NMO but are often classified as NMO spectrum disorder. Many of these patients also test positive for additional autoantibodies or exhibit symptoms of other systemic diseases, frequently Sjögren's syndrome [55]. These patients are often treated as if they have definite NMO [29, 56].

Idiopathic transverse myelitis

ITM, characterized by focal spinal cord inflammation occurring over days to weeks with subsequent stability or improvement, may be caused by a variety of disorders [57]. The true incidence of ITM is difficult to confidently determine, given the inherent limitations of the diagnostic criteria for ITM, but one study estimates an annual incidence of 6/million in New Zealand between 2001 and 2005. If rates are adjusted to include all cases of both complete and partial myelitis, the incidence increases to approximately 25/million [58].

Although much of the data regarding ITM is pediatric, ITM may occur at any age. In studies conducted preceding the establishment of current diagnostic criteria, ITM appeared to have peak onset between 10 and 20 years of age, with a second peak at 30–40 years [59]. Since the current diagnostic criteria were established in 2002, there is less data available on age distribution, but overall mean age of disease onset appears to be between 35 and 40 years [58, 60, 61]. Historically, it was regarded that ITM was evenly represented in both males and females. However, several recent studies suggest there may be a female preponderance [58, 60, 62]. In pediatric patients, approximately 38% occur prior to the age of 3 years, with cases equally distributed between males and females [63].

Diagnosis and risk of clinically definite MS

Clinical features of ITM relate to spinal cord dysfunction and include motor, sensory, and/or autonomic deficits. This may be particularly confounding with MS, since myelitis is frequently the initial clinical manifestation of MS. In these cases, clinicians must rely on clinical and additional ancillary testing to guide appropriate diagnosis and treatment. There are some features of ITM that may assist in determining etiology and possibly predicting individuals with risk for progression to clinically definite MS.

First, it is helpful to distinguish between complete and partial myelitis. The current diagnostic criteria, established in 2002 by the Transverse Myelitis Consortium Working Group [57], suggest complete myelitis, which involves the complete cross-sectional area of the cord, resulting in bilateral deficits below the level of the spinal lesion, tends to be more consistent with ITM (Table 3). Partial myelitis, while still acute or subacute in onset, involves only a partial cross-sectional area of the spinal cord, often manifesting as asymmetric motor or sensory dysfunction, and is the more common form of myelitis observed in MS. Patients presenting with a partial myelitis have a 20–30% transition rate to clinically definite MS at 5-year follow-up, compared to only 2% of complete myelitis patients [64–67].

Additionally, most cases of MS-associated myelitis extend less than three spinal segments in length in the longitudinal plane. This does not explicitly imply that all patients presenting with longitudinally limited, partial myelitis will develop MS, but rather, when MS patients develop myelitis it most often adheres to this pattern. Those with longitudinally extensive spinal lesions (three or more spinal segments in length) should be evaluated for NMO, as well as a variety of other disorders in the appropriate clinical setting, including Sjögren's syndrome, BD, sarcoidosis, metabolic disturbances, and various infectious agents. A complete discussion of the etiology of TM is beyond the scope of this review and can be found elsewhere [36]. However, once all alternative etiologies have been evaluated, the majority of transverse myelitis, whether partial, complete, or longitudinally extensive, will remain idiopathic [65].

The classic clinical course of ITM is monophasic, but recurrence has been documented in up to 25% of cases. Recurrence may manifest as a repeat of the initial event, expansion of previously noted lesions, or new discreet lesions in the spinal cord. Relapsing cases have an increased tendency to be longitudinally extensive, although not every exacerbation will include this characteristic [60, 68, 69].

Table 3 Proposed diagnostic criteria for idiopathic acute transverse myelitis

Sensory, motor, or autonomic dysfunction attributable to the spinal cord
Bilateral signs and/or symptoms (may be asymmetric)
Clearly defined sensory level
Exclusion of compressive or other demyelinating etiology
Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement
Progression to nadir between 4 h and 21 days following onset of symptoms

Transverse Myelitis Consortium Working Group [57]

Pathology

The exact immunologic mechanism underlying ITM remains unclear. Given that an infectious process frequently precedes TM, a microbial-related process has been proposed to cause ITM [69]. While TM may certainly result from direct spinal cord infection, ITM is thought to primarily represent sequelae of either symptomatic or asymptomatic infection precipitating exacerbation of a pre-existing autoimmune process, polyclonal activation of B cells, bystander activation of autoreactive T cells, or possibly molecular mimicry [70]. Histologically, biopsy specimens from ITM demonstrate prominent perivascular inflammation involving monocytes and lymphocytes, with associated astroglial and microglial activation [71]. White matter tract demyelination and axonal injury can also be seen [72].

Treatment

Treatment of ITM is predominantly targeted at halting inflammation, with long-term management focusing on rehabilitation. Despite a lack of controlled clinical trials, acute treatment primarily consists of high-dose intravenous steroids, typically methyl-prednisolone [69, 73, 74]. In those patients lacking an adequate response or who are intolerant of steroids, plasmapheresis is often the next step, with up to 42% of patients experiencing moderate to marked improvement in symptoms following this [75, 76]. In severe cases, in which there is complete loss of sensorimotor function, improvement may be seen with the combination of plasmapheresis and cyclophosphamide [74]. Those with recurrent attacks of myelitis often undergo further therapy with long-term immunosuppression.

Sjögren's syndrome

Sjögren's syndrome (SS), a highly variable clinical disorder, is an autoimmune condition characterized by mononuclear infiltration and destruction of the salivary and lacrimal glands, which accounts for the sicca symptoms typically observed in SS [77]. Typically regarded a rheumatologic disorder, the initial presentation of SS may be neurological in nature, such as acute optic neuritis or TM [78]. Its neurologic manifestations, whether acute, relapsing, or progressive, may even precede the development of sicca symptoms. These factors highlight the variable clinical course of SS, such that neurological involvement of SS may be difficult to distinguish from MS or NMO. There is such overlap in clinical and serologic characteristics between SS and NMO that a Sjögren's-NMO spectrum disorder has been proposed, characterized by optic neuritis,

myelitis, positive NMO IgG, in addition to positive SS associated auto-antibodies including anti-Ro (anti-SSA) and anti-La (anti-SSB) antibodies [79, 80]. The incidence of primary SS has been reported at 4/100,000, with neurological manifestations, commonly myelopathy, occurring in 15–25% [81–83].

Diagnosis

Diagnosis as outlined by the European-American Diagnostic Criteria for Sjögren's Syndrome consists of a constellation of clinical symptoms, as well as an abnormal lip biopsy or positive antibody testing [77]. Diagnosis can be difficult when neurological symptoms predominate. It is vitally important to maintain a high index of suspicion for underlying SS, especially when there are concomitant sicca symptoms or positive SS-associated autoantibodies. CSF profiling in SS may demonstrate elevated protein, with moderate pleocytosis. OCBs are uncommon in SS. There is sufficient overlap between SS and NMO, with many SS myelopathy patients testing positive for NMO IgG, that some have proposed that the CNS manifestations of SS are actually the result of concurrent NMO [79]. MRI findings in SS myelopathy may be similar to those of NMO, often being longitudinally extensive and gadolinium-enhancing [78, 81].

Treatment

The initial acute treatment for SS with neurological involvement is corticosteroids. Subsequent systemic immunosuppression is then implemented to prevent relapses, which often recur after discontinuation of steroids. Methotrexate, azathioprine, and cyclophosphamide are all commonly used for long-term management of SS [84, 85]. Prognosis in SS with neurologic involvement may be similar to that of NMO, with known potential for the development of severe morbidity following SS neurologic relapses. Early aggressive treatment of SS with neurological involvement is thus warranted.

Systemic lupus erythematosus

SLE is a common autoimmune disorder capable of manifesting with a diverse clinical spectrum, owing to its capacity to affect multiple organ systems, including the CNS. Estimates of neurological involvement vary widely, ranging from 6 to 150/100,000, and are highly dependent on sex and racial origin. Risk is significantly higher for females, Asians, and African-Caribbeans [86]. The rate of neurologic involvement is unclear, but ranges of between 14 and 90% have been reported [87].

Table 4 Possible neurologic manifestations of systemic lupus erythematosus

Central nervous system
Headache
Aseptic meningitis
Cerebrovascular disease
Demyelination
Movement disorders
Myelopathy
Seizures
Cognitive dysfunction
Psychosis
Mood disorders
Acute confusional state
Peripheral nervous system
Polyneuropathy
Cranial neuropathy
Acute inflammatory demyelinating polyradiculoneuropathy
Autonomic dysfunction
Mononeuropathy
Plexopathy

The neurologic complications of SLE are highly variable, with the capacity to affect any level of the nervous system (Table 4). SLE may particularly confound the diagnosis of MS since it may present with similar clinical and radiological features. Historically, this has resulted in terms such as lupoid sclerosis. However, pathologic studies have helped to distinguish CNS lupus as a distinct disorder without histologic evidence of demyelination [88]. Lupus myelopathy, although it only occurs in less than 5% of patients, is perhaps the most debilitating complication of SLE [89–91]. Though this frequently occurs concomitantly with other neuropsychiatric complications of SLE, it tends to occur early in the course of disease, and may be the presenting symptom in some cases. Clinically, lupus myelopathy is usually acute and its prognosis tends to be poorer than that of the other neurologic complications associated with SLE. Pathophysiologically, lupus myelopathy may be associated with a thrombotic or vasculitic component [91, 92].

Diagnosis

The diagnosis of SLE is typically based on the recommendations of the American College of Rheumatology (ACR) criteria, which require at least four out of 11 typical features at some time in the course of disease [93]. It is worth highlighting that the necessary features for constitution of a diagnosis of SLE do not need to be present at the same time. Thus, patients who fail to fulfill criteria for diagnosis of SLE at disease onset may still have active

SLE, and as such, a high index of suspicion for SLE needs to be maintained in the appropriate setting.

Further complicating the diagnosis of neurolupus, similar to MS, there is no definitive diagnostic test for neurolupus. In conjunction with the clinical picture, autoantibodies may be helpful in distinguishing SLE from MS. However, these may be nonspecific and some, such as the anti-nuclear antibody (ANA), may also be positive in other conditions, as well as in some healthy individuals [94]. Additional autoantibody testing which may be helpful, but not necessarily diagnostic or highly sensitive, includes anti-double-stranded DNA, anti-ribonuclear P, anti-sn ribonucleoprotein, anti-Sm, anti-Ro (SSA) and anti-La (SSB), anti-histone, and anti-phospholipid antibodies [95]. CSF analysis often yields mild and nonspecific abnormalities in SLE, ranging from normal white cell counts to granulocytic pleocytosis with elevated protein. Hypoglycorrhachia may be observed early in the course of lupus myelitis but is not typical of the other neurologic manifestations of SLE [91, 96].

The imaging pattern of cerebral involvement in SLE often reflects clinical findings and may be similar to that of MS. Acute SLE lesions often enhance with gadolinium. One consistently reported finding in chronic SLE is cortical atrophy [97, 98]. However, this is also frequently seen in MS and, thus, does not help discriminate the two disorders. MRI of the spinal cord may reveal longitudinally extensive lesions, sometimes involving the entire length of the spinal cord in SLE [99, 100], an uncommon finding in MS.

Treatment

Though diagnosis may be difficult, differentiating SLE with neurologic involvement from MS is vital, as SLE is treatable, and without treatment, it could be severely disabling and even fatal. Treatment options for neurolupus are largely based on case reports and small series. However, there is a randomized trial suggesting that steroids plus cyclophosphamide is superior to steroids alone [101, 102]. Often patients are transitioned to other immunosuppressants, such as azathioprine, mycophenolate mofetil, methotrexate or cyclosporine, for long-term maintenance [103, 104]. Plasmapheresis is also frequently attempted in severe cases. Anti-thrombotic therapy has been advocated in some cases, especially those with positive anti-phospholipid antibodies. Early treatment of neurolupus is advocated, as there is evidence that this may improve long-term prognosis [92].

Sarcoidosis

Sarcoidosis is a granulomatous disease of unknown etiology capable of affecting multiple organ systems and presenting with a wide variety of nonspecific symptoms. The lungs are the most commonly affected organ system in sarcoidosis, with the skin and eyes also frequently affected. Common symptoms of pulmonary sarcoidosis include cough and dyspnea on exertion. Pulmonary imaging typically demonstrates lymphadenopathy, often affecting the hilar lymph nodes. CNS involvement (neurosarcoidosis) occurs in 5–26% of sarcoid patients and may involve any part of the neuroaxis [105–107]. The overall prevalence of sarcoidosis in the United States is approximately 40/100,000 and is more frequently seen in northern Europeans and African Americans [108]. It is estimated that the prevalence of CNS sarcoidosis is 0.2/100,000 in Caucasians [109].

CNS involvement in sarcoidosis most frequently affects the leptomeninges. However, the most common presenting symptom of neurosarcoidosis is cranial nerve palsies. These occur in up to 50–75% of symptomatic patients, with the facial nerve being most often affected and the optic nerve the second most affected [110]. Optic nerve involvement in sarcoidosis may mimic the optic neuritis commonly seen in MS. Ophthalmologic examination in sarcoidosis may reveal papilledema, papillitis, and/or optic disc atrophy [111]. Additionally, intraparenchymal infiltration of granulomas may occur in up to 50% of patients with neurosarcoidosis [112]. These lesions may closely resemble MS plaques on MRI. Myelitis, although relatively rare (<10% of patients), may cause significant morbidity in neurosarcoidosis. Sarcoid myelopathy is predominantly subacute or chronic and may be monophasic, relapsing, or progressive [113, 114].

Diagnosis

Diagnosis of neurosarcoidosis can be exceedingly difficult, especially in the absence of systemic involvement. It is important to maintain a high index of suspicion for underlying sarcoidosis in patients with suspected inflammatory conditions, especially those with concurrent respiratory or unexplained systemic symptoms. Even in those without respiratory symptoms, when clinical suspicion is high, it is worthwhile performing a CT thorax or CT-PET scan to look for evidence of subclinical pulmonary sarcoidosis or identification of extraneural areas that may be amenable to biopsy. Blood tests, including serum angiotensin converting enzyme (ACE), are of little diagnostic use. The most frequent abnormal laboratory finding in sarcoidosis is an elevated C-reactive protein (CRP), which is a nonspecific finding [114]. CSF analysis typically reveals elevated protein, pleocytosis, and, in some cases, hypoglycorrhachia. OCBs are present in a minority of neurosarcoidosis patients. CSF ACE is normal in

more than 50% of patients [114–116]. On brain MRI, neurosarcoidosis lesions commonly enhance with gadolinium and may involve the leptomeninges, which is not typically seen in MS, or manifest as discreet parenchymal lesions. On spinal MRI, lesions of sarcoid myelopathy are centrally predominant and most often located in the cervical or thoracic regions [114]. Definitive diagnosis can only be made through biopsy, either of the CNS or another affected organ system.

Treatment

Though there are a variety of treatment regimens utilized for systemic sarcoidosis, few of these have been systematically evaluated in neurosarcoidosis. First-line therapy consists of high-dose corticosteroids. Chronic treatment involves transitioning to steroid-sparing systemic immunosuppression with drugs such as methotrexate, mycophenolate mofetil, cyclophosphamide, cyclosporine, and TNF-alpha inhibitors [117–120]. Prognosis and treatment response in neurosarcoidosis are difficult to predict. However, patients with a progressive disease course tend to have a worse prognosis.

Behçet's disease

BD is a chronic, relapsing inflammatory disease of unclear etiology characterized by aphthous stomatitis, genital ulceration, and uveitis [121]. Arthropathy and thrombosis are also common in BD. Neurologic involvement, known as neuro-Behçet's, is well documented, reportedly occurring in approximately 5–50% of BD patients. BD is more common in eastern Mediterranean countries and Japan; it is rarely encountered in United States or Western European populations [122]. Though the incidence of BD between males and females in the third and fourth decades of life is nearly equal, neurologic symptoms are four times more common in males than females [123].

Neuro-Behçet's is typically classified as parenchymal or nonparenchymal disease. Parenchymal neuro-Behçet's includes meningoencephalitis, which accounts for approximately 75% of cases, as well as basal ganglia and brainstem involvement. Nonparenchymal neuro-Behçet's may include cerebral venous thrombosis, intracranial hypertension, and intracranial aneurysms. Thrombosis often results in secondary parenchymal manifestations [124]. Spinal cord involvement is reported in up to 14% of neuro-Behçet's patients and is often subacute, progressive, and longitudinally extensive [125–128]. The pathology of BD myelitis is poorly understood. Biopsy and post-mortem studies indicate that venous vasculitis may play an etiologic role [129].

Diagnosis

Since there are no definitive diagnostic tests available for BD, diagnosis is based on clinical criteria proposed by the International Study Group for BD, including recurrent aphthous ulcers, which are a requisite for diagnosis, and two additional criteria. The additional criteria may include recurrent genital ulcers, uveitis, skin lesions, or a positive pathergy test [121]. HLA type B51 has been identified in up to 70% of Japanese and Turkish BD patients, but only 10–20% of afflicted Europeans [130]. In patients with parenchymal involvement, CSF analysis may reveal pleocytosis with either lymphocyte or neutrophil predominance, and elevated protein, ranging from 60 to 150 mg/dl. In one BD series, the IgG index was found to be elevated in 73% of patients, while CSF OCBs were only demonstrated in 16% of patients. Of those with OCBs, none had more than two bands [126, 128, 131].

Imaging abnormalities in neuro-Behçet's commonly occur in the basal ganglia and brainstem. Abnormalities typically consist of large, confluent lesions in the brainstem, which may extend into the basal ganglia. Findings are bilateral in approximately one-third of patients. Additional brain abnormalities may include small, scattered, nonspecific hyperintensities in the white matter [126, 132]. Spinal abnormalities, although relatively rare in neuro-Behçet's, are usually longitudinally extensive [133].

Treatment

There are no controlled trials of any treatment regimens in neuro-Behçet's, but standard treatment for acute symptoms in neuro-Behçet's typically include high-dose intravenous corticosteroids. When initiated in the acute or subacute phase, corticosteroids may result in complete resolution of symptoms and imaging findings in many patients, especially those with cerebral and brainstem lesions. However, patients with spinal cord involvement tend to have a more aggressive, and typically progressive, disease course and therefore have a worse prognosis than neuro-Behçet's patients without spinal cord involvement. Despite the lack of large controlled trials, long-term immunotherapy has been attempted with varying degrees of success in neuro-Behçet's with azathioprine, mycophenolate mofetil, infliximab, and methotrexate [125, 134–136].

Primary CNS vasculitis

Primary CNS vasculitis (PCNSV) is a rare disorder characterized by inflammation of the blood vessels in the brain and spinal cord without evidence of vasculitis outside of the CNS [137, 138]. Headache is the most common

Table 5 Differentiating features of neuroinflammatory disorders

Disorder	Clinical	Laboratory	MRI
Multiple sclerosis	Acute relapsing or chronic progressive Isolated CNS involvement	OCBs often present in CSF (79–90%)	Periventricular and juxtacortical lesions ± enhancement Typically well-demarcated ovoid lesions May see T1 hypointensities ("black holes") Spinal lesions usually ≤2 vertebral segments, often only with partial cross-sectional involvement of the spinal cord
Neuromyelitis optica	Acute relapsing Recurrent optic neuritis or myelitis Refractory nausea or hiccups	NMO IgG positive (56–73%)	Typically few cerebral lesions, which may be periventricular, especially in the brainstem Longitudinally extensive spinal cord lesions usually ≥3 vertebral segments in length
Acute disseminated encephalomyelitis	Subacute monophasic Post-infectious or post-vaccination Alteration of consciousness Seizures	Typically OCBs absent in CSF May be anti-MOG Ab positive in pediatric population	Diffuse or multi-lesion enhancement Lesions frequently have indistinct lesion borders
Sjögren's syndrome	Acute relapsing or chronic progressive Sicca symptoms	Anti-SSA/SSB positive (50–60%) NMO IgG positive in some Rarely OCBs present in CSF	Spinal cord lesions often longitudinally extensive (≥3 vertebral segments in length)
Systemic lupus erythematosus	Acute or chronic progressive Other organ system involvement Psychosis Seizures Infarcts	Positive ANA, anti-dsDNA Ab, anti-Sm Ab, anti-snRNP Ab, anti-P Ab, anti-histone Ab, and/or anti-phospholipid Abs	Restricted diffusion on diffusion weighted imaging consistent with ischemic infarcts Cortical atrophy in chronic cases
Neurosarcoidosis	Variable neurologic presentation Uveitis Lung or skin involvement	± ACE (<50%)	Nodular meningeal enhancement Spinal cord lesions often longitudinally extensive
Neuro Behçet's disease	Acute or chronic progressive Meningoencephalitis Cerebral venous thrombosis Oral and genital ulcers Positive pathergy test	HLA-B51 positive in Japanese and Turkish population (70%)	Unilateral or bilateral upper brainstem lesions extending into basal ganglia and thalamus Spinal cord lesions often longitudinally extensive
Primary CNS Vasculitis	Stroke or transient ischemic attack like episodes in multiple vascular distributions	None	Restricted diffusion on diffusion weighted imaging consistent with ischemic infarcts Conventional angiography may reveal vessel wall irregularities (50–60%)

CNS central nervous system, *OCB* oligoclonal bands, *CSF* cerebrospinal fluid, *NMO* neuromyelitis optica, *MOG* myelin oligodendrocyte glycoprotein, *ANA* anti-nuclear antibody, *dsDNA* double-stranded DNA, *snRNP* sn ribonucleoprotein, *Ab* antibody, *ACE* angiotensin converting enzyme

presenting symptom of PCNSV and in some instances, although rare, may even be characterized by a thunderclap headache. Cognitive deficits are also frequently seen in PCNSV [139]. Strokes and transient ischemic attacks occur in 30–50% of PCNSV patients, with several different vessels being affected as opposed to a single vascular territory [137, 140]. PCNSV affects the spinal cord in approximately 5–14% of patients, and most frequently it is preceded by, or occurs concurrently with, cerebral manifestations [140, 141]. Presentation may range from hyperacute to chronic. Peak incidence of PCNSV is in the late 30–50s and is more common in males [139, 142].

Diagnosis

PCNSV often represents a diagnostic challenge, as it does not have systemic manifestations. As with many of the above conditions, a high index of suspicion is required. PCNSV is a diagnosis of exclusion and should be considered in those patients with strokes in multiple vascular territories, headaches with abnormal imaging, or unexplained neurological syndromes that lack any systemic features. Complicating the diagnosis, laboratory studies are frequently unrevealing, and the erythrocyte sedimentation rate (ESR) may be normal in many cases. CSF analysis may also be normal in PCNSV, although in some cases, there may be marked protein elevation. Biopsy is considered the gold standard for diagnosis of PCNSV, with a specificity of nearly 99%. However, biopsy sensitivity is difficult to ascertain accurately. According to some reports it may be as high as 50–75% when both the leptomeninges and cortex are sampled together at the time of biopsy [138, 143]. Biopsy in PCNSV is thought to have a higher yield in patients with both myelopathy and brain involvement than in those with isolated brain involvement, possibly related to more a disseminated and aggressive disease process [140].

MRI abnormalities in the brain in PCNSV are highly variable and may include scattered ischemic-like T2 hyperintensities, intraparenchymal hemorrhages, gadolinium-enhancing masses, or diffuse leptomeningeal enhancement [144, 145]. These findings are not specific to vasculitis and at times may resemble MS lesions. Conventional angiography is often performed in patients with suspected CNS vasculitis to evaluate for vessel wall irregularities characteristic of vasculitis. However, angiography is often negative, with a sensitivity of approximately 50–60% and is not sufficient to exclude the diagnosis. Angiogram abnormalities are less frequent in patients with spinal cord symptoms [138, 141, 145–147].

Treatment

There are no randomized trials evaluating treatment options, so management is based largely on small series and observational studies, as well as clinical experience. Treatment most often consists of corticosteroids, both intravenous and oral, and cyclophosphamide. Other systemic immunosuppression, such as azathioprine and mycophenolate mofetil, is occasionally used as well [148]. While many patients respond to treatment, residual disability is frequently reported. Relapses are common, especially when oral steroids are tapered or immunosuppression weaned.

Alternative diagnoses

The differential diagnosis of MS is far too extensive for it to be clinically and financially practical to routinely assess each patient with suspected MS for every possible condition that is capable of mimicking it. Therefore, the clinical presentation and associated features should always be considered when determining appropriate diagnostic evaluation. Clinical history or features suggestive of further systemic involvement may indicate one of the inflammatory disorders discussed above (Table 5). Patients with appropriate risk factors may warrant an infectious disease evaluation, as human immunodeficiency virus (HIV), progressive multifocal encephalopathy (PML), human T lymphotropic virus (HTLV), and neurosyphilis may result in clinical and radiologic findings resembling MS. Additional disorders, all of which may result in CNS lesions with dissemination in space and time—a key diagnostic feature of MS, are listed in Table 6.

Conclusions

While an important aspect of the diagnostic criteria for MS includes excluding alternative disorders, MS should not be considered a classical "diagnosis of exclusion," as it is a diagnosis that should be actively sought out in suspected cases, recognizing that the majority of patients presenting with the typical clinical symptoms and ancillary testing

Table 6 Differential diagnosis for central nervous system lesions disseminated in space and time

Inflammatory	MS, NMO, ADEM, ITM, SLE, Sjögren's syndrome, Behçet's disease, neurosarcoidosis, Wegener's granulomatosis, CNS vasculitis, Susac's syndrome
Infectious	HIV, HTLV, neurosyphilis, PML, neuroborreliosis, Whipple's disease
Metabolic	Vitamin B12 deficiency, porphyria
Degenerative	Mitochondrial encephalomyopathy, hereditary spastic para-paresis, Fabry's disease, leukodystrophies
Vascular	CADASIL, anti-phospholipid antibody syndrome, multiple emboli, small vessel disease, migraine
Neoplastic	Metastases, lymphoma

MS multiple sclerosis, *NMO* neuromyelitis optica, *ADEM* acute disseminated encephalomyelitis, *ITM* idiopathic transverse myelitis, *SLE* Systemic lupus erythematosus, *HIV* human immunodeficiency virus, *HTLV* human T lymphotropic virus, *PML* Progressive multifocal leukoencephalopathy, *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

suggestive of MS will in fact have MS. However, considering and evaluating patients with suspected MS for alternative etiologies for their neurologic presentation remains imperative, as this may have significant treatment decision and prognostic implications.

Acknowledgments Dr. Christopher Eckstein receives funding through a Sylvia Lawry Physician Fellowship from the National Multiple Sclerosis Society. Dr. Shiv Saidha has received consulting fees from MedicalLogix for the development of continuing medical education programs in neurology and has received educational grant support from TEVA Neurosciences. Dr. Michael Levy receives research funding from the Guthy Jackson Charitable Foundation.

Conflict of interest None.

References

1. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS (2011) Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 69(2):292–302. doi:10.1002/ana.22366
2. Miller DH, Weinshenker BG, Filippi M, Banwell BL, Cohen JA, Freedman MS, Galetta SL, Hutchinson M, Johnson RT, Kappos L, Kira J, Lublin FD, McFarland HF, Montalban X, Panitch H, Richert JR, Reingold SC, Polman CH (2008) Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult Scler 14(9):1157–1174. doi:10.1177/1352458508096878
3. de Seze J (2007) Multiple sclerosis: clinical aspects, acute disseminated encephalomyelitis, neuromyelitis optica and other inflammatory variants. Rev Neurol (Paris) 163(6–7):647–650
4. Torisu H, Kira R, Ishizaki Y, Sanefuji M, Yamaguchi Y, Yasumoto S, Murakami Y, Shimono M, Nagamitsu S, Masuzaki M, Amamoto M, Kondo R, Uozumi T, Aibe M, Gondo K, Hanai T, Hirose S, Matsuishi T, Shirahata A, Mitsudome A, Hara T (2010) Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. Brain Dev 32(6):454–462. doi:10.1016/j.braindev.2009.10.006
5. Tselis A, Lisak R (2005) Acute disseminated encephalomyelitis. In: Antel JP, Birnbaum G, Hartung HP, Vincent A (eds) Clinical neuroimmunology. Oxford University Press, New York, pp 147–171
6. Krupp LB, Banwell B, Tenembaum S (2007) Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology 68(16 Suppl 2):S7–S12. doi:10.1212/01.wnl.0000259422.44235.a8
7. Brinar VV, Poser CM (2006) The spectrum of disseminated encephalomyelitis. Clin Neurol Neurosurg 108(3):295–310. doi:10.1016/j.clineuro.2005.11.017
8. Poser CM, Brinar VV (2004) Diagnostic criteria for multiple sclerosis: an historical review. Clin Neurol Neurosurg 106(3):147–158. doi:10.1016/j.clineuro.2004.02.004
9. Kuker W, Ruff J, Gaertner S, Mehnert F, Mader I, Nagele T (2004) Modern MRI tools for the characterization of acute demyelinating lesions: value of chemical shift and diffusion-weighted imaging. Neuroradiology 46(6):421–426. doi:10.1007/s00234-004-1203-5
10. Callen DJ, Shroff MM, Branson HM, Li DK, Lotze T, Stephens D, Banwell BL (2009) Role of MRI in the differentiation of ADEM from MS in children. Neurology 72(11):968–973. doi:10.1212/01.wnl.0000338630.20412.45
11. Ben Sira L, Miller E, Artzi M, Fattal-Valevski A, Constantini S, Ben Bashat D (2010) 1H-MRS for the diagnosis of acute disseminated encephalomyelitis: insight into the acute-disease stage. Pediatr Radiol 40(1):106–113. doi:10.1007/s00247-009-1372-9
12. Stuve O, Nessler S, Hartung HP, Hemmer B, Wiendl H, Kieseier BC (2005) Acute disseminated encephalomyelitis: pathogenesis, diagnosis, treatment, and prognosis. Nervenarzt 76(6):701–707. doi:0.1007/s00115-004-1842-0
13. Franciotta D, Columba-Cabezas S, Andreoni L, Ravaglia S, Jarius S, Romagnolo S, Tavazzi E, Bergamaschi R, Zardini E, Aloisi F, Marchioni E (2008) Oligoclonal IgG band patterns in inflammatory demyelinating human and mouse diseases. J Neuroimmunol 200(1–2):125–128. doi:10.1016/j.jneuroim.2008.06.004
14. Reindl M, Khalil M, Berger T (2006) Antibodies as biological markers for pathophysiological processes in MS. J Neuroimmunol 180(1–2):50–62. doi:10.1016/j.jneuroim.2006.06.028
15. Lalive PH, Hausler MG, Maurey H, Mikaeloff Y, Tardieu M, Wiendl H, Schroeter M, Hartung HP, Kieseier BC, Menge T (2011) Highly reactive anti-myelin oligodendrocyte glycoprotein antibodies differentiate demyelinating diseases from viral encephalitis in children. Mult Scler 17(3):297–302. doi:10.1177/1352458510389220
16. Tardieu M, Mikaeloff Y (2004) What is acute disseminated encephalomyelitis (ADEM)? Eur J Paediatr Neurol 8(5):239–242. doi:10.1016/j.ejpn.2004.05.006
17. Rodriguez M, Powell H, Lampert W (1983) Demyelination and leukodystrophy in the clinical neurosciences. In: Rosenberg R, Schoclet S (eds) Neuropathology, vol III. Churchill Livinstone, New York, pp 419–443
18. Stricker RB, Miller RG, Kiprov DD (1992) Role of plasmapheresis in acute disseminated (post-infectious) encephalomyelitis. J Clin Apher 7(4):173–179
19. Straub J, Chofflon M, Delavelle J (1997) Early high-dose intravenous methylprednisolone in acute disseminated encephalomyelitis: a successful recovery. Neurology 49(4):1145–1147
20. Dalakas MC (1998) Mechanism of action of intravenous immunoglobulin and therapeutic considerations in the treatment of autoimmune neurologic diseases. Neurology 51(6 Suppl 5):S2–S8
21. Sahlas DJ, Miller SP, Guerin M, Veilleux M, Francis G (2000) Treatment of acute disseminated encephalomyelitis with intravenous immunoglobulin. Neurology 54(6):1370–1372
22. Kleiman M, Brunquell P (1995) Acute disseminated encephalomyelitis: response to intravenous immunoglobulin. J Child Neurol 10(6):481–483
23. Bala B, Banwell B (2010) Cognitive and behavioural outcomes in individuals with a history of childhood acute disseminated encephalomyelitis. 62nd Annual Meeting, American Academy of Neurology, Toronto, pp IN2-2.005
24. Donmez FY, Aslan H, Coskun M (2009) Evaluation of possible prognostic factors of fulminant acute disseminated encephalomyelitis (ADEM) on magnetic resonance imaging with fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging. Acta Radiol 50(3):334–339. doi:10.1080/02841850902736617
25. Banwell BL (2007) The long (-itudinally extensive) and the short of it: transverse myelitis in children. Neurology 68(18):1447–1449. doi:10.1212/01.wnl.0000264553.99997.45
26. Schwarz S, Mohr A, Knauth M, Wildemann B, Storch-Hagenlocher B (2001) Acute disseminated encephalomyelitis: a

follow-up study of 40 adult patients. Neurology 56(10):1313–1318
27. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG (2006) Revised diagnostic criteria for neuromyelitis optica. Neurology 66(10):1485–1489. doi:10.1212/01.wnl.0000216139.44259.74
28. Jacob A, Matiello M, Wingerchuk DM, Lucchinetti CF, Pittock SJ, Weinshenker BG (2007) Neuromyelitis optica: changing concepts. J Neuroimmunol 187(1–2):126–138. doi:10.1016/j.jneuroim.2007.04.009
29. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG (2007) The spectrum of neuromyelitis optica. Lancet Neurol 6(9):805–815. doi:10.1016/S1474-4422(07)70216-8
30. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG (1999) The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 53(5):1107–1114
31. Ghezzi A, Bergamaschi R, Martinelli V, Trojano M, Tola MR, Merelli E, Mancardi L, Gallo P, Filippi M, Zaffaroni M, Comi G (2004) Clinical characteristics, course and prognosis of relapsing Devic's Neuromyelitis Optica. J Neurol 251(1):47–52. doi:10.1007/s00415-004-0271-0
32. Asgari N, Lillevang ST, Skejoe HP, Falah M, Stenager E, Kyvik KO (2011) A population-based study of neuromyelitis optica in Caucasians. Neurology 76(18):1589–1595. doi:10.1212/WNL.0b013e3182190f74
33. Pittock SJ, Weinshenker BG, Lucchinetti CF, Wingerchuk DM, Corboy JR, Lennon VA (2006) Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol 63(7):964–968. doi:10.1001/archneur.63.7.964
34. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR (2005) IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. J Exp Med 202(4):473–477. doi:10.1084/jem.20050304
35. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, Nakashima I, Weinshenker BG (2004) A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 364(9451):2106–2112. doi:10.1016/S0140-6736(04)17551-X
36. Eckstein C, Syc S, Saidha S (2011) Differential diagnosis of longitudinally extensive transverse myelitis in adults. Eur Neurol J 3(1):27–39
37. Matsuoka T, Matsushita T, Osoegawa M, Ochi H, Kawano Y, Mihara F, Ohyagi Y, Kira J (2008) Heterogeneity and continuum of multiple sclerosis in Japanese according to magnetic resonance imaging findings. J Neurol Sci 266(1–2):115–125
38. Kira J (2003) Multiple sclerosis in the Japanese population. Lancet Neurol 2(2):117–127
39. Nakashima I, Fujihara K, Miyazawa I, Misu T, Narikawa K, Nakamura M, Watanabe S, Takahashi T, Nishiyama S, Shiga Y, Sato S, Weinshenker BG, Itoyama Y (2006) Clinical and MRI features of Japanese patients with multiple sclerosis positive for NMO-IgG. J Neurol Neurosurg Psychiatry 77(9):1073–1075. doi:10.1136/jnnp.2005.080390
40. Weinshenker BG, Wingerchuk DM, Nakashima I, Fujihara K, Lennon VA (2006) OSMS is NMO, but not MS: proven clinically and pathologically. Lancet Neurol 5(2):110–111
41. Kira J (2008) Neuromyelitis optica and Asian phenotype of multiple sclerosis. Ann N Y Acad Sci 1142:58–71
42. Lucchinetti CF, Mandler RN, McGavern D, Bruck W, Gleich G, Ransohoff RM, Trebst C, Weinshenker B, Wingerchuk D, Parisi JE, Lassmann H (2002) A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. Brain 125(Pt 7):1450–1461
43. Roemer SF, Parisi JE, Lennon VA, Benarroch EE, Lassmann H, Bruck W, Mandler RN, Weinshenker BG, Pittock SJ, Wingerchuk DM, Lucchinetti CF (2007) Pattern-specific loss of aquaporin-4 immunoreactivity distinguishes neuromyelitis optica from multiple sclerosis. Brain 130(Pt 5):1194–1205. doi:10.1093/brain/awl371
44. Misu T, Fujihara K, Kakita A, Konno H, Nakamura M, Watanabe S, Takahashi T, Nakashima I, Takahashi H, Itoyama Y (2007) Loss of aquaporin 4 in lesions of neuromyelitis optica: distinction from multiple sclerosis. Brain 130(Pt 5):1224–1234. doi:10.1093/brain/awm047
45. Papeix C, Vidal JS, de Seze J, Pierrot-Deseilligny C, Tourbah A, Stankoff B, Lebrun C, Moreau T, Vermersch P, Fontaine B, Lyon-Caen O, Gout O (2007) Immunosuppressive therapy is more effective than interferon in neuromyelitis optica. Mult Scler 13(2):256–259. doi:10.1177/1352458506070732
46. Cree BA, Lamb S, Morgan K, Chen A, Waubant E, Genain C (2005) An open label study of the effects of rituximab in neuromyelitis optica. Neurology 64(7):1270–1272. doi:10.1212/01.WNL.0000159399.81861.D5
47. Capobianco M, Malucchi S, di Sapio A, Gilli F, Sala A, Bottero R, Marnetto F, Doriguzzi Bozzo C, Bertolotto A (2007) Variable responses to rituximab treatment in neuromyelitis optica (Devic's disease). Neurol Sci 28(4):209–211. doi:10.1007/s10072-007-0823-z
48. Kim SH, Kim W, Li XF, Jung IJ, Kim HJ (2011) Repeated treatment with rituximab based on the assessment of peripheral circulating memory B cells in patients with relapsing neuromyelitis optica over 2 years. Arch Neurol. doi:10.1001/archneurol.2011.154
49. Pellkofer HL, Krumbholz M, Berthele A, Hemmer B, Gerdes LA, Havla J, Bittner R, Canis M, Meinl E, Hohlfeld R, Kuempfel T (2011) Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. Neurology 76(15):1310–1315. doi:10.1212/WNL.0b013e3182152881
50. Neuhaus O, Wiendl H, Kieseier BC, Archelos JJ, Hemmer B, Stuve O, Hartung HP (2005) Multiple sclerosis: mitoxantrone promotes differential effects on immunocompetent cells in vitro. J Neuroimmunol 168(1–2):128–137. doi:10.1016/j.jneuroim.2005.01.024
51. Chan A, Weilbach FX, Toyka KV, Gold R (2005) Mitoxantrone induces cell death in peripheral blood leucocytes of multiple sclerosis patients. Clin Exp Immunol 139(1):152–158. doi:10.1111/j.1365-2249.2005.02653.x
52. Duddy M, Niino M, Adatia F, Hebert S, Freedman M, Atkins H, Kim HJ, Bar-Or A (2007) Distinct effector cytokine profiles of memory and naive human B cell subsets and implication in multiple sclerosis. J Immunol 178(10):6092–6099
53. Kim SH, Kim W, Park MS, Sohn EH, Li XF, Kim HJ (2011) Efficacy and safety of mitoxantrone in patients with highly relapsing neuromyelitis optica. Arch Neurol 68(4):473–479. doi:10.1001/archneurol.2010.322
54. Shimizu Y, Yokoyama K, Misu T, Takahashi T, Fujihara K, Kikuchi S, Itoyama Y, Iwata M (2008) Development of extensive brain lesions following interferon beta therapy in relapsing neuromyelitis optica and longitudinally extensive myelitis. J Neurol 255(2):305–307. doi:10.1007/s00415-007-0730-5
55. Pittock SJ, Lennon VA, de Seze J, Vermersch P, Homburger HA, Wingerchuk DM, Lucchinetti CF, Zephir H, Moder K, Weinshenker BG (2008) Neuromyelitis optica and non organ-specific autoimmunity. Arch Neurol 65(1):78–83. doi:10.1001/archneurol.2007.17
56. Wingerchuk DM (2007) Diagnosis and treatment of neuromyelitis optica. Neurologist 13(1):2–11. doi:10.1097/01.nrl.0000250927.21903.f8
57. Transverse Myelitis Consortium Working Group (2002) Proposed diagnostic criteria, nosology of acute transverse myelitis. Neurology 59(4):499–505

58. Young J, Quinn S, Hurrell M, Taylor B (2009) Clinically isolated acute transverse myelitis: prognostic features and incidence. Mult Scler 15(11):1295–1302. doi:10.1177/1352458509345906
59. Altrocchi PH (1963) Acute transverse myelopathy. Arch Neurol 9:111–119
60. de Seze J, Lanctin C, Lebrun C, Malikova I, Papeix C, Wiertlewski S, Pelletier J, Gout O, Clerc C, Moreau C, Defer G, Edan G, Dubas F, Vermersch P (2005) Idiopathic acute transverse myelitis: application of the recent diagnostic criteria. Neurology 65(12):1950–1953. doi:10.1212/01.wnl.0000188896.48308.26
61. Bruna J, Martinez-Yelamos S, Martinez-Yelamos A, Rubio F, Arbizu T (2006) Idiopathic acute transverse myelitis: a clinical study and prognostic markers in 45 cases. Mult Scler 12(2):169–173
62. Alvarenga MP, Thuler LC, Neto SP, Vasconcelos CC, Camargo SG, Papais-Alvarenga RM (2010) The clinical course of idiopathic acute transverse myelitis in patients from Rio de Janeiro. J Neurol 257(6):992–998. doi:10.1007/s00415-009-5450-6
63. Pidcock FS, Krishnan C, Crawford TO, Salorio CF, Trovato M, Kerr DA (2007) Acute transverse myelitis in childhood: center-based analysis of 47 cases. Neurology 68(18):1474–1480. doi:10.1212/01.wnl.0000260609.11357.6f
64. Perumal J, Zabad R, Caon C, MacKenzie M, Tselis A, Bao F, Latif Z, Zak I, Lisak R, Khan O (2008) Acute transverse myelitis with normal brain MRI: long-term risk of MS. J Neurol 255(1):89–93. doi:10.1007/s00415-007-0686-5
65. Scott TF (2007) Nosology of idiopathic transverse myelitis syndromes. Acta Neurol Scand 115(6):371–376. doi:10.1111/j.1600-0404.2007.00835.x
66. Morrissey SP, Miller DH, Kendall BE, Kingsley DP, Kelly MA, Francis DA, MacManus DG, McDonald WI (1993) The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis: a 5-year follow-up study. Brain 116(Pt 1):135–146
67. Bashir K, Whitaker JN (2000) Importance of para-clinical and CSF studies in the diagnosis of MS in patients presenting with partial cervical transverse myelopathy and negative cranial MRI. Mult Scler 6(5):312–316
68. Chan KH, Tsang KL, Fong GC, Ho SL, Cheung RT, Mak W (2006) Idiopathic inflammatory demyelinating disorders after acute transverse myelitis. Eur J Neurol 13(8):862–868. doi:10.1111/j.1468-1331.2006.01376.x
69. Kaplin AI, Krishnan C, Deshpande DM, Pardo CA, Kerr DA (2005) Diagnosis and management of acute myelopathies. Neurologist 11(1):2–18. doi:10.1097/01.nrl.0000149975.39201.0b
70. Borchers AT, Gershwin ME (2011) Transverse myelitis. Autoimmun Rev. doi:10.1016/j.autrev.2011.05.018
71. Lipton HL, Teasdall RD (1973) Acute transverse myelopathy in adults: a follow-up study. Arch Neurol 28(4):252–257
72. Kaplin AI, Deshpande DM, Scott E, Krishnan C, Carmen JS, Shats I, Martinez T, Drummond J, Dike S, Pletnikov M, Keswani SC, Moran TH, Pardo CA, Calabresi PA, Kerr DA (2005) IL-6 induces regionally selective spinal cord injury in patients with the neuroinflammatory disorder transverse myelitis. J Clin Invest 115(10):2731–2741. doi:10.1172/JCI25141
73. Jacob A, Weinshenker BG (2008) An approach to the diagnosis of acute transverse myelitis. Semin Neurol 28(1):105–120. doi:10.1055/s-2007-1019132
74. Greenberg BM, Thomas KP, Krishnan C, Kaplin AI, Calabresi PA, Kerr DA (2007) Idiopathic transverse myelitis: corticosteroids, plasma exchange, or cyclophosphamide. Neurology 68(19):1614–1617. doi:10.1212/01.wnl.0000260970.63493.c8
75. Weinshenker BG, O'Brien PC, Petterson TM, Noseworthy JH, Lucchinetti CF, Dodick DW, Pineda AA, Stevens LN, Rodriguez M (1999) A randomized trial of plasma exchange in acute central nervous system inflammatory demyelinating disease. Ann Neurol 46(6):878–886
76. Bonnan M, Valentino R, Olindo S, Mehdaoui H, Smadja D, Cabre P (2009) Plasma exchange in severe spinal attacks associated with neuromyelitis optica spectrum disorder. Mult Scler 15(4):487–492. doi:10.1177/1352458508100837
77. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH (2002) Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 61(6):554–558
78. Kim SM, Waters P, Vincent A, Kim SY, Kim HJ, Hong YH, Park KS, Min JH, Sung JJ, Lee KW (2009) Sjögren's syndrome myelopathy: spinal cord involvement in Sjögren's syndrome might be a manifestation of neuromyelitis optica. Mult Scler 15(9):1062–1068. doi:10.1177/1352458509106636
79. Kim SM, Waters P, Vincent A, Kim SY, Kim HJ, Hong YH, Park KS, Min JH, Sung JJ, Lee KW (2009) Sjögren's syndrome myelopathy: spinal cord involvement in Sjögren's syndrome might be a manifestation of neuromyelitis optica. Mult Scler 15(9):1062–1068
80. Pericot I, Brieva L, Tintore M, Rio J, Sastre-Garriga J, Nos C, Montalban X (2003) Myelopathy in seronegative Sjögren syndrome and/or primary progressive multiple sclerosis. Mult Scler 9(3):256–259
81. Delalande S, de Seze J, Fauchais AL, Hachulla E, Stojkovic T, Ferriby D, Dubucquoi S, Pruvo JP, Vermersch P, Hatron PY (2004) Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine (Baltimore) 83(5):280–291
82. Binder A, Snaith ML, Isenberg D (1988) Sjögren's syndrome: a study of its neurological complications. Br J Rheumatol 27(4):275–280
83. Pillemer SR, Matteson EL, Jacobsson LT, Martens PB, Melton LJ 3rd, O'Fallon WM, Fox PC (2001) Incidence of physician-diagnosed primary Sjögren syndrome in residents of Olmsted County, Minnesota. Mayo Clin Proc 76(6):593–599
84. Alexander EL, Malinow K, Lejewski JE, Jerdan MS, Provost TT, Alexander GE (1986) Primary Sjögren's syndrome with central nervous system disease mimicking multiple sclerosis. Ann Intern Med 104(3):323–330
85. Williams CS, Butler E, Roman GC (2001) Treatment of myelopathy in Sjögren syndrome with a combination of prednisone and cyclophosphamide. Arch Neurol 58(5):815–819
86. Jimenez S, Cervera R, Font J, Ingelmo M (2003) The epidemiology of systemic lupus erythematosus. Clin Rev Allergy Immunol 25(1):3–12. doi:10.1385/CRIAI:25:1:3
87. Joseph FG, Scolding N (2010) Neurolupus. Pract Neurol 10:4–15
88. Ellis SG, Verity MA (1979) Central nervous system involvement in systemic lupus erythematosus: a review of neuropathologic findings in 57 cases, 1955–1977. Semin Arthritis Rheum 8(3):212–221
89. Kovacs B, Lafferty TL, Brent LH, DeHoratius RJ (2000) Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. Ann Rheum Dis 59(2):120–124
90. Sanna G, Bertolaccini ML, Cuadrado MJ, Laing H, Khamashta MA, Mathieu A, Hughes GR (2003) Neuropsychiatric manifestations in systemic lupus erythematosus: prevalence and association with antiphospholipid antibodies. J Rheumatol 30(5):985–992

91. Espinosa G, Mendizabal A, Minguez S, Ramo-Tello C, Capellades J, Olive A, Cervera R (2010) Transverse myelitis affecting more than 4 spinal segments associated with systemic lupus erythematosus: clinical, immunological, and radiological characteristics of 22 patients. Semin Arthritis Rheum 39(4):246–256. doi:10.1016/j.semarthrit.2008.09.002
92. Sherer Y, Hassin S, Shoenfeld Y, Levy Y, Livneh A, Ohry A, Langevitz P (2002) Transverse myelitis in patients with antiphospholipid antibodies–the importance of early diagnosis and treatment. Clin Rheumatol 21(3):207–210
93. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40(9):1725. doi:10.1002/1529-0131(199709)40:9<1725:AID-ART29>3.0.CO;2-Y
94. Creamer P, Kirwan J (1992) Seronegative systemic lupus erythematosus. Br J Rheumatol 31(9):619–622
95. Joseph FG, Scolding NJ (2010) Neurolupus. Pract Neurol 10(1):4–15. doi:10.1136/jnnp.2009.200071
96. Propper DJ, Bucknall RC (1989) Acute transverse myelopathy complicating systemic lupus erythematosus. Ann Rheum Dis 48(6):512–515
97. Appenzeller S, Vasconcelos Faria A, Li LM, Costallat LT, Cendes F (2008) Quantitative magnetic resonance imaging analyses and clinical significance of hyperintense white matter lesions in systemic lupus erythematosus patients. Ann Neurol 64(6):635–643. doi:10.1002/ana.21483
98. Graham JW, Jan W (2003) MRI and the brain in systemic lupus erythematosus. Lupus 12(12):891–896
99. Boumpas DT, Patronas NJ, Dalakas MC, Hakim CA, Klippel JH, Balow JE (1990) Acute transverse myelitis in systemic lupus erythematosus: magnetic resonance imaging and review of the literature. J Rheumatol 17(1):89–92
100. Salmaggi A, Lamperti E, Eoli M, Venegoni E, Bruzzone MG, Riccio G, La Mantia L (1994) Spinal cord involvement and systemic lupus erythematosus: clinical and magnetic resonance findings in 5 patients. Clin Exp Rheumatol 12(4):389–394
101. Trevisani VF, Castro AA, Neves Neto JF, Atallah AN (2006) Cyclophosphamide versus methylprednisolone for treating neuropsychiatric involvement in systemic lupus erythematosus. Cochrane Database Syst Rev 2:CD002265. doi:10.1002/14651858.CD002265.pub2
102. Barile-Fabris L, Ariza-Andraca R, Olguin-Ortega L, Jara LJ, Fraga-Mouret A, Miranda-Limon JM, Fuentes de la Mata J, Clark P, Vargas F, Alocer-Varela J (2005) Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis 64(4):620–625. doi:10.1136/ard.2004.025528
103. Fortin PR, Abrahamowicz M, Ferland D, Lacaille D, Smith CD, Zummer M (2008) Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. Arthritis Rheum 59(12):1796–1804. doi:10.1002/art.24068
104. Walsh M, James M, Jayne D, Tonelli M, Manns BJ, Hemmelgarn BR (2007) Mycophenolate mofetil for induction therapy of lupus nephritis: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2(5):968–975. doi:10.2215/CJN.01200307
105. Perry A, Vuitch F (1995) Causes of death in patients with sarcoidosis: a morphologic study of 38 autopsies with clinicopathologic correlations. Arch Pathol Lab Med 119(2):167–172
106. Chapelon-Abric C (2001) Neurosarcoidosis. Ann Med Interne (Paris) 152(2):113–124
107. James DG (1967) Sarcoidosis. Curr Med Drugs 7(9):10–21
108. Rybicki BA, Major M, Popovich J Jr, Maliarik MJ, Iannuzzi MC (1997) Racial differences in sarcoidosis incidence: a 5-year study in a health maintenance organization. Am J Epidemiol 145(3):234–241
109. Vargas DL, Stern BJ (2010) Neurosarcoidosis: diagnosis and management. Semin Respir Crit Care Med 31(4):419–427. doi:10.1055/s-0030-1262210
110. Zajicek JP, Scolding NJ, Foster O, Rovaris M, Evanson J, Moseley IF, Scadding JW, Thompson EJ, Chamoun V, Miller DH, McDonald WI, Mitchell D (1999) Central nervous system sarcoidosis–diagnosis and management. Qjm 92(2):103–117
111. Hoitsma E, Faber CG, Drent M, Sharma OP (2004) Neurosarcoidosis: a clinical dilemma. Lancet Neurol 3(7):397–407. doi:10.1016/S1474-4422(04)00805-1
112. Lower EE, Weiss KL (2008) Neurosarcoidosis. Clin Chest Med 29 (3):475–492, ix. doi:10.1016/j.ccm.2008.03.016
113. Stern BJ, Krumholz A, Johns C, Scott P, Nissim J (1985) Sarcoidosis and its neurological manifestations. Arch Neurol 42(9):909–917
114. Cohen-Aubart F, Galanaud D, Grabli D, Haroche J, Amoura Z, Chalpelon-Abric C, Lyon-Caen O, Valeyre D, Piette JC (2010) Spinal cord sarcoidosis: clinical and laboratory profile and outcome of 31 patients in a case-control study. Medicine (Baltimore) 89(2):133–140
115. Dale JC, O'Brien JF (1999) Determination of angiotensin-converting enzyme levels in cerebrospinal fluid is not a useful test for the diagnosis of neurosarcoidosis. Mayo Clin Proc 74(5):535
116. Baughman RP, Iannuzzi MC (2000) Diagnosis of sarcoidosis: when is a peek good enough? Chest 117(4):931–932
117. Kouba DJ, Mimouni D, Rencic A, Nousari HC (2003) Mycophenolate mofetil may serve as a steroid-sparing agent for sarcoidosis. Br J Dermatol 148(1):147–148
118. Doty JD, Mazur JE, Judson MA (2003) Treatment of corticosteroid-resistant neurosarcoidosis with a short-course cyclophosphamide regimen. Chest 124(5):2023–2026
119. Carter JD, Valeriano J, Vasey FB, Bognar B (2004) Refractory neurosarcoidosis: a dramatic response to infliximab. Am J Med 117(4):277–279
120. Duna GF, Calabrese LH (1995) Limitations of invasive modalities in the diagnosis of primary angiitis of the central nervous system. J Rheumatol 22(4):662–667
121. International Study Group for Behçet's Disease (1990) Criteria for diagnosis of Behçet's disease. Lancet 335(8697):1078–1080
122. Yazici H, Yurdakul S, Hamuryudan V (2001) Behçet disease. Curr Opin Rheumatol 13(1):18–22
123. Siva A, Altintas A, Saip S (2004) Behçet's syndrome and the nervous system. Curr Opin Neurol 17(3):347–357
124. Al-Araji A, Kidd DP (2009) Neuro-Behçet's disease: epidemiology, clinical characteristics, and management. Lancet Neurol 8(2):192–204
125. Mullins GM, Elamin M, Saidha S, Ali E, Jennings L, Counihan TJ, Hennessy M (2009) Acute aseptic meningitis and diffuse myelitis as the presenting features of neurological Behçet disease. J Clin Neurosci 16(12):1702–1704. doi:10.1016/j.jocn.2009.06.002
126. Akman-Demir G, Serdaroglu P, Tasci B (1999) Clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients: the Neuro-Behçet study group. Brain 122(Pt 11):2171–2182
127. Serdaroglu P (1998) Behçet's disease and the nervous system. J Neurol 245(4):197–205
128. Kidd D, Steuer A, Denman AM, Rudge P (1999) Neurological complications in Behçet's syndrome. Brain 122(Pt 11):2183–2194
129. Saruhan-Direskeneli G, Yentur SP, Akman-Demir G, Isik N, Serdaroglu P (2003) Cytokines and chemokines in neuro-Behçet's disease compared to multiple sclerosis and other neurological diseases. J Neuroimmunol 145(1–2):127–134

130. Yazici H, Fresko I, Yurdakul S (2007) Behçet's syndrome: disease manifestations, management, and advances in treatment. Nat Clin Pract Rheumatol 3(3):148–155
131. Siva A, Kantarci OH, Saip S, Altintas A, Hamuryudan V, Islak C, Kocer N, Yazici H (2001) Behçet's disease: diagnostic and prognostic aspects of neurological involvement. J Neurol 248(2):95–103
132. Kocer N, Islak C, Siva A, Saip S, Akman C, Kantarci O, Hamuryudan V (1999) CNS involvement in neuro-Behçet syndrome: an MR study. AJNR Am J Neuroradiol 20(6):1015–1024
133. Yesilot N, Mutlu M, Gungor O, Baykal B, Serdaroglu P, Akman-Demir G (2007) Clinical characteristics and course of spinal cord involvement in Behçet's disease. Eur J Neurol 14(7):729–737
134. Kidd D, Beynon HL (2003) The neurological complications of systemic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 20(2):85–94
135. Kikuchi H, Aramaki K, Hirohata S (2008) Effect of infliximab in progressive neuro-Behçet's syndrome. J Neurol Sci 272(1–2): 99–105
136. Siva A, Fresko II (2000) Behçet's disease. Curr Treat Options Neurol 2(5):435–448
137. Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Weigand SD, Miller DV, Giannini C, Meschia JF, Huston J 3rd, Hunder GG (2007) Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol 62(5):442–451
138. Benseler S, Schneider R (2004) Central nervous system vasculitis in children. Curr Opin Rheumatol 16(1):43–50
139. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH (2011) Primary angiitis of the CNS. Lancet Neurol 10(6):561–572. doi:10.1016/S1474-4422(11)70081-3
140. Calabrese LH, Duna GF, Lie JT (1997) Vasculitis in the central nervous system. Arthritis Rheum 40(7):1189–1201
141. Salvarani C, Brown RD Jr, Calamia KT, Christianson TJ, Huston J 3rd, Meschia JF, Giannini C, Miller DV, Hunder GG (2008) Primary central nervous system vasculitis: comparison of patients with and without cerebral amyloid angiopathy. Rheumatology (Oxford) 47(11):1671–1677
142. Lie JT (1992) Primary (granulomatous) angiitis of the central nervous system: a clinicopathologic analysis of 15 new cases and a review of the literature. Hum Pathol 23(2):164–171
143. Pomper MG, Miller TJ, Stone JH, Tidmore WC, Hellmann DB (1999) CNS vasculitis in autoimmune disease: MR imaging findings and correlation with angiography. AJNR Am J Neuroradiol 20(1):75–85
144. Harris KG, Tran DD, Sickels WJ, Cornell SH, Yuh WT (1994) Diagnosing intracranial vasculitis: the roles of MR and angiography. AJNR Am J Neuroradiol 15(2):317–330
145. Calabrese LH (2003) Clinical management issues in vasculitis: angiographically defined angiitis of the central nervous system—diagnostic and therapeutic dilemmas. Clin Exp Rheumatol 21(6 Suppl 32):S127–S130
146. Vollmer TL, Guarnaccia J, Harrington W, Pacia SV, Petroff OA (1993) Idiopathic granulomatous angiitis of the central nervous system: diagnostic challenges. Arch Neurol 50(9):925–930
147. Birnbaum J, Hellmann DB (2009) Primary angiitis of the central nervous system. Arch Neurol 66(6):704–709
148. Levy JA, Shimabukuro J, Hollander H, Mills J, Kaminsky L (1985) Isolation of AIDS-associated retroviruses from cerebrospinal fluid and brain of patients with neurological symptoms. Lancet 2(8455):586–588