Demyelinating Disorders: Update on Transverse Myelitis

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Transverse myelitis (TM) is a focal inflammatory disorder of the spinal cord. Perivascular monocytic and lymphocytic infiltration, demyelination, and axonal injury are prominent histopathogic features of TM. The clinical manifestations of TM are consequent to dysfunction of motor, sensory, and autonomic pathways. At peak deficit, 50% of patients with TM are completely paraplegic (with no volitional movements of legs), virtually all have some degree of bladder dysfunction, and 80% to 94% have numbness, paresthesias, or band-like dysesthesias. Longitudinal case series of TM reveal that approximately one third of patients recover with little to no sequelae, one third are left with a moderate degree of permanent disability, and one third have severe disability. Recent studies have shown that the cytokine interleukin-6 may be a useful biomarker, as the levels of interleukin-6 in the cerebrospinal fluid of acute TM patients strongly correlate with and are highly predictive of disability. Clinical trials testing the efficacy of promising axonoprotective agents in combination with intravenous steroids in the treatment of TM are currently underway.

Introduction

Transverse myelitis (TM) is a potentially devastating focal inflammatory disorder of the spinal cord with an incidence of between one and eight new cases per 1 million people per year [1]. To reduce diagnostic confusion and to lay the groundwork necessary for clinical trials, a set of uniform diagnostic criteria and nosology for TM was recently proposed by the Transverse Myelitis Consortium Working Group [2••]. These criteria define TM as a monofocal inflammatory process of the spinal cord and distinguish it from noninflammatory myelopathies (eg, radiation-induced myelopathy or ischemic vascular myelopathy). Extra-axial compressive etiologies need to be excluded by neuroimaging (MRI or myelography). In order to make a diagnosis of TM, there must be evidence of inflammation within the spinal cord, as demonstrated by cerebrospinal fluid (CSF) pleocytosis, elevated CSF IgG index, or abnormal gadolinium enhancement of the spinal cord on MRI.

Transverse myelitis can be etiologically classified into "idiopathic TM" and "disease-associated TM." Disease-associated TM consists of cases of TM that are associated with evidence of a connective tissue disease known to cause TM (eg, sarcoidosis, Behçet's disease, Sjogren's syndrome, systemic lupus erythematosus), and those cases of TM associated with a central nervous system (CNS) infection (eg, syphilis, Lyme disease, HIV, human T-cell leukemia/lymphoma virus-1, Mycoplasma, herpes viruses). When an extensive search fails to determine such causes, idiopathic TM is defined. In the experience of the Transverse Myelitis Group at Johns Hopkins Hospital, most cases of TM fall into the idiopathic category. We have seen 354 patients with TM in the past 36 months: 128 of them have been identified as having disease-associated TM whereas 226 of them have been diagnosed with idiopathic TM. TM can be the presenting feature of multiple sclerosis (MS). Patients with TM who are ultimately diagnosed with MS are much more likely to have an abnormal brain MRI. Indeed, it has been shown that patients who present with monofocal CNS demyelination (TM or optic neuritis) have an 83% chance of meeting clinical criteria for MS over the subsequent decade if their brain MRI scans show lesions consistent with demyelination, compared with only an 11% chance if their brain MRI scans were normal [3]. Consequently, the Transverse Myelitis Working Consortium Group proposed that the presence of brain MRI abnormalities suggestive of MS excludes the diagnosis of idiopathic TM.

Clinical Features of Transverse Myelitis

Transverse myelitis affects individuals of all ages with bimodal peaks between the ages of 10 and 19 years and

30 and 39 years [1,4–6]. There are approximately 1400 new cases diagnosed in the United States per year, and 34,000 people have chronic morbidity from TM at any given time. Approximately 28% of reported TM cases are in children (Johns Hopkins Transverse Myelitis Center [JHTMC] case series). There is no sex or familial predisposition to TM. A preceding illness including nonspecific symptoms such as fever, nausea, and muscle pain has been reported in about 40% of pediatric cases within 3 weeks of the onset of the disorder (JHTMC case series) [7,8]. At our institution, 30% of all cases of pediatric TM cases have a history of an immunization within 1 month of the onset of symptoms (JHTMC case series).

Transverse myelitis is characterized clinically by acutely or subacutely developing symptoms and signs of neurologic dysfunction in motor, sensory, and autonomic nerve tracts of the spinal cord. Weakness is described as a rapidly progressive paraparesis that occasionally progresses to involve the arms as well. Akin to spinal shock, limb flaccidity is often noted initially, with spasticity beginning to develop 2 weeks after onset of the illness. A sensory level is detected on examination in most cases. In adults, the sensory level is usually in the mid-thoracic region. As children with TM have a higher frequency of cervical spinal cord involvement, a cervical sensory level is often detected. Pain may occur in the back, extremities, or abdomen. Paresthesias are a common initial symptom in adults with TM but are unusual for children [9]. Autonomic symptoms in patients with TM include increased urinary urgency, bowel or bladder incontinence, difficulty or inability to void, incomplete evacuation, and bowel constipation [10]. Sexual dysfunction due to sensory and autonomic nervous system involvement is a common problem in TM [11,12].

It is being increasingly appreciated that depression often occurs in patients with TM, reminiscent of what has been described in MS (Kaplin, Unpublished observations) [13]. Of note, depression does not correlate significantly with the patient's degree of physical disability, and it has been hypothesized that depression may occur as a result of the effect of proinflammatory cytokines on the brain. It is important to detect depression in TM, as it can have lethal consequences if left untreated. In our case series, depression resulting in suicide is the leading cause of mortality in TM, accounting for 60% of the deaths that we have seen in our clinic (Kaplin, Unpublished observations).

In our case series of 170 idiopathic TM cases (children and adults), spinal MRI showed a cervical T2 signal abnormality in 44% and a thoracic T2 signal abnormality in 37% of cases. Five percent of patients had multifocal spinal cord lesions and 6% had a T1 hypointense spinal cord lesion. This corresponded to the following clinical sensory levels: 22% cervical, 63% thoracic, 9% lumbar, 6% sacral, and no sensory level in 7%. The rostral-caudal extent of the lesion ranged from one vertebral segment in many to spanning the entire spinal cord in two patients from the case series. In 74% of patients, the spinal cord lesions enhanced with gadolinium. Forty-two percent of patients had a CSF pleocytosis with a mean leukocyte count of 38 ± 13 cells (range, 0–950 cells). Fifty percent of the patients revealed an elevated protein level (mean protein level, 75 ± 14 mg/dL).

Monophasic versus recurrent transverse myelitis

Seventy-five percent to 90% of TM patients experience monophasic disease and have no evidence of multisystemic or multiphasic disease. Most commonly, symptoms will stop progressing after 2 to 3 weeks, and spinal fluid and MRI abnormalities will stabilize and then begin to resolve spontaneously. There are several features, however, that predict recurrent disease. Patients with multifocal lesions within the spinal cord, demyelinating lesions in the brain, oligoclonal bands in the spinal fluid, mixed connective tissue disorder, or serum autoantibodies (most notably SS-A) are at a greater risk of recurrence [14]. Preliminary studies suggest that patients who have persistently abnormal CSF cytokine profiles (notably interleukin-6 [IL-6]) may also be at increased risk for recurrent TM, though these findings must be validated before they are utilized clinically (Kaplin, Unpublished data). At the present time, we do not yet have enough information to assess whether chronic immunomodulatory treatment is warranted in patients at high risk of recurrence.

Prognosis

Most patients with TM do experience some spontaneous recovery in neurologic function within 6 months after symptom onset (JHTMC case series) [9]. Recovery may continue, albeit at a slower rate, for up to 2 years [8]. However, the majority of patients are still left with significant permanent neurologic deficit. Longitudinal case series of TM reveal that approximately one third of patients recover with little to no sequelae, one third are left with a moderate degree of permanent disability, and one third have severe disabilities [5–8,15]. Knebusch et al. [8] estimated from their case series that a good outcome as indicated by normal gait, mild urinary symptoms, and minimal sensory and upper motor neuron signs occurred in 44% of patients with TM. A fair outcome with mild spasticity but independent ambulation, urgency and/or constipation, and some sensory signs occurred in 33%, and a poor outcome with the inability to walk or severe gait disturbance, absence of sphincter control, and sensory deficit in 23%. The patient cohort we follow at Johns Hopkins is, however, more severe, with only 20% experiencing a good outcome by those definitions, which is likely a reflection of referral bias to a tertiary care center. Symptoms associated with poor outcome include back pain as an initial complaint, rapid progression to maximal symptoms within hours of onset, spinal shock, and sensory disturbance up to the cervical level [9].

The presence of 14-3-3 protein, a marker of neuronal injury, in the CSF during the acute phase of TM is

predictive of a poor outcome [16]. Our recent studies suggest that CSF IL-6 levels at acute presentation are proportional to, and highly predictive of, long-term disability (Kaplin et al, Unpublished data). If confirmed by future studies, CSF IL-6 levels could be utilized as a biomarker to help guide the aggressiveness of interventions employed in treating patients presenting with acute TM. Electromyographic evidence of limb muscle denervation (suggestive of motor neuron/axon loss) is also predictive of a poor outcome with little neurologic recovery.

Pathology and Pathogenesis of Idiopathic Transverse Myelitis

Our histopathologic studies of spinal cord tissue obtained from biopsies and autopsies of TM patients have shown evidence of focal spinal cord inflammatory changes, consistent with previously published pathologic descriptions [17–19]. In affected segments of the spinal cord, there is perivascular infiltration by monocytes and lymphocytes in addition to astroglial and microglial activation. Demyelination is a prominent feature in spinal cord white matter tracts. Another prominent pathologic finding is axonal injury and loss affecting white matter and often gray matter of involved spinal cord (Fig. 1). It should be noted that axonal loss, rather than demyelination, correlates with disability in a number of neurologic diseases, including MS and the inherited demyelinating peripheral neuropathies. This is also likely to be the case in TM.

The fact that idiopathic TM often follows a respiratory tract, gastrointestinal, or systemic illness raises the hypothesis that TM may result from a post-infectious autoimmune process. The latter may arise from molecular mimicry (ie, the sharing of epitopes between a microbe and a spinal cord antigen). This was postulated to be the case in a patient who contracted TM following infection with *Enterobium vermicularis* (perianal pinworm) and was found to have elevated titers of cross-reacting antibodies [20]. Another potential link between an antecedent infection and the development of idiopathic TM is lymphocyte activation by microbial superantigens, which have been implicated in the etiology of a number of autoimmune diseases [21••].

In a recent study (Kaplin et al, Unpublished data), we noted that the levels of the proinflammatory cytokine IL-6 were markedly elevated in the CSF of patients with acute TM as compared with CSF from control patients and patients with acute MS flares. Of importance, the CSF level of IL-6 in acute TM patients strongly correlated with and was highly predictive of disability. Our group has carried out preliminary in vitro and animal studies demonstrating that IL-6 causes spinal cord neurotoxicity via the induction of nitric oxide. This correlates with our observation that CSF IL-6 levels in TM patients correlated with the CSF levels of nitric oxide metabolites, which also correlated with disability.

Clinical Evaluation of Transverse Myelitis

We recently proposed a systematic diagnostic approach for evaluating patients with acute myelopathies [21••]. A modified version of this algorithm is presented in Figure 2, with additional details presented in Table 1, Table 2, and Table 3. For further details, readers are urged to refer to our recent review on this topic.

Management of Transverse Myelitis

Intravenous steroids

On the basis of the presumptive immunopathogenic mechanisms in TM, several recent studies have investigated the role for intravenous methylprednisone (Solu-medrol; Pfizer, New York, NY) in the acute phase of TM. These studies are limited by being open-label and retrospective with small numbers of subjects. They nevertheless suggested that high-dose intravenous steroids improved time to ambulation and ultimate motor recovery [22–28]. At our institution, the standard of care of patients with acute TM consists of a 5-day course of intravenous Solu-medrol, 1000 mg/d followed by a steroid taper.

Plasma exchange

At our center, we initiate plasma exchange (PLEX) if a patient has moderate to severe TM (ie, inability to walk, markedly impaired autonomic function, and sensory loss in the lower extremities) and exhibits little clinical improvement after instituting 5 to 7 days of intravenous steroids. PLEX has been shown to be effective in adults with TM and other inflammatory disorders of the CNS [29••,30,31]. Predictors of good response to PLEX include early treatment (< 20 days from symptom onset), male sex, and a clinically incomplete lesion (ie, some motor function in the lower extremities, intact or brisk reflexes) [32••]. It is our experience that PLEX may significantly improve outcomes of patients with severe (though incomplete) TM who have not significantly improved on intravenous steroids.

Other immunomodulatory treatments

We consider pulse dose intravenous cyclophosphamide (500–1000 mg/m^2) for patients with TM that continues to progress despite intravenous steroid therapy. Cyclophosphamide, a bifunctional alkylating agent, forms reactive metabolites that cross-link with DNA. This results in apoptosis of rapidly dividing immune cells and is believed to underlie the immunosuppressive properties of this medication. It is the experience at our center that some patients will respond significantly to intravenous cyclophosphamide, and this treatment is worthy of consideration while we await double-blinded placebo trials. However, cyclophosphamide should be administered under the auspices of an experienced oncology team, and caregivers should monitor the patient carefully for hemorrhagic cystitis and cytopenias.

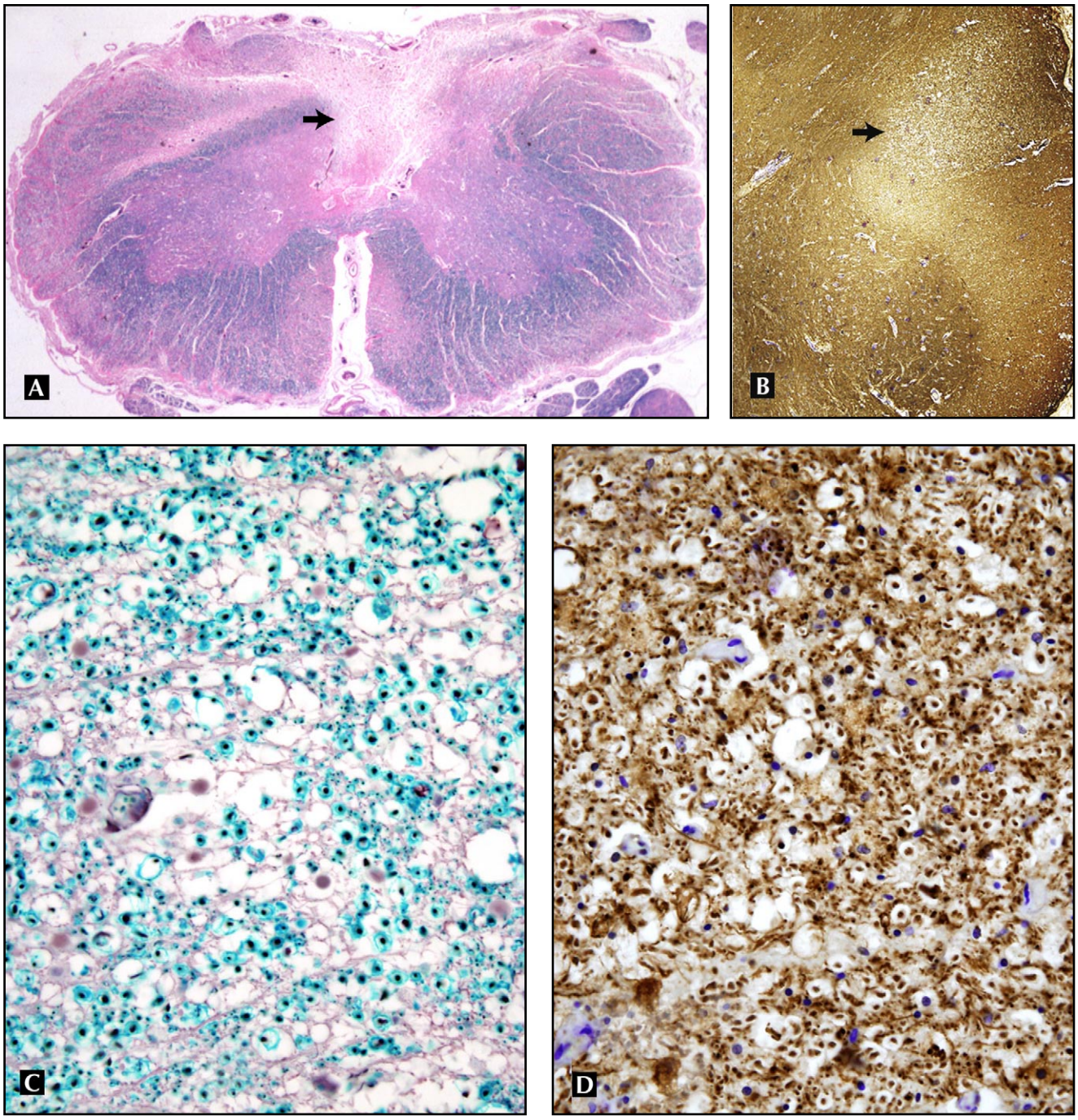

Figure 1. An example of the histology of transverse myelitis (TM). **A,** Section of the lumbar spinal cord from a patient with TM. Note the extensive loss of myelin in spinal cord white matter and the substantial axonal degeneration in the posterior columns (*arrow*) (Myelin stain, Luxol fast blue and H&E). **B,** Focal area of axonal loss (*arrow*) in the lateral column of the lumbar cord visualized after immunostaining with antibodies against phosphorylated neurofilament, an axonal marker. **C** and **D,** Focal areas of axonal loss and degeneration in white matter tracts of the lateral column from the same spinal cord as **B**. There is evidence of vacuolation and axonal loss as shown by staining with Luxol fast blue and a silver stain for axon (**C**) and immunostaining with antiphosphorylated neurofilament (**D**).

Cerebrospinal fluid filtration is a new therapy, not yet available in the United States, in which spinal fluid is filtered to remove inflammatory factors (including cells, complement, cytokines, and antibodies) and then reinfused into the patient. In a randomized trial of CSF filtration versus PLEX for acute inflammatory demyelinating polyneuropathy, CSF filtration was better tolerated and was at least as effective [33••]. Clinical trials for CSF filtration in TM are currently being initiated.

Chronic immunomodulatory therapy should be considered for the small subgroup of patients who

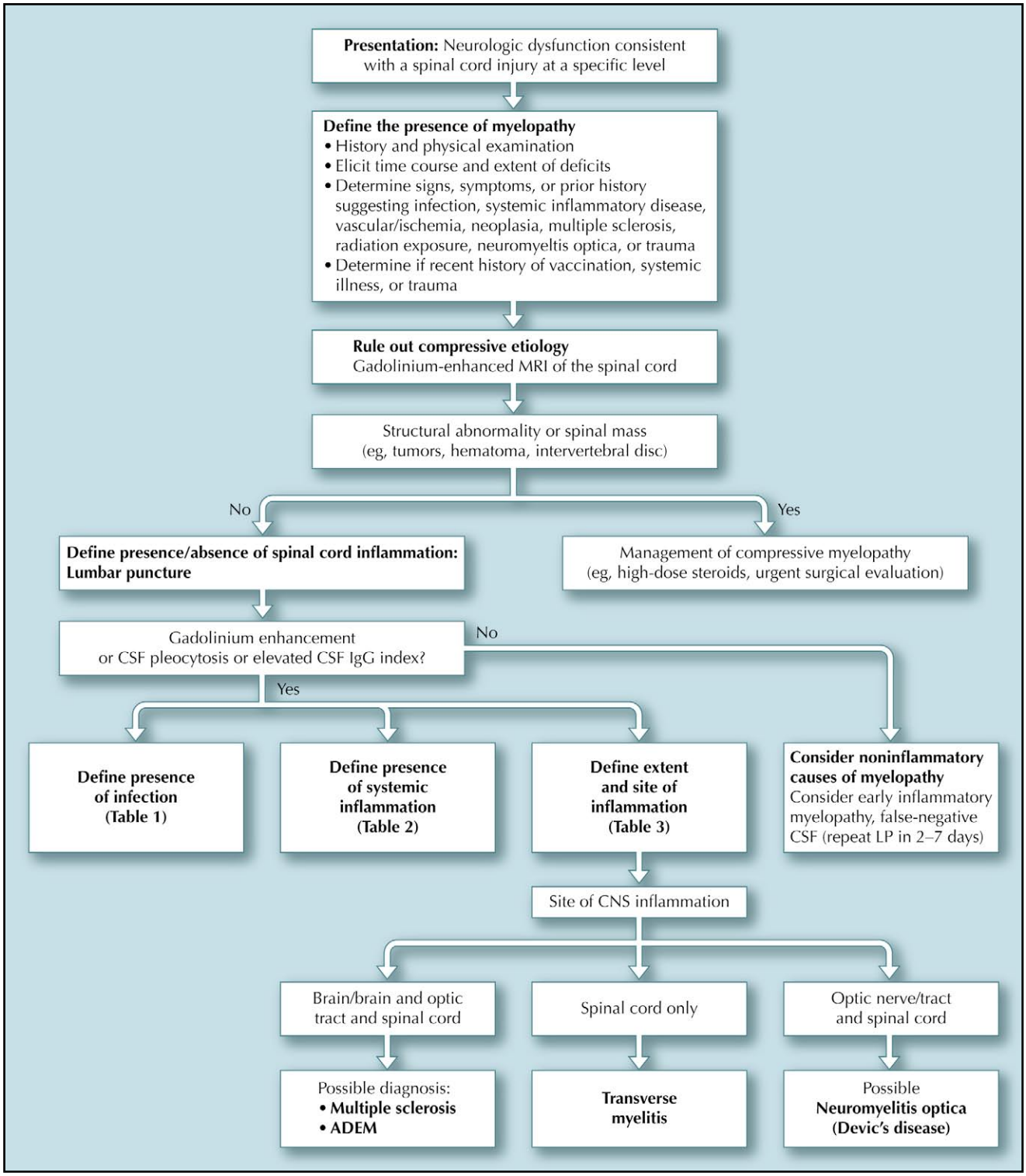

Figure 2. Algorithm of systematic diagnostic approach for evaluating patients with acute myelopathies. ADEM—acute disseminated encephalomyelitis; CNS—central nervous system; CSF—cerebrospinal fluid; LP—lumbar puncture.

have recurrent TM. Although the ideal treatment regimen is not known, we consider a 2-year course of oral immunomodulatory treatment in patients with two or more distinct episodes of TM. We most commonly treat patients with azathioprine (150–200 mg/d), methotrexate (15–20 mg/wk), or mycophenolate (2–3 g/d), although oral cyclophosphamide (2 g/kg/d) may also be used in patients with systemic inflammatory disease. On any of these medicines, patients must be followed for transaminitis or leukopenias.

Table 1. Potential work-up for infectious disease in a patient with acute myelopathy

Indicative signs and symptoms
Fever
Meningismus
Rash
Concurrent systemic infection
Immunocompromised state
Recurrent genital infection
Symptoms of zoster radiculopathy
Adenopathy
Residence in area endemic for parasitic infections
Potential evaluation
CSF Gram's stain and bacterial culture
CSF PCR: HSV-1, HSV-2, HHV-6, VZV, CMV, EBV, enteroviruses, HIV
CSF viral culture
CSF acid-fast bacilli smear and tuberculosis culture
CSF HSV, VZV, and HTLV-1 antibodies
CSF *anti-Borrelia burgdorferi* antibodies
CSF VDRL
CSF India ink and fungal culture
Chest radiograph
Serology for antibodies to HSV, VZV, HTLV-1, *Borrelia burgdorferi*
Serology for hepatitis A, B, C, and Mycoplasma
Consider serology for parasites
Blood cultures

CMV—cytomegalovirus; CSF—cerebrospinal fluid; EBV—Epstein-Barr virus; HHV—human herpes virus; HSV—herpes simplex virus; HTLV-1—human T-cell leukemia/lymphoma virus-1; PCR—polymerase chain reaction; VDRL—Venereal Disease Research Laboratory; VZV—varicella zoster virus.

Table 2. Potential work-up for systemic inflammatory disease in a patient with acute myelopathy

Indicative signs and symptoms
Rash
Oral or genital ulcers
Adenopathy
Livedo reticularis
Serositis
Photosensitivity
Inflammatory arthritis
Erythema nodosum
Xerostomia
Keratitis
Conjunctivitis
Contractures or thickening of skin
Anemia/leukopenia/thrombocytopenia
Raynaud's phenomenon
History of arterial and venous thrombosis
Potential evaluation
Serum angitotensin-converting enzyme/chest CT with intravenous contrast/gallium scan
Auto-antibodies: ANA, ds-DNA, SS-A (Ro), SS-B (La), Sm (Smith), RNP
Complement levels
Urinalysis with microscopic analysis for hematuria
Lip/salivary gland biopsy
Chest CT with intravenous contrast
Shirmer's test
Chest radiograph
Antiphospholipid antibodies, Russel viper venom time, partial thromboplastin time

Nonpharmacologic management

Patients with TM will require rehabilitative care to prevent secondary complications of immobility [21]. Occupational and physical therapies should begin early to prevent the inactivity-related problems of skin breakdown and soft tissue contractures that lead to loss of range of motion. Splints should be designed to passively maintain an optimal position for limbs that cannot be actively moved. Family education is essential to develop a strategic plan for dealing with the challenges to independence following return to the community.

The goal of spasticity management is to maintain flexibility using active stretching exercises. An appropriate strengthening program for the weaker of the spastic muscles acting on a joint and an aerobic conditioning regimen is also recommended. These interventions should be supported by adjunctive measures that include antispasticity drugs (eg, diazepam, baclofen, dantrolene, tizanidine, and tiagabine), therapeutic botulinum toxin injections, and serial casting.

Another major area of concern is effective management of bowel function. A high-fiber diet, adequate and timely fluid intake, and medications to regulate bowel evacuations are the basic components to success. Regular evaluations by medical specialists for adjustment of the bowel program are recommended to prevent potentially serious complications.

Bladder function is almost always at least transiently impaired in patients with TM. Immediately after the onset of TM, as in the aftermath of traumatic spinal cord injury, there is frequently a period of transient loss or depression of neural activity below the involved

spinal cord lesion. This phenomenon is often referred to as "spinal shock," which lasts about 3 weeks, during which there is an interruption of descending excitatory influence with resultant bladder flaccidity. Following this period, bladder dysfunction can be classified into two syndromes involving either upper motor neurons (UMN) or lower motor neurons (LMN).

Upper motor neuron bladder dysfunction results from lesions above S1-S2 and is characterized by reflexive emptying with bladder filling if the injury is complete, and urge incontinence if the neurologic involvement is incomplete. In addition, detrusor-sphincter dyssynergia results from impaired communication between the sacral and brain stem micturition centers. In the case of UMN dysfunction, anticholinergic medications, α-blockers, or electric stimulation are used to restore adequate bladder storage and drainage. LMN bladder dysfunction with either direct involvement of S2-S4 or indirect involvement, including the conus medullaris and cauda equina, results in detrusor areflexia and requires clean intermittent self-catheterization.

Transverse myelitis–induced sexual dysfunction involves similar innervation and analogous syndromes as those found in bladder dysfunction. Because of the similarities in innervation between sexual and bladder function, patients with UMN-mediated sexual dysfunction should be encouraged to empty their bladders before sexual stimulation to prevent untimely incontinence. The mainstays of treatment for erectile dysfunction in men are inhibitors of cGMP phosphodiesterase type 5, which will allow the vast majority of men with TM to achieve adequate erections for success in intercourse through a combination of reflex and/or psychogenic mechanisms. Although less effective in women, these same types of medications have been shown capable of enhancing sexual functioning in women.

Promising neuroprotective therapies

Substantial spinal cord axonal injury and loss occurs in TM, and it is likely that this correlates with permanent neurologic disability. Indeed, in other demyelinating disorders, such as MS and the inherited demyelinating peripheral neuropathies, neurologic disability at a particular time point does not correlate with the number of demyelinating lesions but rather correlates with the degree of axonal loss. The above-mentioned anti-inflammatory therapies would be expected to decrease the amount of inflammatory-mediated axonal damage occurring in acute TM, but a combination therapy that also includes a neuroprotective or "axonoprotective" agent would likely be more efficacious. Erythropoietin, neurotrophin-3, and the neuro-immunophilin ligands are promising agents with recently demonstrated axonoprotective properties. A double-blind, randomized clinical trial investigating the efficacy of erythropoietin (in combination with intravenous steroids) in acute TM has just commenced at our institution.

Table 3. Potential work-up for multifocal CNS inflammation in a patient with acute myelopathy

Indicative signs and symptoms
Previous demyelination event
Incomplete deficit clinically with MRI abnormality
< 2 spinal segments and < 50% of cord diameter
CSF oligoclonal bands
Optic pallor, red desaturation, visual field defect, afferent papillary defect
Presence of multiple autoantibodies (more common in NMO)
Potential evaluation
Brain MRI (FLAIR with and without gadolinium)
Evoked potentials (VEP, BAER, SSEP)
NMO antibody testing (Mayo Clinic)

BAER—brainstem auditory evoked response; CNS—central nervous system; CSF—cerebrospinal fluid; FLAIR—fluid-attenuated inversion recovery; NMO—neuromyelitis optica; SSEP—somatosensory evoked potential; VEP—visual evoked potential.

Conclusions

Idiopathic TM can be placed at one end of the spectrum of CNS inflammatory demyelinating disorders, being typically monophasic and monofocal, in contrast to MS, which is typically multifocal and relapsing. Despite the use of potent anti-inflammatory therapies, patients with acute TM are often left with permanent neurologic deficit. This disability is likely related to the substantial degree of spinal cord axonal injury and loss that is observed in histopathologic studies. The cytokine IL-6 may be a useful biomarker, as the level of IL-6 in the CSF of acute TM patients strongly correlates with and is highly predictive of disability. Clinical trials testing the efficacy of promising axonoprotective agents in combination with intravenous steroids in the treatment of TM are currently underway.

Acknowledgment

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