Immunopathogenesis of acute transverse myelitis

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Acute transverse myelitis is a group of disorders characterized by focal inflammation of the spinal cord and resultant neural injury. Acute transverse myelitis may be an isolated entity or may occur in the context of multifocal or even multisystemic disease. It is clear that the pathological substrate – injury and dysfunction of neural cells within the spinal cord – may be caused by a variety of immunological mechanisms. For example, in acute transverse myelitis associated with systemic disease (i.e. systemic lupus erythematosus or sarcoidosis), a vasculitic or granulomatous process can often be identified. In idiopathic acute transverse myelitis, there is an intraparenchymal or perivascular cellular influx into the spinal cord, resulting in the breakdown of the blood–brain barrier and variable demyelination and neuronal injury. There are several critical questions that must be answered before we truly understand acute transverse myelitis: (1) What are the various triggers for the inflammatory process that induces neural injury in the spinal cord? (2) What are the cellular and humoral factors that induce this neural injury? and (3) Is there a way to modulate the inflammatory response in order to improve patient outcome? Although much remains to be elucidated about the causes of acute transverse myelitis, tantalizing clues as to the potential immunopathogenic mechanisms in acute transverse myelitis and related inflammatory disorders of the spinal cord have recently emerged. It is the purpose of this review to illustrate recent discoveries that shed light on this topic, relying when necessary on data from related diseases such as acute disseminated encephalomyelitis, Guillain–Barré syndrome and neuromyelitis optica. Developing a further understanding of how the immune system induces neural injury will depend upon confirmation and extension of these findings and will require multicenter collaborative efforts. Curr Opin Neurol 15:339–347.

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Abbreviations

ATM	acute transverse myelitis
CNS	central nervous system
CSF	cerebrospinal fluid
GBS	Guillain–Barré syndrome
MRI	magnetic resonance imaging
MS	multiple sclerosis
NMO	neuromyelitis optica
SLE	systemic lupus erythematosus

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Introduction

Acute transverse myelitis (ATM) is a group of poorly understood inflammatory disorders resulting in neural injury to the spinal cord. It is unclear what are the triggers and effector mechanisms resulting in neural injury, although tantalizing clues have emerged. ATM exists on a continuum of neuroinflammatory disorders that also includes Guillain–Barré syndrome (GBS), multiple sclerosis (MS), acute disseminated encephalomyelitis and neuromyelitis optica (NMO). Each of these disorders differs in the spatial and temporal restriction of inflammation within the nervous system. However, clinical and pathological studies support the notion that there are many common features of the inflammation and neural injury. In the current review, we will examine recent evidence that shed light on the immunopathogenesis of ATM and, where applicable, related neuroinflammatory disorders. Such studies point to a variety of humoral and cellular immune derangements that potentially result in neuronal injury and demyelination. Further advances in understanding the immunopathogenesis of ATM will require controlled studies with epidemiological and clinical–pathological correlation. It is only then that we will be able to establish rational intervention strategies designed to improve the outcome of patients with ATM.

History of acute transverse myelitis

Several cases of 'acute myelitis' were described in 1882, and pathological analysis revealed that some were caused by vascular lesions and others by acute inflammation [1,2]. In 1922 and 1923, physicians in England and Holland became aware of a rare complication of smallpox vaccination: inflammation of the spinal cord and brain [3]. Given the term 'post-vaccinal encephalomyelitis', over 200 cases were reported in those 2 years alone. Pathological analyses of fatal cases revealed inflammatory cells and demyelination. In 1928, it was first postulated that many cases of acute myelitis are 'post-infectious rather than infectious in cause' because for many patients the 'fever had fallen and the rash had begun to fade' when the myelitis symptoms began [4]. It was proposed, therefore, that the myelitis was an 'allergic' response to a virus rather than the virus itself that caused the spinal cord damage. It was in 1948 that the term 'acute transverse myelitis' was utilized in reporting a case of fulminant inflammatory myelopathy complicating pneumonia [5].

Diagnosis of acute transverse myelitis

ATM is an inflammatory process affecting a restricted area of the spinal cord. It is characterized clinically by

acutely or subacutely developing symptoms and signs of neurological dysfunction in motor, sensory and autonomic nerves and nerve tracts of the spinal cord. There is often a clearly defined rostral border of sensory dysfunction and a spinal magnetic resonance imaging (MRI) and lumbar puncture shows evidence of acute inflammation. When the maximal level of deficit is reached, approximately 50% of patients have lost all movements of their legs, virtually all patients have some degree of bladder dysfunction, and 80–94% of patients have numbness, paresthesias or band-like dysesthesias [6–11]. Autonomic symptoms consist variably of increased urinary urgency, bowel or bladder incontinence, difficulty voiding, or bowel constipation [12].

Classification of acute transverse myelitis

Recently, a diagnostic and nosology scheme has been proposed that defines ATM according to the inclusion and exclusion criteria set forth in Table 1 (The Transverse Myelitis Consortium Working Group, 2002, in preparation). These criteria have attempted to define ATM as a monofocal inflammatory process of the spinal cord and to distinguish it from non-inflammatory myelopathies (i.e. radiation-induced myelopathy or ischemic vascular myelopathy). It further attempts to distinguish various etiologies for ATM. Two diagnostic categories of 'idiopathic ATM' and 'disease-associated ATM' [i.e. systemic lupus erythematosus (SLE)-associated ATM] are thus proposed, provided that other criteria are met. Disease-associated ATM is diagnosed when the patient meets standard criteria for other known inflammatory diseases (e.g. MS, sarcoidosis, SLE, Sjogren's syndrome) or direct infection of the spinal cord. When an extensive search fails to determine such a cause, idiopathic ATM is defined. On the basis of these criteria, an algorithm has been proposed to guide clinical management research protocols for individuals with suspected ATM (Fig. 1).

Immunopathogenesis of acute transverse myelitis

The immunopathogenesis of disease-associated ATM is varied. For example, pathological data confirm that many cases of lupus-associated transverse myelitis are associated with central nervous system (CNS) vasculitis [13–15], whereas others may be associated with thrombotic infarction of the spinal cord [16,17]. Neurosarcoid is often pathologically associated with non-caseating granulomas within the spinal cord [18], whereas transverse myelitis associated with MS often has perivascular lymphocytic cuffing and mononuclear cell infiltration immunopathogenically and with variable complement and antibody deposition [19]. As these diseases have such varied (albeit poorly understood) immunopathogenic and effector mechanisms, they will not be discussed further here. Rather, the subsequent discussion will focus on findings potentially related to idiopathic ATM.

Post-vaccination acute transverse myelitis

Several reports of ATM following vaccination have recently been published. Indeed, it is widely reported in neurology texts that ATM is a post-vaccination event. One publication reports a case of post 'flu vaccine myelitis in which a 42-year-old man with a history of bilateral optic neuritis developed ATM 2 days after an influenza vaccination [20]. A separate study [21] reported a 36-year-old individual who developed a progressive and ultimately fatal, inflammatory myelopathy/polyradiculopathy 9 days after a booster hepatitis B vaccination.

Table 1. Idiopathic acute transverse myelitis criteria

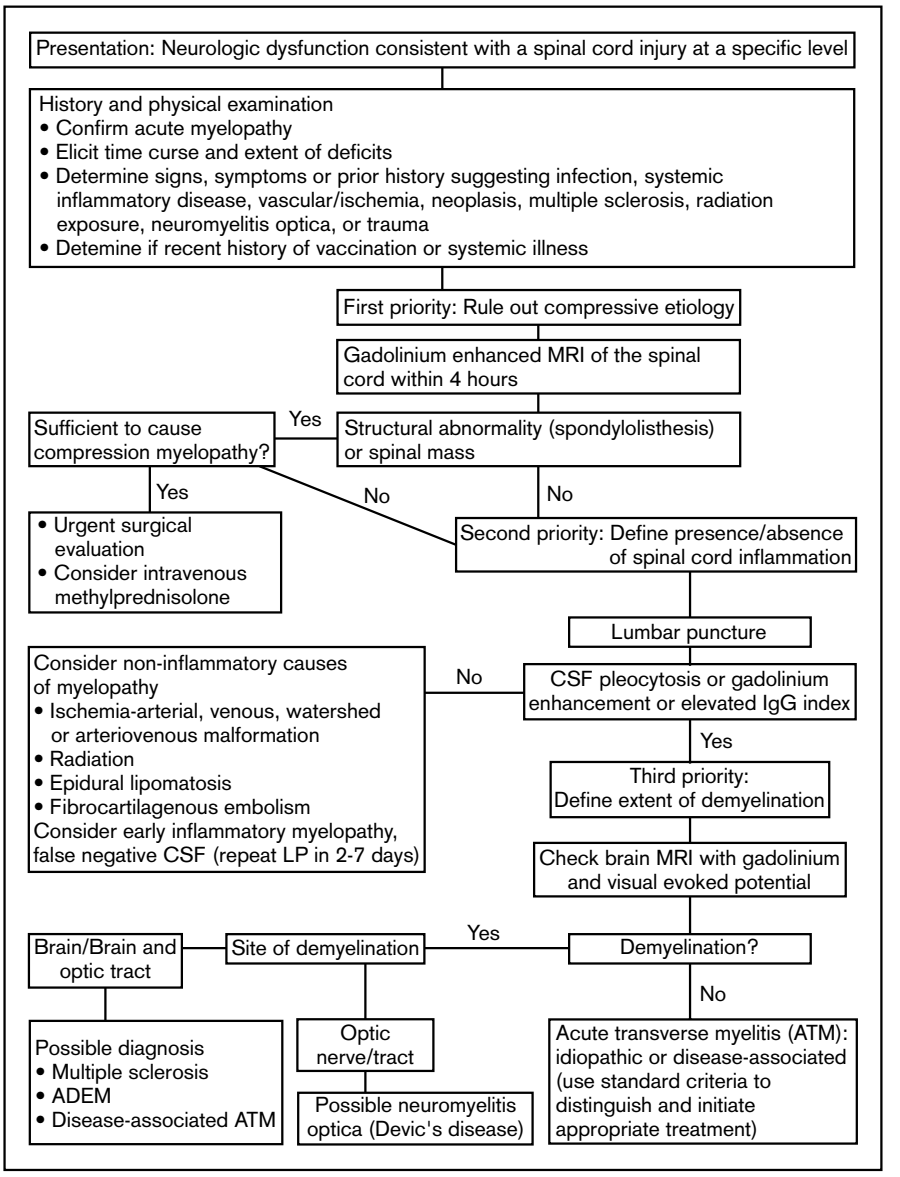
Inclusion criteria
(1) Development of sensory, motor or autonomic dysfunction attributable to the spinal cord
(2) Bilateral signs or symptoms (although not necessarily symmetric)
(3) Clearly-defined sensory level
(4) Exclusion of extra-axial compressive etiology by neuroimaging (MRI or myelography; CT of spine not adequate)
(5) Inflammation within the spinal cord demonstrated by CSF pleocytosis or elevated IgG index or gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MRI and LP evaluation between 2 and 7 days after symptom onset meets criteria
(6) Progression to nadir between 4 h and 21 days after the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)

Exclusion criteria
(1) History of previous radiation to the spine within the past 10 years
(2) Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery
(3) Abnormal flow voids on the surface of the spinal cord consistent with AVM
(4) Serological or clinical evidence of connective tissue disease (sarcoidosis, Behcet's disease, Sjogren's syndrome, SLE, mixed connective tissue disorder, etc.)[a]
(5) CNS manifestations of syphilis, Lyme disease, HIV, HTLV-1, mycoplasma, other viral infection (e.g. HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, enteroviruses)[a]
    (a) Brain MRI abnormalities suggestive of MS[a]
    (b) History of clinically apparent optic neuritis[a]

AVM, Arteriovenous malformation; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein–Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; HTLV, human T cell leukemia virus; LP, lumbar puncture; MRI, magnetic resonance imaging; MS, multiple sclerosis; SLE, systemic lupus erythematosus. [a]Do not exclude disease-associated acute transverse myelitis.

Figure 1. Immediate diagnostic approach to acute myelopathy

ADEM, Acute disseminated encephalomyelitis; ATM, acute transverse myelitis; CSF, cerebrospinal fluid; LP, lumbar puncture; MRI, magnetic resonance imaging.



The patient had no fever or systemic illness and did not respond to extensive immunotherapy. Autopsy evaluation of the spinal cord revealed severe axonal loss with mild demyelination and a mononuclear infiltrate, predominantly T lymphocytes in nerve roots and spinal ganglia. The spinal cord had perivascular and parenchymal lymphocytic cell infiltrates in the grey matter, especially the anterior horns. The suggestion from such studies is that a vaccination may induce an autoimmune process resulting in ATM. However, it should be noted that extensive data continue to show overwhelmingly that vaccinations are safe and are not associated with an increased incidence of neurological complications [22–29]. Therefore, such case reports must be viewed with caution, as it is entirely possible that two events occurred in close proximity by chance alone.

Parainfectious acute transverse myelitis

In 30–60% of the idiopathic ATM cases, there is an antecedent respiratory, gastrointestinal or systemic illness [6–10,30,31]. The term 'parainfectious' has been used to suggest that the neurological injury may be associated with direct microbial infection and injury as a result of the infection, direct microbial infection with immune-mediated damage against the agent, or remote infection followed by a systemic response that induces neural injury. An expanding list of antecedent infections is now recognized, although in the vast majority of these

cases causality cannot be established. Several of the herpes viruses have been associated with myelitis, and are probably caused by direct infection of neural cells within the spinal cord [32–34]. Other agents, such as *Listeria monocytogenes* may be transported intra-axonally to neurons in the spinal cord [35•]. By using such a strategy, an agent may be able to gain access to a relatively immune privileged site, avoiding the immune surveillance present in other organs. Such a mechanism may also explain the limited inflammation to a focal region of the spinal cord seen in some patients with ATM.

Although the infectious agent in these cases is required within the CNS, other mechanisms of autoimmunity, such as molecular mimicry and superantigen-mediated disease, require only peripheral immune activation and may account for other cases of ATM.

Molecular mimicry

Molecular mimicry as a mechanism to explain an inflammatory nervous system disorder has been best described in GBS. First referred to as an 'acute post-infectious polyneuritis' by Osler in 1892, GBS is preceded in 75% of cases by an acute infection [36–39]. *Campylobacter jejuni* infection has emerged as the most important antecedent event in GBS, occurring in up to 41% of cases [40–43]. Human neural tissue contains several subtypes of ganglioside moieties such as GM1, GM2 and GQ1b within their cell walls [44,45]. A characteristic component of human gangliosides, sialic acid [46], is also found as a surface antigen on *C. jejuni* within its lipopolysaccharide outer coat [47]. Antibodies that crossreact with gangliosides from *C. jejuni* have been found in serum from patients with GBS [48–50], and have been shown to bind peripheral nerves, fix complement and impair neural transmission in experimental conditions that mimic GBS [44,51–53].

Susceptibility to the development of GBS is dependent upon both strain-specific features of the *C. jejuni* and host genetic factors. Enterogenic strains of *C. jejuni* differ from strains likely to induce GBS [43,45,54,55]. However, the susceptibility to develop GBS also depends on host genetic factors. In a recent study, several members of the same family became infected with a single strain of *C. jejuni*, yet only one patient developed a humoral response against the lipopolysaccharide extract, and that patient was the only one to develop GBS [56]. In addition, recent studies have suggested a predominance of certain HLA alleles – HLA-B35, HLA-B54, HLA-Cwl and HLA-DQB1*0 – in GBS patients, suggesting a genetic restriction [40,57].

Molecular mimicry in ATM may also occur and may be associated with the development of autoantibodies in response to an antecedent infection. One ATM patient developed elevated titers of lupus anticoagulant IgG, antisulfatide antibodies (1 : 6400) and anti-GM1 antibodies (1 : 600 IgG and 1 : 3200 IgM) after *Enterobium vermicularis* (perianal pinworm) infection [58]. As *E. vermicularis* has been shown to contain cardiolipin, ganglioside GM1, and sulfatides within their lipid composition, it was postulated that in the proper genetic and hormonal background, the infection triggered the pathogenic antibodies. Several additional studies have suggested how this process could cause neural injury and will be discussed below.

Microbial superantigen-mediated inflammation

Another link between an antecedent infection and the development of ATM may be the fulminant activation of lymphocytes by microbial superantigens. Superantigens are microbial peptides that have a unique capacity to stimulate the immune system, and may contribute to a variety of autoimmune diseases. The best-studied superantigens are staphylococcal enterotoxins A to I, toxic shock syndrome toxin-1 and *Streptococcus pyogenes* exotoxin, although many viruses also encode superantigens [59–62]. Superantigens activate T lymphocytes in a unique manner compared with conventional antigens: instead of binding to the highly variable peptide groove of the T cell receptor, superantigens interact with the more conserved Vβ region [63–66]. In addition, unlike conventional antigens, superantigens are capable of activating T lymphocytes in the absence of co-stimulatory molecules. As a result of these differences, a single superantigen may activate between 2 and 20% of circulating T lymphocytes compared with 0.001–0.01% with conventional antigens [67–69]. Interestingly, superantigens often cause expansion followed by deletion of T lymphocyte clones with particular Vβ regions resulting in 'holes' in the T lymphocyte repertoire for some time after the activation [63–66,70]. Therefore, patients can often be tested for presumptive evidence of previous superantigen exposure through T cell receptor Vβ usage frequencies.

The stimulation of large numbers of lymphocytes may trigger autoimmune disease by activating autoreactive T cell clones [71,72]. In humans, there are many reports of the expansion of selected Vβ families in patients with autoimmune diseases, suggesting a previous superantigen exposure [71,73]. As this limited expansion was not seen in serum and non-inflamed tissues, it was proposed that superantigens activated previously quiescent autoreactive T cells, which then entered a tissue and were retained in that tissue by repeated exposure to the autoantigen [74]. In the CNS, superantigens isolated from *Staphylococcus* induced paralysis in mice with experimental autoimmune encephalomyelitis through its ability directly to stimulate Vβ8-expressing T cells specific for the myelin basic protein peptide Ac1-11

[67,68,75]. In humans, a patient with acute disseminated encephalomyelitis and necrotizing myelopathy was found to have *Streptococcus pyogenes* superantigen-induced T cell activation against myelin basic protein [76].

Humoral derangements

Either of the above processes may result in abnormal immune function, with a blurred distinction between self and non-self. The development of abnormal antibodies may then potentially activate other components of the immune system or recruit additional cellular elements to the spinal cord. Recent studies have emphasized distinct autoantibodies in patients with NMO [77–81] and recurrent ATM [82–84]. The high prevalence of various autoantibodies seen in such patients suggests polyclonal derangement of the immune system.

However, it may not just be autoantibodies, but high levels of even normal circulating antibodies that play a causative role in ATM. A case of ATM was described in a patient with extremely high serum and cerebrospinal fluid (CSF) antibody levels to hepatitis B surface antigen after booster immunization [85]. Such circulating antibodies may form immune complexes that deposit in focal areas of the spinal cord. Such a mechanism has been proposed to describe a patient with recurrent transverse myelitis and high titers of hepatitis B surface antigen [86]. Circulating immune complexes containing hepatitis B surface antigen were detected in the serum and CSF during the acute phase, and the disappearance of these complexes after treatment correlated with functional recovery.

Several Japanese patients with ATM were found to have much higher serum IgE levels than MS patients or controls (360 versus 52 versus 85 U/ml) [87]. Virtually all the patients in that study had specific serum IgE to household mites (*Dermatophagoides pteronyssinus* or *Dermatophagoides farinae*), whereas fewer than a third of MS and control patients did. One potential mechanism to explain ATM in such patients is the deposition of IgE with the subsequent recruitment of cellular elements. Indeed, biopsy specimens of two ATM patients with elevated total and specific serum IgE revealed antibody deposition within the spinal cord, perivascular lymphocyte cuffing and the infiltration of eosinophils [88•]. It was postulated that eosinophils recruited to the spinal cord degranulated and induced the neural injury in these patients.

Recently, several reports have suggested that elevated prolactin levels occur in some patients with NMO [89,90]. The elevated prolactin levels were limited to Asian and black women and correlated with involvement of the optic nerve. It may therefore be that the extension of inflammation to the hypothalamus results in diminished hypothalamic dopamine and increased pituitary secretion of prolactin. Furthermore, as prolactin is a potent immune stimulant for T helper cell type 1 responses, it is possible that the enhanced prolactin leads to an augmentation of disease activity elsewhere in the neuraxis.

It may even be that autoantibodies initiate a direct injury of neurons. A particular pentapeptide sequence found on microbial agents is a molecular mimic of double-stranded DNA, and antibodies raised against this sequence react against dsDNA [91]. This pentapeptide sequence is also present in the extracellular region of the glutamate receptor subunits NR2a and NR2b, present on neurons in the CNS. dsDNA antibodies recognize glutamate receptors *in vitro* and *in vivo*, and can induce neuronal death. Other studies have shown that the IgG repertoire from active plaque and periplaque regions in the MS brain and from B cells from the CSF of a patient with MS consisted of anti-DNA antibodies [92]. These antibodies bind to the surface of neuronal cells and oligodendrocytes. Therefore, molecular mimicry may cause the development of antibodies that interact with neuronal surface proteins and induce neural injury through the activation of neural pathways.

Potential treatment options in acute transverse myelitis

There is currently no treatment that has been clearly shown to modulate the outcome in patients with ATM. Indeed, with such varied immunopathogenesis, it may be that distinct treatment options need to be employed for different subsets of ATM patients. Recent studies that have investigated potential strategies to modulate neural injury associated with ATM will be reviewed.

Methylprednisolone

On the basis of the presumptive immunopathogenic mechanisms in ATM, several recent studies have investigated a role for intravenous methylprednisolone in the acute phase. All studies evaluated a series of patients with ATM treated with methylprednisolone in open-label studies [93•,94•,95]. Two of the studies suggested a role for methylprednisolone in small, open label trials [93•,95], whereas one suggested no improvement in outcome [94•]. In one study [95], 12 children with severe ATM were treated with methylprednisolone and were compared with a historical group of 17 patients. Follow-up evaluation revealed the following in the methylprednisolone versus the non-methylprednisolone group: 66 versus 17.6% were walking independently at one month; 54.6 versus 11.7% had made a full recovery at one year; and 25 versus 120 days was the median time to independent walking. Subsequently, in a multicenter open label study of 12 children with severe ATM [93•],

outcome measures were compared with historical controls and suggested a beneficial outcome at one month and one year.

However, in a prospective, hospital-based study [94•], outcome evaluations and electrophysiological studies were used to evaluate a potential effect of methylprednisolone in 21 ATM patients. It was found that patients in both groups with positive physiological studies (recordable central conduction time on evoked potential and absent denervation) improved, whereas those with negative physiological studies did not. There was no observed difference in the outcome caused by methylprednisolone either in patients with mild or with severe symptoms.

Therefore, there remains uncertainty as to the beneficial effect of steroids in ATM, although this treatment is widely offered to patients in the acute phase. The limitations in such studies – heterogeneous patient population, small study size, open label, and the use of a historical control population – led to the conclusion that the further definition of a role for steroids in ATM will require controlled studies on more defined patient populations.

Cyclophosphamide

Several reports have suggested a role for cyclophosphamide and steroids in lupus-associated ATM [96–98]. However, the role of immunomodulatory treatments in other forms of ATM remains unclear.

Plasma exchange

Plasma exchange was recently shown to be effective in patients with severe, isolated CNS demyelination [99,100]. In a randomized, sham-controlled, crossover-design study, 44% of patients with severe inflammatory demyelination who had not responded to steroids improved after plasma exchange. It was reasoned that plasma exchange may remove humoral factors (including antibodies, endotoxins or cytokines) contributing to inflammation.

Cerebrospinal fluid filtration

CSF filtration was recently proposed and investigated for patients with the related monophasic inflammatory disease GBS [101•]. In that study 37 patients were randomly selected to receive CSF filtration or plasma exchange during the acute phase of GBS. CSF filtration consisted of the placement of a spinal catheter and the removal of 30–50 cc of CSF via a filter bypass designed for the elimination of cells, bacteria, endotoxins, immunoglobulins and inflammatory mediators. A filtration session consisted of several such cycles (five to six times, of 30–50 cc each), repeated daily for 5–15 consecutive days compared with a standard plasma exchange regimen for GBS. CSF filtration showed equal effectiveness compared with plasma exchange, with fewer complications. The rationale for this treatment – that cellular or humoral factors in the CSF may contribute to the dysfunction and injury of peripheral nerves and nerve roots – is even stronger in ATM patients in whom the inflammation is largely or entirely within the CNS. Therefore, it is worthy of further investigation in such patients.

Protective autoimmunity

Although this review has focused on how the immune system may damage the neural system, recent evidence suggests that in certain situations, the immune system may play a role in the recovery from spinal cord injury [102•,103]. In those studies, active or passive immunization of animals against CNS antigens resulted in improved functional status and diminished neuronal death after spinal cord contusion. The benefit was mediated by T lymphocytes, and may indicate that the removal of damaged neural tissue facilitates enhanced recovery.

Conclusion

In summary, emerging evidence suggests that a variety of immune stimuli, through such processes as molecular mimicry or superantigen-mediated immune activation, may trigger the immune system to injure the nervous system. The activation of previously quiescent autoreactive T lymphocytes or the generation of humoral derangements may be effector mechanisms in this process. Several recent studies have highlighted the importance of specific immune system components in inducing neural injury: IgE and hypereosinophilia, autoantibodies, complement fixation, and the deposition of immune complexes within the spinal cord. It is our current challenge to define clinical, genetic and serological characteristics that predict this pathological heterogeneity. Only then can rational, targeted therapies be envisioned.

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