INTRODUCTION

Encephalitis/myelitis is an acute inflammatory process that affects brain or spinal cord tissue and is almost always accompanied by inflammation of the adjacent meninges. The disease is most commonly caused by viral infection (Whitley&Gnann, 2002; Kennedy, 2004).

Encephalitis resulting from viral infection manifests as either acute viral encephalitis or Postinfectious encephalomyelitis. Acute viral encephalitis is caused by direct viral infection of neural cells with associated perivascular inflammation and destruction of gray matter. Postinfectious encephalomyelitis follows infection with various viral or bacterial agents; the primary pathologic finding is demyelination of white matter (Whitley&Gnann, 2002; Kennedy, 2004).

Postinfectious demyelinating neurological disorders comprise a group of neurological disorders which represent a clinical continuum rather than separate diseases entities. These disorders might coexist in various combinations in the same patient. Some patients having their optic nerves,
cerebrum, and spinal cord involved (acute disseminated encephalomyelitis), other patients having their optic nerves and spinal cord involved (neuromyelitis optica) or might present clinically as an isolated disease (Kaplin et al., 2005).

These disorders share a common aetiopathogenic factors (antecedent viral infection that evokes antibodies that cross react with the myelin basic protein of the peripheral and central nervous system). They also share a common pathological picture (demyelination of the white matter of the CNS and demyelinating polyneuropathy) and a common prognosis (They all have a good prognosis in most cases (Metwally, 2009).

Acute disseminated encephalomyelitis (ADEM) is a monophasic autoimmune demyelinating disease of the central nervous system that typically follows a febrile infection or a vaccination. Children are predominantly affected. A plethora of viral and bacterial pathogens and a number of vaccinations have been associated with ADEM (Menge et al., 2005).

The focal presentation of ADEM is heterogeneous and dependent upon the location and degree of the inflammatory-demyelinating process within the CNS. Multifocal neurological deficits consisting of combinations of pyramidal and cerebellar signs are very common, as are cranial neuropathies, including bilateral optic neuritis encountered more frequently in ADEM than multiple sclerosis (MS). Isolated transverse myelitis is usually considered a separate, although related, entity to ADEM (Stuve & Zamvil., 1999).

The neurologic injury in transverse myelitis 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, though in the vast majority of these cases, causality cannot be established (Christensen et al., 1990).

Neuromyelitis optica (NMO) is frequently preceded by infection in pediatric cases which typically have a monophasic course and many have complete neurological recovery. Because of pediatric NMO's frequent association with preceding infection, monophasic course, and generally good outcome, some authors consider pediatric NMO to be a variant of ADEM (Jeffery & Buncic., 1996).

Cerebellitis is an inflammatory syndrome resulting in acute cerebellar dysfunction, which may occur as a primary infectious, Postinfectious, or post-vaccination disorder. Cerebellitis occurs most commonly in young children and may be difficult to diagnose on routine clinical and laboratory studies. Encephalitis largely restricted to the cerebellum, called cerebellitis. Cerebellitis may occur due to a host of viral agents, including enteroviruses, herpes viruses, HIV, and rabies. Bacterial infections have also been associated with cerebellitis, including Borrelia burgdorferi (Lyme disease), Mycoplasma pneumonia, Legionella, and Coxiella burnetti (Q fever). In addition, cerebellitis may follow immunizations such as hepatitis, smallpox, and measles vaccination (Bruecker et al., 2004; Tlili et al., 2006).

**PATHOLOGY & PATHOGENESIS**

Direct viral infection of the brain and spinal cord involves mainly the gray matter (neurons), while Postinfectious or para-infectious neurological disorders is simply a white matter disease in which there is immune mediated demyelination of the white matter long tracts and the association fibers in the cerebrum, cerebellum, brain stem and spinal cord also. The viral or bacterial antigens in the CNS is absent in these disorders (Metwally, 2009).

The distinction between infective (neuronal) and Postinfectious (immune-mediated demyelinating white matter disease) might be difficult or even impossible on clinical background; however table
1 demonstrates the main differences between the two pathologies (Metwally, 2009).

Table 1. Differences between infectious and Postinfectious encephalitis/myelitis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Infectious</th>
<th>Postinfectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site of involvement</td>
<td>Cortical gray matter</td>
<td>Demyelinative, white matter disease</td>
</tr>
<tr>
<td>Mental state</td>
<td>Impaired</td>
<td>Less impaired, might be clear</td>
</tr>
<tr>
<td>The interval between the first sign of infection and the onset of neurological disorders</td>
<td>Briefer (Few days)</td>
<td>Prolonged (7-21 days)</td>
</tr>
<tr>
<td>CSF examination</td>
<td>Abnormal</td>
<td>May be normal</td>
</tr>
</tbody>
</table>

Before widespread vaccination, Postinfectious encephalomyelitis most commonly occurred after smallpox and measles infections. In recent years, the disease has been associated with various viral and bacterial infections as shown in table 2. Patients may have a history of exanthema or a nonspecific respiratory or gastrointestinal illness 1 to 3 weeks before onset of neurologic symptoms (Khong et al., 2002; Metwally, 2009).

Table 2. Infections alleged to cause demyelinating neurological disorders.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Viral</th>
<th>Bacterial</th>
<th>Vaccination</th>
<th>Drugs</th>
<th>Miscellaneous</th>
</tr>
</thead>
</table>

Postinfectious demyelinating white matter diseases represent an autoimmune response to proteins, most probably myelin- basic proteins, in the CNS with perivenous inflammation and demyelination found in autopsy and biopsy studies (Phol-Koppe et al., 1998).

Myelin basic protein (which is the main antigen that is targeted in the immune mechanism that ends in myelin destruction) is different in different parts of the CNS. The myelin basic protein in the peripheral nerves is different from that of the CNS and this might explain why the demyelinating process may preferentially involve some parts of the CNS and spare other parts in different patients (depending upon the antigenic properties of the myelin basic protein of the involved sites) resulting in a protean clinical presentations of the same disease in different patients (Metwally, 2009).

What accounts for this regional specificity is a subject of considerable research interest, for which there is no current consensus explanation. Presumably, this regional specification could result from differences inherent in CNS tissue at different sites (such as varying threshold for injury or distinct localization of signal transduction machinery or antigens) or from differential access to
distinct regions of the CNS by exogenous pathogenic mechanisms (Kaplin et al., 2005).

Different areas of the white matter within the CNS and the peripheral nervous system are targeted by the inflammatory demyelinating pathological process in various combinations in different patients. Resulting that some patients having their optic nerves, cerebrum, and spinal cord involved (acute disseminated encephalomyelitis), other patients having their optic nerves and spinal cord involved (neuromyelitis optica) and so on (Kaplin et al., 2005).

- **Pathogenesis of acute disseminated encephalomyelitis (ADEM)**

The precise pathogenesis of acute disseminated encephalomyelitis (ADEM) is still unclear; however given its histological features, it has been likened to the animal model of experimental autoimmune encephalomyelitis (EAE) and Theiler murine encephalomyelitis. In EAE, animals are immunized with a combination of encephalitogenic myelin proteins or peptides, developing a monophasic syndrome of motor weakness and incontinence, associated with diffuse CNS inflammatory demyelination. Viral or bacterial epitopes resembling myelin antigens have the capacity to activate myelin-reactive T cell clones through molecular mimicry, and can thereby elicit a CNS-specific autoimmune response. Thus, it has been suggested that preceding infections in disseminated encephalomyelitis (DEM) may elicit a cross-reactive anti-myelin reaction through a mechanism of molecular mimicry (O'Connor et al., 2005).

Another animal model, putatively mimicking Postinfectious ADEM, is created by direct inoculation of genetically susceptible mice with Theiler murine encephalomyelitis virus (TMEV) (picornavirus), inducing widespread CNS inflammatory demyelination through an immune-mediated reaction primarily involving TMEV specific CD4 and CD8 T cells (O'Connor et al., 2005).

The TMEV model highlights the phenomenon of epitope spreading secondary to a destructive CNS viral infection resulting in a secondary autoimmune response and chronic inflammation. Although this model superficially bears some resemblance to ADEM, the epitope spreading is more likely to be an important phenomenon in chronic inflammatory disorders such as MS. Alternatively, the molecular mimicry hypothesis suggests that structural similarities between the pathogen (viral/vaccine polypeptides) and the host (central or peripheral nerve myelin) are sufficient to induce T cell activation but not sufficient to induce tolerance (McMahon et al., 2005).

Elevated titers of anti-myelin antibodies in sera from DEM patients have recently been demonstrated as compared to patients with MS or viral encephalitis (O'Connor et al., 2005).

A recently published study reported the presence of circulating conformation-dependent auto antibodies to MOG in a subset of children and adults with DEM, but only rarely in adult-onset MS cases (O'Connor et al., 2007).

- **Molecular mimicry**

This mechanism is well established in GBS, a monophasic, usually Postinfectious, inflammatory disorder of peripheral nerves. More recent studies have implicated this mechanism in a variety of CNS inflammatory diseases as well (Stocks et al., 2001; Kerr et al., 2002).

Antigenic epitopes, comprising of delicate structural or partial amino-acid sequence homologies, are shared between an inoculated pathogen or vaccine, and a host CNS protein. As a result, the pathogen is not recognized as "foreign for elimination, or "self for immune tolerance. At the inoculation site the pathogen is initially processed by T cell activation and cross activation of antigen-specific B cells (Menge et al., 2007).
These auto reactive cells can enter the CNS during immune surveillance and by chance, may encounter the homologous myelin protein. The local reactivation by antigen presenting cells subsequently culminates in a destructive autoimmune process in the CNS (Menge et al., 2007).

Much research has focused on T cell mediated autoimmune response to myelin auto antigens, such as MBP, proteolipid protein and myelin oligodendrocyte glycoprotein, which can induce ADEM. Some studies have suggested a role for B cells and antibodies to gangliosides such as GM1 and GD1a, while others have identified T helper 2 cells reactive to MBP, which were found in the peripheral blood of ADEM patients (Stuv et al., 1999).

- **The re-infectious etiology**

The re-infectious etiology theory postulates that CNS demyelination occurs as a possible result of direct neurotoxicity of a neurotropic virus, and that vaccination with an attenuated virus strain may cause problems only if administered during a preceding infection, in which previously primed virus-specific cytotoxic T cells are reactivated (Menge et al., 2007).

- **The post-infectious etiology**

The disruption of the blood-brain barrier sustained after direct CNS infection with a neurotropic virus may subsequently result in the leakage of CNS auto antigens into the systemic circulation. These auto antigens are then processed in the systemic lymphatic organs leading to a breakdown in tolerance and emergence of a self-reactive and encephalitogenic T cell response. Possibly secondary to the secretion of proinflammatory cytokines, chemoattractants or other soluble factors in situ, this CNS inflammation perpetuates itself even further (Menge et al., 2007).

Studies on patients who developed ADEM following anti-rabies vaccination suggest that MBP may be encephalitogenic in this scenario (Murthy., 2002).

- **Immuno-inflammatory model**

The immuno-inflammatory model combines the concept of molecular mimicry with the inflammatory cascade process. A "first hit" is experienced after an antecedent infection with a virus that expresses determinants allowing molecular mimicry. This need not be clinically eventful or significant. A second infection with an unrelated virus results in sufficient reactivation of the primed auto reactive T cells to eventuate in demyelination of the CNS. This constitutes the "second hit" (Menge et al., 2007).

- **Pathogenesis of transverse myelitis (TM)**

The immunopathogenesis of disease- associated TM is varied. For example, pathological data confirm that many cases of lupus-associated TM are associated with CNS vasculitis while others may be associated with thrombotic infarction of the spinal cord. Neurosarcoidosis is often associated with non-caseating granulomas within the spinal cord, while TM associated with MS often has perivascular lymphocytic cuffing and mononuclear cell infiltration with variable complement and antibody deposition (Kaplin et al, 2005).

Most patients have CSF pleocytosis and blood-brain barrier breakdown within a focal area of the spinal cord, and conventional treatments are aimed at ameliorating immune activation. In patients with TM, it is likely that abnormal activation of the immune system is present, resulting in inflammation and injury within the spinal cord. Thus, an understanding of the immune pathogenesis of TM must account for abnormal or excessive incitement of immune activation and effector mechanisms by which immune activation leads to CNS injury (Kaplin et al, 2005).
In 30% to 60% of the idiopathic TM cases, an antecedent respiratory, gastrointestinal, or systemic illness exists. One mechanism to explain this association is the molecular mimicry mechanism. A variety of infectious agents encode molecular mimics (e.g., proteins, glycolipids, or proteoglycans) that resemble self-antigens (Kerr et al., 2002).

Another link between an antecedent infection and the development of TM may be the fulminant activation of lymphocytes by microbial super antigens (SAGs). The best-studied super antigens are staphylococcal enterotoxins A through I, toxic shock syndrome toxin-1and Streptococcus pyogenes exotoxin, although many viruses encode SAGs as well (Kerr et al., 2002).

SAGs 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 SAGs interact with the more conserved Vβ region. Additionally, unlike conventional antigens, SAGs are capable of activating T lymphocytes in the absence of co stimulatory molecules (Kerr et al., 2002).

As a result of these differences, single SAG may activate between 2% and 20% of circulating T lymphocytes compared with 0.001% to 0.01% with conventional antigens. Stimulation of large numbers of lymphocytes may trigger autoimmune disease by activating auto reactive T-cell clones (Kerr et al., 2002).

- **Humoral derangement**

Either of the above processes may result in abnormal immune function with blurred distinction between self and non self. The development of abnormal antibodies potentially may then activate other components of the immune system and/or recruit additional cellular elements to the spinal cord (Kerr et al., 2002).

The high prevalence of various auto antibodies seen in such patients suggests polyclonal derangement of the immune system. It may also be that some auto antibodies initiate a direct and selective injury of neurons that contain antigens that cross-react with antibodies directed against infectious pathogens. However it may not just be auto antibodies, however, but high levels of even normal circulating antibodies that have a causative role in TM (Renard et al, 1999).

A case of TM was described in a patient with extremely high serum and CSF antibody levels to hepatitis B surface antigen following Booster immunization 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 TM and high titers of hepatitis B surface antigen following booster immunization (Renard et al, 1999).

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 following treatment correlated with functional recovery (Renard et al, 1999).

Several Japanese patients with TM were found to have much higher serum IgE levels than patients with MS or controls (360 versus 52 versus 85 U/mL) (Kira et al, 1998). One potential mechanism to explain the TM in such patients is the deposition of IgE with subsequent recruitment of cellular elements. Indeed, biopsy specimens of two patients with TM with elevated total and specific serum IgE revealed antibody deposition within the spinal cord, perivascular lymphocyte cuffing, and infiltration of eosinophils. It was postulated that eosinophils recruited to the spinal cord de granulated and induce the neural injury in these patients(Kikuchi et al.,2001).

In a series of recent investigations that describe immune derangements in patients with TM, IL-6 levels in the spinal fluid of patients with TM were markedly elevated compared with control
patients and patients with MS. While relatively low levels of IL-6 in patients with MS did not correlate with disability, IL-6 levels in patients with TM strongly correlated with and were highly predictive of disability. IL-6 levels in the CSF of patients with TM correlated with nitric oxide metabolites, which also correlated with disability. It is suggested, therefore, that marked up regulation of IL-6 correlates with increased nitric oxide production and that this elevation is etiologically related to tissue injury leading to clinical disability in TM (Kikuchi et al., 2001).

- Pathogenesis of Neuromyelitis optica (NMO)

Humeral immunity, including complement activation, plays an important role in the pathogenesis of NMO. In contrast to MS, NMO attacks are not mediated by T cells but rather by B cells. The findings of prominent IgG and complement deposition in 100% of lesions suggest participation of B-cell mediated autoimmunity (Lucchinetti et al., 2002).

Circulating auto-antibodies are frequently found in NMO at frequencies that exceed those seen in classical MS and their presence may also reflect a more widespread B-cell response. These auto-antibodies might cause damage directly through the recognition of epitopes on normal cells, or indirectly through the formation of immune complexes that deposit in normal tissue and activate the complement cascade. The prominent antibody responses to endogenous myelin antigens, such as pathogenic myelin oligodendrocyte glycoprotein, in NMO are also in keeping with a widespread B cell immune response (Lucchinetti et al., 2002).

NMO attacks are also mediated by antibodies, called NMO-IgG. NMO-IgG target aquaporin 4 that is a water channel located in the foot processes of the astrocytes surrounding the blood-brain barrier. T cells may also play a role in the initiation and perpetuation of NMO, but aquaporin epitopes recognized by T cells have not as yet been mapped. Unlike the minor contribution of aquaporin 4 to water homoeostasis in parts outside CNS, its role as the most abundant water channel in the CNS was early detected (Lucchinetti et al., 2002; Amiry-Moghaddam & Ottersen, 2003).

NMO-IgG bind selectively to several CNS sites, i.e. abluminal face of micro vessels that are closely related to sites of immune complex deposition in NMO lesions. Thus, the immune histochemical-staining pattern of NMO-IgG is characteristic diagnostically (Lucchinetti et al., 2002; Scott et al., 2006).

PATHOLOGY

Histologically, the acute lesions in Postinfectious neurological disorders are characterized by an extensive loss of myelin (perivenous cuffing with inflammatory cells, especially lymphocytes and macrophages, and loss of myelin). This may be in the form of a well-demarcated area of demyelination, although in the acute situation, the edges of the demyelinated lesions often are less well defined, and the demyelination and attendant cellular processes extend into the surrounding rim (Idrissova et al., 2003).

Demyelinated fibers may be recognized by an axon devoid of a sheath, as seen histochemically, or immunohistochemically, or on electron microscopy by the presence of naked axons. In addition, thinly myelinated fibers may be seen within the lesion, suggesting partially demyelinated or remyelinated fibers. The presence of oligodendrocytes showing the re-expression of myelination proteins suggests the latter event is occurring in a least a significant number of these fibers (Metwally, 2009).

Accompanying the myelin loss is a large infiltrate of foamy or debris-filled macrophages lying in sheets that appear to have replaced the normal neutrophil. They also may be around the blood
vessels, or infiltrating the more preserved areas of tissue as single cells (Hemmer et al., 2002).

The inflammatory infiltrate varies, but in most acute cases will be of some significance. Lymphocytes staining with the leukocyte common antigen comprise most cells, although polymorphonuclear leukocytes, eosinophils, plasma cells, and even mast cells have been found, together with less well-characterized monocytes. Although they may be present throughout the tissue, they are particularly prominent around the blood vessels, and at times may be so severe as to mimic a vasculitis (Hemmer et al., 2002).

Both CD4 helper cells and CD8 suppressor cells may be found in the lesions. In the past, there have been suggestions that CD4 cells predominate in early lesions, with CD8 cells taking over at later stages, but this is variable, and a fixed pattern has not been defined (Hemmer et al., 2002).

Many workers also have described the occurrence of gamma-delta lymphocytes in these lesions, and their association with acute phase reactant or stress proteins such as heat shock protein on oligodendrocytes (Hemmer et al., 2002; Khong et al., 2002).

Demyelination of the white matter is associated with breakdown of the blood brain barrier and the development of Vasogenic edema. Vasogenic edema is the most common type of edema results from local disruption of the blood brain barrier. This leads to extravasation of protein-rich filtrate of plasma into the interstitial space, with subsequent accumulation of vascular fluid (Metwally, 2009).

This disruption results from loosening of the tight junctions between endothelial cells, and the neoformation of pinocytic vesicles. Once the barrier is breached, hydrostatic and osmotic forces work together to extravasate intravascular fluid. Once extravasated, fluid is retained outside the vasculature, mostly in the white matter of the brain, and within the bundles of myelinated axons of long tracts and commissural fibers. This is because axons run in parallel bundles of fibers with loose extracellular space (that offer low resistance and facilitates the extension of Vasogenic edema along myelinated axons which are spread apart by the edema) as opposed to gray matter, which has high cell density and is enmeshed in an interwoven network of connecting fibers that offer high resistance to the formation and spread of edema (Metwally, 2009).

Vasogenic edema is responsible for the MRI T2 hyper intensity and MRI T1 hypo intensity and The MRI T1 contrast enhancement frequently observed in these disorders (Kumar et al., 1997).

- **ADEM Pathology**

There are certain distinctions between the histopathological findings in ADEM and MS. MS lesions are heterogeneous in terms of lesion age and composition of the cellular components. At least four lesion patterns have been described (Lucchinetti et al., 2000).

In contrast, ADEM lesions are almost always of similar age, and consist of mostly one distinct pattern: perivenous inflammation around small vessels in both CNS white and gray matter. The areas of disease are not necessarily confined to the periventricular areas. Lesions are infiltrated by lymphocytes, macrophages and to lesser extent neutrophils. In addition, there is perivascular edema, endothelial swelling and vascular endothelial infiltrations (not resembling vasculitis). Demyelination may not be present in hyper acute or acute lesions, but may develop later in the lesion's evolution in a rather pathognomonic 'sleeve-like' fashion; that is, confined to the hyper cellular areas. In general, there is only slight damage to axons (Prineas et al., 2002; Menge et al., 2007).

While pathogenic involvement of cytokines and chemokines has been unequivocally established in
**Studies conducted in ADEM so far have yielded conflicting data:**

1. The proinflammatory cytokines tumor necrosis factor (TNF)-a and interleukin (IL)-1b, but not IL-6 are expressed in situ in lesions of one adult ADEM patient (Kadhim et al., 2003).

2. In contrast, IL-6 and TNF-a, but not IL-1b levels were found elevated in the cerebrospinal fluid (CSF) of 18 ADEM patients (Ichiyama et al., 2002).

3. Production of interferon (IFN)-g, a proinflammatory signature T helper type 1 (Th1) cytokine, causally related to autoimmunity but not IL-4 by CD3? peripheral blood T cells, was found to be elevated in four ADEM cases compared with controls (Yoshitomi et al., 2000).

4. Predominant IL-4, but not IFN-g secretion, was detected in myelin-reactive peripheral T cells from ADEM patients compared with controls (Pohl-Koppe et al., 1998).

5. In the CSF, one study reported a predominant Th1 cytokine profile, with decreased IL-17 levels, a cytokine recently associated with the pathogenesis of MS, in 14 ADEM patients compared with controls (Ishizu et al., 2006).

6. Two other groups could not detect either Th1 or Th2 cytokine profiles in the CSF of 17 ADEM cases (Franciotta et al., 2006) Or elevated levels for IFN-g, IL-10 or IL-12 (Leake et al., 2004).

In MS, the roles of pathogenic autoantibodies and in particular of antimyelin antibodies as biomarkers of disease etiology and prognosis have been a major focus of research efforts recently (Archemos et al., 2000; Reindlet al., 2006). Recently, assays involving native myelin oligodendrocyte glycoprotein (MOG), a putative target auto antigen in MS, yielded promising results discriminating MS from other diseases (Lalive et al., 2006; Zhou et al., 2006).

ADEM cases have not yet been included in any of the studies, possibly due to the much lower incidence of this disease. A recent study, however, undertook the effort to compare anti-MOG antibody reactivities of 56 pediatric ADEM cases by a number of commonly employed assays, such as enzyme-linked immunosorbent assay (ELISA), radioimmunoassay, cytometry against native MOG, and a new genetically engineered tetrameric MOG molecule (O'Connor et al., 2007); only by the latter (tetramer) assay, performed under solution-phase conditions and hence detecting conformation-dependent antibodies of higher affinity, anti-MOG antibodies could be detected in 18% of ADEM cases, but in less than 1% of MS cases (O'Connor et al., 2007).

Additionally, a subgroup of ADEM cases, those with a novel clinical phenotype of dystonic extra pyramidal movement disorders and a behavioral syndrome after group A b-hemolytic streptococcal infection, were found to be positive for anti basal ganglia antibodies, providing a possible link to humoral molecular mimicry (Dale et al., 2001).

Despite the discrepancies described, which may be due to low patient numbers and different assay and study designs, a pathogenic involvement of T cells and macrophages/monocytes secreting chemokines and cytokines appears likely. Their role in the initiation or perpetuation of ADEM, however, has to be further clarified (Ishizu et al., 2006).

CNS specific auto antibodies may play a pathogenic role in a subset of patients. These findings corroborate the autoimmune nature of the disease and potentially provide avenues for therapeutic
strategies. They also, however, underscore the pathogenic heterogeneity of ADEM, despite clinical similarities (Ishizu et al., 2006).

**Transverse myelitis pathology**

TM is an inflammatory condition associated with immune-mediated mechanisms. Indeed, all patients who met criteria for the diagnosis of TM and had tissue sampling of the spinal cord (biopsy or autopsy) had inflammatory changes. These pathological abnormalities invariably included focal infiltration by monocytes and lymphocytes into segments of the spinal cord and perivascular spaces and an invariable astroglial and microglial activation (Krishnan et al, 2004).

The magnitude and extension of these inflammatory features vary and are determined by the etiological factors and temporal profile of the myelopathic changes. The presence of white matter changes, demyelination, and axonal injury is prominent in Postinfectious myelitis. However, involvement of the central compartment of the cord, gray matter, or neurons is also prominent in some cases, a finding that supports the view that in TM, both gray and white matter compartments may be equally affected (Krishnan et al, 2004).

In some biopsies obtained during the acute phases of myelitis, infiltration of CD4+ and CD8+ lymphocytes along with an increased presence of monocytes is quite prominent. In biopsies obtained during sub acute phases of myelopathic lesions, prominent monocyte and phagocytic-macrophage infiltration is observed. In some cases, autoimmune disorders, such as SLE, lead to vasculitic lesions that produce focal areas of spinal cord ischemia without prominent inflammation. These immunopathological observations further confirm that TM is an immunemediated disorder that involves cellular reactions and perhaps humoral factors that injure compartments of the spinal cord (Krishnan et al, 2004).
Figure 2. Histology of transverse myelitis (TM). A, Myelin staining of cervical spinal cord section from a patient who died during a subacute stage of TM. There are a few myelinated areas left (asterisk) and foci of cystic degeneration in the anterior horns (arrow). The remaining spinal cord shows chronic inflammation and demyelination (LFB/HE stain). B, Perivascular infiltration by inflammatory cells in an area of active inflammation in a patient with TM. C, Infiltration by microglial cells in an area of inflammation (HLA-DR immunostain). D, High-magnification view of few myelinated fibers left in areas of active inflammation (arrows) (LFB/HE stain) (Kaplin et al., 2005).

- Pathology of Neuromyelitis Optica (NMO)

The damage in the spinal cord in NMO can range from inflammatory demyelination to necrotic damage, extending across multiple sections. The inflammatory lesions are associated with cavitations, necrosis and acute axonal pathology (spheroids), in both grey and white matter of the spinal cord and optic nerves (Lucchinetti et al., 2002).

The pathology of active lesions from nine autopsy cases of clinically confirmed NMO, showed prominent perivascular deposition of immunoglobulin's (mainly IgM) and complement C9 neoantigen (Lucchinetti et al., 2002).

Immunoglobulin and complement components are found in a specific vasculocentric rim and rosette pattern. Immune complexes are also deposited along myelin sheaths and within macrophages in pattern II (complement-mediated demyelination) subsets of MS, whereas the penetrating spinal vessels are usually degenerated, being associated with cord necrosis and a macrophage predominant inflammatory infiltrate (Lucchinetti et al., 2000).

Active lesions of NMO are also distinct from that seen in MS because their prominent perivascular distribution of immune complexes corresponds to the normal expression of aquaporin 4 in the end feet of astrocytes (Roemer et al., 2007).

Aquaporin 4 is not identified in neuromyelitis optica lesions. Pathological analysis of NMO lesions in the spinal cord and medullary tegmentum shows loss of aquaporin 4 with inflammation and oedema, without demyelination or necrosis (Sinclair et al., 2007).
Figure 3. (NMO)- (Ig)G and Immunopathology. (A, B) Immunofluorescence pattern of bound NMO-IgG are seen in mouse (CNS) and kidney. (A) Prominent microvessel and pia (around large unstained vessel [V]) staining in cerebellar cortex (molecular layer [ML], granular layer [GL]) and midbrain (MB). (B) NMO-IgG is bound to distal-collecting tubules in kidney medulla. (C-F) Images showing acute NMO. (C) Spinal cord, classic cavitory actively demyelinating NMO lesion involving both gray and white matter, peripheral myelin sparing is noted (Luxol fast blue-periodic acid Schiff [LFB-PAS]). (D, E) Perivascular complement (D, arrow) and Ig (E, arrow) deposition in a rosette pattern (immunohistochemistry against C9neoand IgG). (F) Image demonstrates complete AQP4 loss (immunohistochemistry against AQP4). (G) Image shows acute active MS lesion. Increased AQP4 is seen perivascularly and in the cytoplasm of reactive astrocytes (immunohistochemistry against AQP4). (H, I) Novel lesion type is seen in acute NMO. Spinal cord demonstrates complete AQP4 loss in the white matter (H). Note residual AQP4 immunoreactivity is seen in gray matter (immunohistochemistry against AQP4) but myelin (I) and tissue integrity are preserved (LFB-PAS) (Pittock.,2006)

CLINICAL SUBTYPES

- Acute disseminated encephalomyelitis (ADEM) (Postinfectious cerebritis)

Disseminated encephalomyelitis (DEM) is an immune mediated inflammatory disorder of the central nervous system (CNS); characterized by a widespread demyelination that predominantly involves the white matter of the brain and spinal cord. The condition is usually preceded by a viral infection or vaccination, and the presenting features include an acute encephalopathy with multifocal neurological signs and deficits (Rust, 2000; Boz et al., 2003).

The lack of uniform definitions and clear clinical and neuroimaging diagnostic criteria has led that different conditions being classified as DEM. Although disseminated encephalomyelitis usually has a monophasic course (ADEM), multiphasic forms (MDEM) have been reported, raising diagnostic difficulties in distinguishing these cases from multiple sclerosis (MS). The diagnostic differentiation between DEM and MS is important for prognostic reasons and treatment decision (Jones, 2003).

- Consensus Definition for ADEM
Clinical research in ADEM has always been hampered by the lack of a uniform case definition, resulting in heterogeneous, incomparable study populations. The recent introduction of consensus definitions for children by the International Pediatric MS Study Group is likely to facilitate the differentiation of monophasic ADEM from other acquired demyelinating conditions (Krupp et al., 2007).

According to the consensus definition patients should have an acute or sub acute onset of the first clinical event of multifocal CNS affection, characterized by polysymptomatic neurological dysfunction. Encephalopathy is an essential clinical feature; it is defined as either behavioral changes, alteration in consciousness, or both. MRI brain must show focal or multifocal lesions greater than 1-2 cm in size, which must be predominantly in the white matter, though it may also be present in the grey matter such as the basal ganglia or thalamus. In addition, the spinal cord may show confluent lesions. The clinical event must have a presumed inflammatory or demyelination basis, without other etiologies. It should be followed by improvement, either clinically or on MRI, though there may be residual deficits. New or fluctuating symptoms and signs or MRI findings within three months of the initial event are considered part of the initial acute event (Krupp et al., 2007).

- **Epidemiology**

The incidence of ADEM has been estimated to be 0.4 per 100,000 populations per year and it may represent 30% of all childhood encephalitic illnesses. ADEM more commonly affects children and young adults, probably because of exposure to frequent vaccinations, exanthematous fever and upper respiratory tract infections in this age-group (Murthy et al., 2002). The mean age of onset in children ranges from 5 to 8 years. ADEM generally does not show a predilection for any one sex, though two recent studies have shown a male predominance among the victims. ADEM occurs throughout the year, but there is a significant increase in incidence during winter and spring (Leake et al., 2004).

- **Triggering Events**

ADEM typically follows an antigenic challenge, such as infection or vaccination, which activates the immune system. Recently, there has been a distinct change in the trend and, in regions with extensive immunization coverage, nonspecific upper respiratory tract infections are the most common triggering events (Menge et al., 2005; Sell & Minassian, 2006).

ADEM is associated with a preceding or concomitant infection that is most commonly viral. Measles, mumps, rubella, varicella-zoster, Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus, hepatitis A or B, Coxsackie virus, influenza A or B, human immunodeficiency virus (HIV), human T-cell lymphotropic virus-1 (HTLV-1), human herpes virus 6, vaccinia, Rocky Mountain spotted fever, and human corona virus have been implicated as causing post-infectious ADEM (Narciso et al., 2001; Madan et al., 2005).

Bacterial infections are also associated with post-infectious forms of ADEM, most commonly Mycoplasma pneumoniae. Other pathogens include Borrelia, Campylobacter, Leptospira, Chlamydia, Legionella, and group A beta-haemolytic streptococci (Murthy et al., 2002).

ADEM is associated with several vaccines including those for rabies, diphtheria-tetanus-polio, smallpox, measles, mumps, rubella, Japanese B encephalitis, pertussis, influenza, and hepatitis B. For most vaccines, incidence rates are as low as 0.1 to 0.2 per 100,000 vaccinated individuals (Kashyap et al., 2004; Menge et al., 2007). ADEM following immunization seems to occur significantly more frequently after primary vaccination as compared to revaccination (Booss et al., 2003). Post-vaccination encephalomyelitis accounts for less than 5% of cases of ADEM (Sejvar et
The time interval from immunization to the onset of the clinical event is not considered part of the definition itself. The neurological adverse events associated with the smallpox vaccination in the USA between 2002 and 2004 found to be 214 such occurrences with only 3 of these suspected of being ADEM, giving an estimated rate of 5 cases per million vaccines (Sejvar et al., 2007). Reported rates vary from 1 in 4000 to 1 in 80,000 after primary vaccination, and from 1 in 50,000 to 1 in 450,000 after revaccination (Johnson et al., 2003).

Post-vaccination ADEM was thought to be caused by the vaccine's viral component but it was later recognized that it could also be related to contamination with CNS tissue in which the vaccine was propagated. For example, the anti-rabies vaccine had been cultured from rabbit, sheep or goat brain, and the Japanese encephalitis vaccine from murine brain. This theory has been highlighted by a significant drop in post-vaccination ADEM incidence rates after the development of vaccines based on recombinant proteins rather than from in-vivo infected tissue (Menge et al., 2007; Gupta et al., 2004).

Results from experimental allergic encephalomyelitis (EAE) also support this concept. In EAE, a disease that clinically and pathologically resembles ADEM, inflammation is produced when an experimental animal is inoculated with myelin or myelin antigens. High-affinity antibodies directed against myelin-basic protein (MBP) have been identified in ADEM patients, but not MS patients (Menge et al., 2007).

The most common vaccinations associated with ADEM are the non-neural measles, mumps and rubella vaccines. The incidence of 1-2 per million for live measles vaccine is less than the reported 1 in 1000 incidence of post-infectious ADEM following infection with the measles virus itself. Arguably, with both the virus and the vaccine as causes, vaccination dramatically reduces the incidence of ADEM (Bennetto & scolding., 2004).

Reports of ADEM following solid organ transplantation are rare, and include one in which EBV was identified as the pathogen. It is unclear, however, whether the overall incidence of ADEM is higher in recipients of organ transplantation than in the general population. ADEM has also been described as a paraneoplastic disorder in some cases of leukemia and non-Hodgkin's lymphoma (Tomonari et al., 2003; Madan et al., 2005).

Clinical picture

The spectrum of neurological symptoms and signs in ADEM is broad, reflecting widespread central and peripheral nervous system (PNS) involvement. There may be a prodrome consisting of fever, headache, vomiting, and malaise. Neurological dysfunction generally occurs within 3-6 weeks of the triggering event and may appear abruptly or may progress over several days. Generally, ADEM is a monophasic illness and its severity may range from mild disease, with headache, subtle drowsiness, and irritability, to fulminant disease characterized by coma, decerebration, and respiratory failure (Hynson et al., 2001; John et al., 2004).

The distribution of the lesions in the nervous system determines the clinical presentation, and the commonest features are altered sensorium, pyramidal dysfunction, cerebellar ataxia, optic neuritis, and/or myelitis. Retention of urine, urinary frequency, urgency, or incontinence may occur during the acute stage and lower urinary tract dysfunction may persist even after disappearance of other neurological deficits. Seizures are not uncommon and may be of focal or generalized type. There may be additional features such as fever, headache, and meningismus, with the disease mimicking meningitis. Children under 3 years generally present only with encephalopathy, probably because they have immature myelin (Dale et al., 2000; Murthy et al.,
ADEM may have various atypical presentations. Behavioral disturbances may occasionally be the sole symptom. Presence of flaccidity and areflexia in an otherwise typical case of ADEM betrays additional PNS involvement, which is most commonly at the level of the spinal roots. This picture is frequently seen in anti-rabies vaccination-related ADEM (Marchioni et al., 2005).

Combined CNS and PNS demyelination may suggest the possibility of shared pathological epitopes. There is evidence to suggest that central (ADEM) and peripheral (acute and chronic inflammatory demyelinating polyradiculoneuropathy) demyelinating disorders represent two ends of a spectrum and overlap of clinical features may occur (Krivickas et al., 2006).

Extra pyramidal manifestations such as chorea and dystonia are rare but may be prominent in ADEM following group A streptococcal infection (Dale et al., 2001).

Occasionally patients may present with focal deficits, clinical features of raised intracranial pressure, and imaging results suggesting a mass lesion. Such a presentation of ADEM, tumefactive demyelination, may be mistaken for neoplasm till histopathology establishes the diagnosis. The pattern of neurological dysfunction may be influenced by the type of triggering event. For example, post-mumps demyelination commonly presents as myelitis, post-varicella demyelination has cerebellar ataxia as its hallmark, and rubella-associated ADEM often has an explosive onset of symptoms, seizures and mild pyramidal dysfunction (Idrissova et al., 2003; Singhi et al., 2006).

Acute hemorrhagic leukoencephalitis (AHLE) and acute necrotizing hemorrhagic leukoencephalitis (ANHLE) of Weston Hurst represent the hyper acute, fulminant form of Postinfectious demyelination as shown in table 3 (Coyle et al. 2000).

Table 3. Difference between ADEM and AHLE.

<table>
<thead>
<tr>
<th>Feature</th>
<th>ADEM</th>
<th>AHLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>Children</td>
<td>Young adult</td>
</tr>
<tr>
<td>Triggering events</td>
<td>Viral exanthema, respiratory tract infection, vaccination</td>
<td>respiratory tract infection</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Hyperacute, fulminant</td>
</tr>
<tr>
<td>Blood picture</td>
<td>Normal</td>
<td>Leukocytosis</td>
</tr>
<tr>
<td>ESR/acute phase reactant</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Urine</td>
<td>Normal</td>
<td>Proteinuria</td>
</tr>
<tr>
<td>CSF cellularity</td>
<td>Mononuclear</td>
<td>Neutrophils, red blood cells</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>Multifocal white matter lesions</td>
<td>Large lesions, mass effect, hemorrhage, necrosis</td>
</tr>
<tr>
<td>Pathology</td>
<td>Periventricular demyelination, inflammation</td>
<td>Fibrinoid necrosis, hemorrhage, necrosis, demyelination</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good</td>
<td>Bad</td>
</tr>
</tbody>
</table>

- Multiphasic disseminated encephalomyelitis

Recurrent ADEM where episodes differ clinically is termed multiphasic disseminated encephalomyelitis (MDEM). In some cases of ADEM, the premature cessation or tapering of
therapy may lead to symptom recurrence. Hence, the monophasic nature of ADEM is defined as a lack of recurrence (within 3 months) in the absence of treatment or while on appropriate treatment; and relapse that occurs during cessation or tapering of treatment should be considered as belonging to one monophasic episode (Sejvar et al., 2007).

- **Investigations**
  
  - **Cerebrospinal fluid**

  Cerebrospinal fluid (CSF) should be analyzed to exclude the differential diagnoses of ADEM, especially the CNS infections. CSF is abnormal in nearly three-fourth of ADEM patients and is characterized by pleocytosis, elevated proteins, and normal sugar values (Hynson et al., 2001). Cellular response is usually lymphocytic and counts are moderately elevated. Intrathecal oligoclonal immunoglobulin synthesis is rare and usually disappears after clinical recovery (Tenembaum et al., 2002).

  - **Electrophysiology**

  Generalized slowing is the most common finding in electroencephalography and is nonspecific. Patients with spinal cord, brain stem, or optic nerve involvement may have abnormal somatosensory, brain stem auditory or visual evoked potentials, respectively (Coyle et al., 2000).

  - **Differential Diagnosis**

In the absence of specific biological markers, the diagnosis of ADEM is based upon clinical and imaging features. Clinical evaluation, neuroimaging, and blood and CSF analysis can help to distinguish ADEM from other conditions (Hahn et al., 2007).

Herpes simplex encephalitis commonly presents with abnormal behavior and focal/secondary generalized seizures, which are more frequent and difficult to treat than in ADEM. MRI, EEG, and CSF polymerase chain reaction for Herpes simplex virus help in confirmation of the diagnosis (Hahn et al., 2007).

Japanese encephalitis presents with acute encephalopathy. MRI may show bilateral thalamic lesions, akin to ADEM. History, EEG findings, and CSF evidence of antibodies to the virus are useful for differentiation. Other infections such as bacterial meningitis and brain abscess can be ruled out by relevant investigations such as imaging and lumbar puncture. Complicated tuberculous meningitis may sometimes mimic ADEM and can be excluded if CSF sugar is normal and cultures are sterile (Hahn et al., 2007).

Neuromyelitis optica is characterized by optic neuritis and myelitis, with spinal lesions extending over three or more segments, features that may also be seen in ADEM. It may be distinguished from ADEM by the relative paucity of white matter lesions in MRI of the brain and presence of antibodies to aquaporin 4 (NMO-IgG) (Wingerchuk et al., 2006).

Patients with Behcet’s disease may present with multifocal neurological signs due to brain and spinal cord involvement. Clinical and imaging features may resemble ADEM, and the history of recurrent mucocutaneous ulcers of the mouth and genitalia will be essential to establish the diagnosis (Cikes, 2006).

Antiphospholipid antibody syndrome may also mimic the clinical and MRI features of ADEM and should be ruled out by measuring the specific antibodies (Lockshin et al., 2000).
Immune-mediated disorders such as systemic lupus erythematosus, Sjögren syndrome, and sarcoidosis may present with neurological dysfunction and multifocal white matter changes and can be diagnosed by history and relevant blood tests. Susac's syndrome may present with subacute encephalopathy, with MRI of the brain showing multiple white matter lesions; however, it can be differentiated from ADEM based on additional features such as the presence of headache, visual impairment due to retinal artery branch occlusion, sensorineural hearing loss, and specific involvement of central corpus callosum in MRI (Theodoridou & Settas., 2008).

Features that strongly favor ADEM include a history of preceding infection, polysymptomatic neurological dysfunction, encephalopathy, grey matter involvement on MRI, and absence of oligoclonal bands in CSF (Hynson et al., 2001). Distinction between these two conditions cannot be made with certainty and follow-up with serial MRI may be necessary to establish the diagnosis (Garg., 2003).

The following criteria apply when differentiating MS and MDEM (Bonev et al., 2002).

a) Altered mental state, relapses <5 months apart, rapidly evolving deficits and swift, complete recovery favour MDEM. Diplopia and asymmetrical deficits mainly favour MS.

b) The number, morphology and distribution of lesions on MRI, with lesions >1 cm or involving the cortical ribbon or thalamus, or located infratentorially, and the later disappearance of T2 abnormalities, being distinctive of ADEM. The subsequent development of new lesions on MRI is quite typical of MS.

c) Marked cerebrospinal fluid (CSF) pleocytosis and a normal IgG index are typical for ADEM and would be highly unusual in MS.

d) Bilateral prolonged visual evoked potentials (VEPs) with no history of optic neuritis occurs commonly in MS, but rarely in ADEM.

- **Postinfectious cerebellitis**

Cerebellitis is an inflammatory syndrome resulting in acute cerebellar dysfunction, which may occur as a primary infectious, Postinfectious, or post-vaccination disorder. Also known as acute cerebellar ataxia, cerebellitis occurs most commonly in young children and may be difficult to diagnose on routine clinical and laboratory studies. Encephalitis largely restricted to the cerebellum, called cerebellitis. The clinical course of acute cerebellitis is usually benign. Acute cerebellitis resulting in severe cerebellar swelling, hydrocephalus and brainstem compression is relatively rare. There have been few case reports of cerebellitis presenting with hydrocephalus in children (Van Lierde et al., 2004; Melaiki et al., 2007).

Cerebellitis may occur due to a host of viral agents, including enteroviruses, herpes viruses, HIV, and rabies. Bacterial infections have also been associated with cerebellitis, including Borrelia burgdorferi (Lyme disease), Mycoplasma pneumoniae, Legionella, and Coxiella burnettii (Q fever). In addition, cerebellitis may follow immunizations such as hepatitis, smallpox, and measles vaccination, or may occur without evidence for an antecedent or concurrent factor (Tlili et al., 2006).

Postinfectious cerebellitis is thought to be an immune-mediated response to viral infection occurring 1 to 3 weeks later (range, 1 to 43 days), characterized by ataxia and dysmetria with minimal CSF leukocytosis, no systemic features. Neuropsychiatric features are also observed. MRI is usually normal, but SPECT scans may show decreased or increased perfusion. Reports generally stress the benign nature of Postinfectious cerebellar ataxia, but residual motor and
cognitive deficits persisted for months or years, and in some cases deficits were permanent. Persistent cerebellar ataxia has also been noted in adults (Nussinovitch et al., 2003).

Differential diagnosis of Postinfectious cerebellitis should include drug overdose. A history of recent exposure to drugs such as phenytoin, carbamazepine or alcohol must be ruled out in every patient (Metwally, 2009).

- **Postinfectious Transverse myelitis**

TM exists on a spectrum of neuroinflammatory CNS conditions (Table 1), characterized by abrupt neurologic deficits associated with inflammatory cell infiltrates and demyelination. This can occur as a single episode (eg, TM, optic neuritis, or acute disseminated encephalomyelitis) or as a multiphasic condition (eg, recurrent TM, recurrent ON, neuromyelitis optica _NMO_, and MS) (kaplin et al., 2005).

Acute transverse myelitis (ATM) is a pathogenetically heterogeneous inflammatory disorder of the spinal cord, characterized clinically by symptoms and signs of neurologic dysfunction resulting in weakness, sensory loss (with or without a sensory level) and autonomic dysfunction with acute or sub acute onset. The etiologies of ATM are diverse and include vascular, infectious, Postinfectious, neoplastic, paraneoplastic, collagen vascular and iatrogenic causes (Krishnan et al., 2004).

- **Epidemiology and Clinical Picture.**

TM affects individuals of all ages, with bimodal peaks between the ages of 10 and 19 years and 30 and 39 years (Jeffery et al., 1993). Approximately 28% of reported TM cases are in children. There is no sex or familial predisposition to TM. 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. Thirty percent of all cases of pediatric TM cases referred to an academic center had a history of an immunization within 1 month of the onset of symptoms. A history of an immunization preceding the onset of TM is commonly reported (Knebusch et al., 1998).

TM is characterized clinically by acutely or sub acutely developing symptoms and signs of neurologic dysfunction in motor, sensory and autonomic nerves, and nerve tracts of the spinal cord. Weakness is described as a rapidly progressive paraparesis starting with the legs that occasionally progresses to involve the arms as well. Flaccidity maybe noted initially, with gradually appearing pyramidal signs by the second week of the illness. A sensory level can be documented in most cases. The most common sensory level in adults is the mid thoracic region, though children may have a higher frequency of cervical spinal cord involvement and a cervical sensory level (Pidcock et al., 2003).

Pain may occur in the back, extremities, or abdomen. Paresthesias are a common initial symptom in adults with TM but are unusual for children. Autonomic symptoms consist variably of increased urinary urgency, bowel or bladder incontinence, difficulty or inability to void, incomplete evacuation, or bowel constipation. Also commonly the result of sensory and autonomic nervous system involvement in TM is sexual dysfunction (Burns et al., 2001). Genital anesthesia from pudendal nerve involvement (S2-S4) results in impaired sensation in men and women. Additional male sexual problems with parasympathetic (S2-S4) and sympathetic (T10-L2) dysfunction in TM patients include erectile dysfunction, ejaculatory disorders and difficulty reaching orgasm. Corresponding female sexual problems include reduced lubrication and difficulty reaching orgasm (DasGupta et al., 2002).

In addition to the signs and symptoms of direct spinal cord involvement by the immune system in
TM, there also appears to be indirect effects manifested as depression and selective cognitive impairment that are reminiscent of what has been described in MS (unpublished observations) (Patten et al., 1997).

This depression or cognitive impairment does not correlate significantly with the patient's degree of physical disability and can have lethal consequences, resulting in suicide in severe cases if left untreated. 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% to 94% of patients have numbness, paresthesias, or band-like dysesthesias. In more than 80% of cases, patients reach their clinical nadir within 10 days of the onset of symptoms (Knebusch et al., 1998).

Acute noncompressive myelopathies were classified according to an etiologic scheme: those related to MS; systemic disease (e.g., SLE, antiphospholipid syndrome, Sjogren disease); Postinfectious; delayed radiation myelopathy; spinal cord infarct; and idiopathic myelopathy. The presence of MS or systemic disease was determined by standard criteria, whereas Parainfectious myelopathies were diagnosed on the basis of positive IgM serology or a 4-fold or greater increase in IgG levels on 2 successive tests to a specific candidate/infectious agent. Delayed radiation myelopathy was diagnosed according to clinical history, and spinal cord infarction was diagnosed on the basis of appropriate clinical and imaging findings in the absence of other likely etiologies. Idiopathic transverse myelopathy was defined in those individuals that could not be otherwise categorized (de Seze et al., 2001).

A set of diagnostic criteria were serve to distinguish TM from non inflammatory myelopathies and to distinguish idiopathic TM from TM associated with multifocal CNS and multisystemic inflammatory disorders. These criteria include Sensory, motor, or autonomic dysfunction attributable to the spinal cord, Bilateral signs and/or symptoms, Clearly defined sensory level, Inflammation defined by CSF pleocytosis or elevated IgG index or gadolinium enhancement and Progression to nadir between 4 hours and 21 days. A diagnosis of TM requires evidence of inflammation within the spinal cord. Because spinal cord biopsy is not a practical option in the routine evaluation of these patients, spinal MRI and CSF analysis are the only tools currently available to determine the presence of inflammation within the involved lesion. Gadolinium-enhanced spinal MRI and a lumbar puncture are mandatory in the evaluation of suspected TM, and it was proposed that abnormal gadolinium enhancement of the spinal cord or CSF pleocytosis or elevated CSF IgG index be required for a diagnosis of TM (Transverse MCWG., 2002).

If none of the inflammatory criteria are met at symptom onset, MRI and lumbar puncture evaluation should be repeated between 2 and 7 days following symptom onset to determine if these inflammatory criteria are met. IgG synthesis rate is a less specific indicator of CNS inflammation than is CSF IgG index and should not be used in the diagnosis (Hung et al., 1991).

Vascular myelopathies can be differentiated from TM by a progression of symptoms to maximal severity in less than 4 hours and the lack of inflammation as defined above. However, these criteria do not completely distinguish vascular myelopathies from TM, since myelopathies associated with venous infarcts or with vascular malformations may be more slowly progressive and may meet the other criteria for TM (though not an elevated IgG index) (Kaplin et al., 2005).

Differentiating idiopathic TM from TM attributed to an underlying disease is also important. Many systemic inflammatory disorders (e.g., sarcoidosis, SLE, Behcet disease, Sjogren syndrome) may involve the nervous system and TM may be one of the possible presentations. Therefore, all patients presenting with TM should be investigated for the presence of systemic inflammatory disease. Important historical information should be obtained from the patient regarding the presence of rashes, night sweats, oral or genital ulcers, shortness of breath, pleuritic pain, or
hematuria. Examination should attempt to detect the presence of uveitis or retinitis, decreased lacrimation or salivation, skin rash (malar, livedo reticularis, erythema nodosum), oral or genital ulcers, adenopathy, pleuritic or pericardial friction rub, or organomegaly. Laboratory studies should include the following: CBC with differential and smear, anti nuclear antibodies (ANA), SS-A (Sjogren syndrome-anti Ro), SS-B (Sjogren syndrome-anti La), erythrocytic sedimentation rate (ESR) and complement. Additional laboratory testing may be required if signs of a systemic vasculitis are detected (Kaplin et al., 2005).

From this evaluation, it may be possible to distinguish idiopathic TM from disease-associated TM (ie, TM associated with multifocal CNS disease or systemic inflammatory disease). This distinction is important since patients at high risk of developing MS may be evaluated more closely or may be offered immunomodulatory treatment. Similarly, patients with disease-associated TM may need to be closely followed for recurrent systemic and neurologic complications and should be offered immunosuppressive treatment to decrease the risk of recurrence (Jacobs et al., 2000).

- Neuromyelitis optica (NMO)

Since NMO was first described by Eugene Devic in 1894 as a neuroimmunological disorder characterized by simultaneous onset of bilateral optic neuritis (ON) and acute myelitis, these strict criteria had to be loosened with a growing understanding of the disease. There is now increasing evidence that NMO has to be regarded as part of a broad spectrum of diseases sharing a common pathogenesis and a comparable therapeutic responsivity (Poser&Briner, 2004; Jacob et al., 2005). In contrast to the initial understanding of NMO as a variant of MS characterized by a special regional lesion pattern, it is now considered an essentially distinct disease entity in terms of its pathogenesis. Many typical features point to a humoral, B-cell dependent origin. In addition to the identification of NMO-IgG as a biomarker of the disease, this hypothesis is supported by histopathologically detectable, perivascular deposition of antibodies and complement components (Lucchinetti et al., 2002).

NMO is often fulminant and acute, as described in the early literature. Some patients have a monophasic illness, especially in the pediatric population. Others have polyphasic illness characterized by relapses and remissions with variable degrees of recovery between episodes. In the pediatric population, NMO is frequently preceded by infection (72%). Pediatric cases typically have a monophasic course and many have complete neurological recovery. Because of pediatric NMO's frequent association with preceding infection, monophasic course, and generally good outcome, some authors consider pediatric NMO to be a variant of ADEM (Jeffery&Buncic, 1996).

The cardinal clinical features of the disorder are transverse myelitis, which is often longitudinally extensive, and optic neuritis. These two index events can occur simultaneously, in rapid succession, or they can be separated by many years. The optic neuritis can be unilateral or bilateral. Some patients have repeated episodes of optic neuritis before myelitis occurs and vice versa. In general we would consider the diagnosis in the presence of longitudinally extensive myelitis (usually more than three vertebral segments), optic neuritis and normal brain MRI, or if abnormal, atypical for MS (Cree et al., 2002).

Cerebrospinal fluid acutely may reveal a prominent pleocytosis of either lymphocytes or neutrophils and raised protein. In contrast to MS, there are usually no oligoclonal bands (in over 80%). Mayo clinic workers recently reported the discovery of NMO-IgG, which may be the first "disease specific" antibody in CNS demyelinating disease (Lennon et al., 2004).

The antibody, identified initially from Western blots in patients screened for possible paraneoplastic antibodies, is reported to have a sensitivity of 73% and specificity 91% for
neuromyelitis optica and was also positive in a significant proportion of patients deemed to be at high risk of neuromyelitis optica (that is, patients with recurrent optic neuritis or myelitis). Despite the apparent association of NMO-IgG with neuromyelitis optica, independent confirmation of this finding and indeed evidence of pathogenesis is still awaited. The Mayo group has also recently reported that the target antigen for NMO-IgG appears to be the aquaporin-4 water channel, located in astrocytic foot processes at the blood-brain barrier (Lennon et al., 2005).

A range of positive auto-antibodies (including ds-DNA) have been reported in up to 40% of patients. This can give rise to diagnostic difficulties. However there are reports of patients with unambiguous systemic lupus erythematosus, Sjögren's syndrome, and mixed connective tissue disease who have developed neuromyelitis optica. Whether they have two separate autoimmune diseases, or neuromyelitis optica is a consequence of the primary disorder, is impossible to determine clinically. Testing for NMO-IgG and pathological examination in such cases may be able to clarify this (Jacob et al., 2005).

- **Optic neuritis in children**

Childhood optic neuritis is a rare condition that differs from adult-onset optic neuritis in some clinical and evaluative aspects as discussed in table 4. It is widely accepted that in children, attacks of optic neuritis usually occur following a febrile illness, tend to affect both eyes, are frequently associated with swollen discs, improve rapidly, and have a low conversion rate to multiple sclerosis (MS). On the other hand, optic neuritis in adults is usually unilateral, predominantly affects the retrobulbar portion of the optic nerve, and presents a high conversion rate to MS. Although these facts have been accepted on a worldwide basis few series of children with optic neuritis have been studied (Lana-Peixoto et al., 2001).

**Table 4. Comparison of features of optic neuritis in adults and children**

<table>
<thead>
<tr>
<th>Adult Optic Neuritis</th>
<th>Pediatric Optic Neuritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Retrobulbar optic neuritis</td>
<td>Papillitis</td>
</tr>
<tr>
<td>Commonly associated with pain on eye movements</td>
<td>Commonly associated with headache</td>
</tr>
<tr>
<td>Most often idiopathic</td>
<td>Most often postinfectious or postimmunization</td>
</tr>
<tr>
<td>High probability of recurrent inflammatory demyelinating events in the CNS and a diagnosis of MS</td>
<td>Low probability of recurrent demyelinating events and a diagnosis of MS</td>
</tr>
</tbody>
</table>

Postinfectious optic neuritis usually develops 1 to 3 weeks after the onset of a viral or bacterial infection. It is more common in children than in adults and may be unilateral, but it is more often bilateral. It is usually caused by demyelination associated with swollen optic discs. It may occur with no evidence of neurological dysfunction or with a meningitis, meningoencephalitis, or encephalomyelitis (Selbst et al., 1983).

- **Triggering events**

Optic neuritis in children is often associated with a postinfectious or post immunization etiology. It is often preceded by a febrile prodromal illness, such as a bacterial or viral infection Post viral optic neuritis may be caused by underlying adenovirus, coxsackievirus, hepatitis A and B,
cytomegalovirus, Epstein-Barr virus (EBV), human immunodeficiency virus type 1 (HIV-1), measles, mumps, rubella, varicella zoster, and herpes zoster. Optic neuritis may also be seen in bacterial infections including anthrax, beta-hemolytic streptococcal infections, brucellosis, cat scratch disease, meningococcal infection, pertussis, tuberculosis, typhoid fever, and Whipple's disease. Post vaccination optic neuritis is more often anterior and bilateral. It may develop after vaccination with Bacillus Calmette-Guerin (BCG), hepatitis B, rabies virus, tetanus toxoid, variola virus, and influenza virus (Dadeya et al., 2004; Payne et al., 2006).

Clinical picture

Pediatric optic neuritis usually presents bilaterally associated with headache. Periorbital pain that worsens with eye movements supports a diagnosis of optic neuritis. It is not often related to MS, but is often associated with a Postinfectious or post immunization etiology. It is often preceded by a febrile prodromal illness, such as a bacterial or viral infection (Morales et al., 2000).

Optic neuritis in children usually presents with visual loss, relative afferent papillary defect, abnormal optic disc appearance, visual field defects, and color vision abnormalities. Papillitis is seen in 60% to 70% of children and in only 35% of adults (Keas et al., 1980). Both clinical and VEP parameters improve until vision recovers. In a recent 1-year follow-up study of 12 children with optic neuritis (6 with bilateral and 6 with unilateral optic neuritis), 14% of all eyes had residual visual loss and 85% had abnormal optic disc appearance; relative afferent papillary defects (67% at onset), visual field defects (58.5% at onset), and color vision defects (56% at onset) resolved 1 year later. VEP were abnormal in 83% of eyes initially and in 56% at the end of 1 year. Complete clinical and VEP recovery occurred in 3 children. Visual recovery in the other children was attained within 1 year (Tekavcic et al., 2003).

NEUROIMAGING

- **Acute disseminated encephalomyelitis**

CT scans of the brain in ADEM can be normal but when abnormal, usually shows non-specific, low attenuation sub cortical white matter lesions that may or may not enhance. In cases of acute hemorrhagic encephalomyelitis, CT scans may reveal hemorrhage and edema associated structural changes (Bennetto & scolding., 2004).

MRI is considered the imaging modality of choice. It can be normal at initial presentation and delays between 5 and 14 days from symptom onset to MRI abnormalities may occur (Bennetto & scolding., 2004; Menge et al., 2007). Cerebral lesions are usually disseminated but solitary lesions occur in about 10% to 30% of cases (Harloff et al., 2005).

Lesion patterns often seen in ADEM include widespread, multifocal or extensive white matter lesions and lesions in the deep grey matter (the thalamus and basal ganglia) with the lesion load greater than 50% of the total white matter volume (Menge et al., 2007).

Although there is no pathognomonic MRI appearance for ADEM, in one study cortical involvement or lesions in the basal ganglia were present exclusively in patients with ADEM as compared to MS (Schwarz et al., 2001).

Certain authors suggested that the diagnostic hallmark of ADEM is the demonstration of scattered, focal or multifocal (disseminated) areas of inflammation and demyelination within cerebral sub cortical and deep cortical white matter, while grey matter involvement is also seen (particularly in the thalamus) (Sejvar et al., 2007).
Five patterns of cerebral involvement have been proposed to describe the MRI findings in DEM: (a) DEM with small lesions (less than 5 mm); (b) DEM with large, confluent or tumefactive lesions, with frequent extensive perilesional edema and mass effect; (c) DEM with additional symmetric bithalamic involvement; (d) acute hemorrhagic encephalomyelitis (AHEM), when some evidence of haemorrhage can be identified into the large demyelinating lesions and (e) DEM with a pseudo-leukodystrophic pattern, with a diffuse, bilateral, symmetric and usually non-enhanced white matter involvement (Tenembaum et al., 2007).

The MRI pattern does not appear to correlate with any particular outcome or disability, as observed in a large pediatric cohort since most lesions tend to resolve on follow-up imaging studies. Spinal cord involvement in DEM has been described in 11-28%. The typical spinal cord lesion is large, swollen, showing variable enhancement and predominantly affects the thoracic region (Mikaeloff et al., 2004).

It was previously claimed that, all lesions should enhance equally following gadolinium contrast since all lesions should be active and of the same age. Newer studies, however, have shown that lesions in ADEM may evolve over several weeks and consequently only some lesions may be enhanced, or there may also be no enhancement (Schwarz et al., 2001).

Follow-up MRI scans after a minimum interval of 6 months is recommended to establish or confirm the diagnosis of ADEM at which time there should be a resolution, partial or complete, of old lesions and no new lesions. The appearance of new lesions is strongly suggestive of MS (Bennetto& scolding., 2004; Menge et al., 2007).

![Figure 4. MRI brain T1 weighted image show contrast enhancement which is characteristic of acute lesions. Also notice that many lesions are situated at the junction of deep cortical gray and subcortical white matter which is characteristic of ADEM (Metwally, 2009).](image1)

![Figure 5. Acute disseminated encephalomyelitis with small lesions. (A) Axial T2-weighted MRI showing bilateral, poorly marginated hyperintense lesions in central, periventricular, and juxtacortical white matter, (B) also involving both thalami and internal capsules, in a 17-month-old boy, 2 weeks after measles vaccination(Tenembaum et al.,2007).](image2)
Quantitative proton MR spectroscopic imaging has shown low N-acetylaspartate (NAA) and high lactate levels in acute lesions, which normalize after recovery (Mader et al., 2005).

Abnormalities in 99m Tc-HMPAO SPECT appear as areas of hypo perfusion, which are more extensive than the abnormalities seen in MRI and may parallel the time course of the disease more accurately (Itti et al., 2002). Notably, in patients with residual cognitive deficits, SPECT with acetazolamide is able to detect persistent abnormalities from areas where lesions had apparently resolved on MRI (Hahn et al., 2003).

- **Postinfectious Cerebellitis**

The sensitivity of MRI for the detection of cerebellitis is not known. A few patients with cerebellitis have presented with a normal MRI. Abnormal noncontrast MRI findings in cerebellitis have only been described in a few case reports, many of which occurred in young children (Ravi & Rozen, 2000).

Isolated cerebellar abnormalities were noted, including parenchymal hyperintensities on T2-WI, swelling, and secondary obstructive hydrocephalus. Follow-up studies showed reversals of the acute changes and the development of atrophy years later in severe cases (Hayakawa & Katoh, 1995). Abnormal MRI enhancement may be seen in some but not all cases in acute and sub acute
In Postinfectious cerebellitis the white matter show c-shaped appearance due to vasogenic edema that totally disappeared on MRI follow-up studies following complete clinical recovery. Any involvement of the cerebellar gray matter in postinfectious cerebellitis is probably secondary to white matter edema and is due to spreading of edema to the nearby neurons. Vasogenic edema fluid is retained outside the vasculature, mostly in the white matter of the brain, and within the bundles of myelinated axons of long tracts and commissural fibers (Lester et al., 1995).

This is because axons run in parallel bundles of fibers with loose extracellular space (that offer low resistance and facilitates the extension of vasogenic edema along myelinated axons which are spread apart by the edema) as opposed to gray matter, which has high cell density and is enmeshed in an interwoven network of connecting fibers that offer high resistance to the formation and spread of edema. Although the cerebellar MRI signal changes are commonly bilateral and symmetrical, cases with unilateral cerebellar abnormalities are reported (Lester et al., 1995).

As the differential diagnosis includes tumors and infarcts, DWI and FLAIR sequences should be included in all these cases. The lack of contrast enhancement helps to exclude a tumor and diffusion weighted imaging helps differentiate cerebellitis from infarction (Van et al., 2004).

**Postinfectious Transverse myelitis**

A centrally located multisegmental (3 to 8 spinal segments) MRI T2 hyper intensity that occupies more than two thirds of the cross-sectional area of the cord is characteristic of transverse myelitis. The MRI T2 hyper intensity commonly shows a slow regression with clinical improvement. The central spinal cord MRI T2 hyper intensity represents evenly distributed central cord edema. MRI T1 Hypo intensity might be present in the same spinal segments that show T2 hyper intensity although to a lesser extent. The MRI T2 hyper intensity is central, bilateral, more or less symmetrical and multi segmental (Scotti&Gerevini, 2001).
MRI T2 central isointensity or dot (within and in the core of the MRI T2 hyper intensity) might be present and is believed to represent central gray matter squeezed by the uniform, evenly distributed edematous changes of the cord (Central dot sign). It might not be of any clinical significance (Metwally, 2009).

Contrast enhancement is commonly focal or peripheral and maximal at or near the segmental MRI T2 hyper intensity. In idiopathic transverse myelitis enhancement is peripheral to the centrally located area of high T2 signal intensity rather than in the same area. The prevalence of cord enhancement is significantly higher in patients with cord expansion (Garcia-Merino et al., 2000).

Spinal cord expansion might or might not be present and when present is usually multi segmental and better appreciated on the sagittal MRI T1 images. Spinal cord expansion tapers smoothly to the normal cord, and is of lesser extent than the high T2 signal abnormality (Garcia-Merino et al., 2000).

On the other hand Multiple sclerosis (MS) plaques (and subsequent T2 hyper intensity) are located peripherally, are less than 2 vertebral segments in length, and occupies less than half the cross-sectional area of the cord. In contrast to transverse myelitis, enhancement in MS occurs in the same location of high-signal-intensity lesions seen on T2-weighted images as shown in table 5 (Metwally, 2009).

Table 5. Differences between idiopathic transverse myelitis and spinal multiple sclerosis

<table>
<thead>
<tr>
<th>Disease entity</th>
<th>T2 hyperintensity</th>
<th>Number of segments involved</th>
<th>Contrast element</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic transverse myelitis</td>
<td>Central, multisegmental</td>
<td>4-8</td>
<td>In transverse myelitis enhancement is peripheral to the centrally located area of high T2 signal intensity rather than in the very same area.</td>
<td>Nonspecific necrosis that affects gray and white matter indiscriminately and destroys axons and cell bodies as well as myelin.</td>
</tr>
<tr>
<td>Spinal multiple sclerosis</td>
<td>Peripheral</td>
<td>1-2</td>
<td>In contrast to transverse myelitis, enhancement in MS occurs in the same location of high-signal-intensity lesions seen on T2-weighted images.</td>
<td>White matter demyelination only.</td>
</tr>
</tbody>
</table>
Figure 10. (A, Precontrast MRI T1 image, B MRI T2 image) MRI study of the cervico-dorsal region in a case of acute idiopathic transverse myelitis showing multisegmental (almost 8 spinal segments) T2 hyper intensity T1 hypo intensity (representing central cord edema) occupying centrally more than 2/3 of the cross section of the spinal cord and causing mild spinal cord enlargement at the affected zone. Notice the peripheral enhancement on post contrast MRI T1 image (C) (Metwally, 2009).

Figure 11. A case with acute idiopathic transverse myelitis. Notice spinal cord swelling and the MRI T2 signal changes. Also notice the involvement of the complete cross section of the spinal cord (Metwally, 2009).

Figure 12. MRI T2 cross sectional images showing central hyper intensity occupying more than 2/3 of the cross sections of the spinal cord with central dot sign (Metwally, 2009).

- Neuromyelitis optica (NMO)
  - Imaging of brain and spinal cord

The most characteristic neuroimaging feature of NMO is longitudinally extensive T2-weighted (T2W) signal abnormality involving at least three vertebral segments. This finding is the single most useful diagnostic feature for an NMO spectrum disorder in adults. The spinal cord lesions in NMO often enhance during a relapse, although the enhancement may be patchy and may be shorter than the more extensive T2W signal abnormality (Wingerchuk et al., 2006).

The brain MRI is often normal or may show nonspecific changes. One study directly compared brain MRI scans from typical MS patients with those in NMO and found lesions in T2-weighted images in one of seven NMO patients in contrast to multiple lesions observed in all patients with MS (Wingerchuk et al., 2006).

Another study noted that with serial scans intraparenchymal white matter lesions can evolve over time in patients with NMO. A brain MRI study without evidence of demyelination at the time of presentation is considered by some to be important in establishing a diagnosis of NMO (de Seze et al., 2002).
Figure 13. Cervical spinal cord MRI in the sagittal plane of a 28-year-old woman with polyphasic neuromyelitis optica. (A) T1-weighted image showing thickening of the cord from C7 to T2 with patchy areas of subtle intraparenchymal hyper intensity. (B) T1-weighted image, post gadolinium contrast administration, showing several enhancing lesions from C7 to T2. (C) T2-weighted image showing a continuous area of increased signal intensity spanning from C6 to T3 (Metwally, 2009)

- Imaging of optic neuritis

MR imaging is more sensitive for imaging multifocal plaques in the optic nerve, chiasm or white matter. MR imaging abnormalities, reflected by increased signal intensities on the T2-weighted images and enhancement post gadolinium introduction have been demonstrated in 56% to 72% of adult patients with isolated optic neuritis and in 90% to 98% of patients with clinically definitive MS. The diagnostic yield is increased when inversion recovery sequences are used and possibly with the addition of a surface coil. The demonstration of increased signal intensity of the optic nerve and chiasm, however, are nonspecific and do not allow a diagnosis of MS (Werring et al., 2000).

The site of the lesion and the length of the longitudinal extent vary. They may be located anterior near the optic nerve head, throughout the entire orbital optic nerve, intracanalicular, and intracranial portions of the optic nerve. A single lesion or several discontinuous lesions may be present within the respective optic nerves. The retrobulbar segment is most commonly involved (Werring et al., 2000).

In cases of an acute inflammation or demyelination of one or both optic nerves, which is often a manifestation of multiple sclerosis, diffuse enlargement of the optic nerve in a cylindrical fashion will be appreciated, owing to a generalized edema of the nerve. This is easily appreciated in cases of unilateral neuritis. In cases of bilateral optic neuritis, the nerves must be measured and compared with the normal standard in order to make the determination of optic nerve widening (Noseworthy et al., 2000).

Enhancement of the optic nerve in optic neuritis is unusual but has been reported, presumably as a result of increased vascular permeability. CT scans in the coronal plane simply demonstrate a widened nerve with a homogeneous density throughout its width. In cases of optic neuritis owing to inflammatory conditions such as syphilis, toxoplasmosis, tuberculosis, or to viral infections, the CT findings are similar to those seen in the acute demyelinating process. The findings are usually totally reversible following appropriate medical treatment. In patients presenting with acute papilitis only, a normal CT scan may be obtained (Werring et al., 2000).

- Optic neuritis in children
Enhancement of the optic nerve in the orbit or the intracranial segment of the optic nerve or of the chiasm is helpful in confirming the diagnosis. Some enlargement of the optic nerve is present in optic neuritis, and a diagnosis of optic nerve glioma should not be made unless the clinical course dictates reconsideration of the diagnosis of optic neuritis (Morales et al., 2000).

Changes in the CNS white matter may confirm other neurologic involvement found on physical examination, may affect the prognosis of MS in the future, or may indicate the presence of acute disseminated encephalomyelitis (Morales et al., 2000).

**PROGNOSIS**

Postinfectious demyelinating neurological disorders are a white matter demyelinating monophasic pathological process that has a regressive, benign and self-limiting course. They must be differentiated from the more malignant and progressive Postinfectious neurological disorders such as sub acute sclerosing panencephalomyelitis (SSPE) and rubella panencephalitis (Anlar et al., 2003; Menge et al., 2007).

In Postinfectious cerebritis (ADEM), full recovery is the expected outcome in most cases and is seen in about 50% to 75% with a higher proportion (between 70% and 90%) if minor residual deficits are considered (Bennetto & Scolding., 2004; Menge et al., 2007). The average time to recovery ranges from 1 to 6 months (Bennetto & Scolding., 2004).

Suggested predictors of poor outcome include older age, female gender, degree of functional impairment at clinical onset, CSF protein level, spinal cord involvement, peripheral nervous system damage, and poor response to corticosteroids (Marchion et al., 2005; Menge et al., 2007).

The prognosis of Postinfectious Cerebellitis is usually good. Even patients with severe symptoms and increased intracranial pressure can recover completely without any sequelae. Steroids are the first line of treatment when symptoms are moderate to severe; however, most patients will recover without steroids or any specific treatment (De Bruecker et al., 2004).

Sudden deaths have been reported following fulminant cerebellitis (Levy et al., 2001). Death in acute cerebellitis is usually due to severe cerebellar swelling resulting in transtentorial and transforaminal herniations (Tlili-Graiess et al., 2006).

The visual recovery in childhood ON is usually rapid and relatively complete with more than 80% of children achieving excellent vision (20/40) (Wilejto et al., 2006). Favorable prognostic factors for visual recovery include unilateral ON and younger age of onset (Morales et al., 2001).

NMO is often fulminant and acute, as described in the early literature. Some patients have a monophasic illness, especially in the pediatric population (Jeffery & Buncic., 1996). Others have polyphasic illness characterized by relapses and remissions with variable degrees of recovery.

![Figure 14. A) T1-weighted image, post gadolinium contrast administration, coronal section of an MRI of the orbital optic nerve of a child with optic neuritis on the left side showing enhanced left optic nerve. B) T1-weighted image, post gadolinium contrast administration, axial section of the child showing enhanced left optic nerve. The arrows point to the left optic nerve that enhances along its entire orbital course (Metwally, 2009).](image)
between episodes. The proportion of patients in each of these two groups varies depending on the criteria used to define NMO. One series found that approximately one third of patients with relapsing NMO die from respiratory failure as a consequence of diaphragmatic paralysis from cervical cord lesions (Wingerchuk et al., 1999).

In this series, the most important prognostic factor was whether the disease had a monophasic or polyphasic course. The 5-year survival rate for patients with a monophasic course, typified by closely clustered occurrence of bilateral optic neuritis with myelitis (occurring within 1 month), was 90%. In contrast, the 5-year survival rate for patients with recurrent disease was 68% (Wingerchuk et al., 1999).

In the pediatric population, NMO is frequently preceded by infection (72%). Pediatric cases typically have a monophasic course and many have complete neurological recovery. Because of pediatric NMO's frequent association with preceding infection, monophasic course, and generally good outcome, some authors consider pediatric NMO to be a variant of ADEM (Jeffery et al., 1996).

Some patients with TM may experience recovery in neurological function regardless of whether specific therapy was instituted. Recovery, if it occurs, should begin within 6 months, and the vast majority of patients show some restoration of neurological function within 8 weeks (Kaplin et al., 2005).

Recovery may be rapid during the 3- to 6-month period after symptom onset and may continue at a slower rate, for up to 2 years (Pidcock et al., 2003).

Longitudinal case series of TM reveal that approximately one third of patients recover with little to no sequelae, one third are left with moderate degree of permanent disability, and one third have severe disabilities. Good outcome with normal gait, mild urinary symptoms, and minimal sensory and upper motor neuron signs occurred in 44% of patients. 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 occurred in 23% (Knebusch et al., 1998).

The patient cohort followed at Johns Hopkins is more severe with only 20% experiencing a good outcome by those definitions, likely a reflection of referral bias to a tertiary care center (Knebusch et al., 1998).

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 (Knebusch et al., 1998). The presence of 14-3-3 protein, a marker of neuronal injury, in the CSF during the acute phase may also predict a poor outcome (Irani & Kerr, 2000).

Seventy-five percent to 90% of TM patients experience monophasic disease and have no evidence of multisystem 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 (Hummers et al., 2004).

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 auto antibodies are at a greater risk of recurrence. Preliminary studies suggest that patients who have persistently abnormal CSF cytokine profiles (notably IL-6) may also be at increased risk for recurrent TM, though these findings must be validated before they are used clinically. At the current time, we do not
understand the relative contribution of these factors to gauge whether chronic immunomodulatory treatment is warranted in high-risk patients (Hummers et al., 2004).

**TREATMENT**

Public health initiatives are important for minimizing exposure to the triggering events of Postinfectious demyelinating disorders. These include implementing effective vaccination programs and avoiding vaccines containing neural tissues or enveloped viruses (Coyle., 2002).

The Treatment involves immunomodulation that aims to counter autoimmune-mediated inflammation. Though spontaneous resolution has been described, recovery is usually incomplete and hence patients presenting in the acute stage with significant, progressive neurological deficits should receive treatment (Rust et al., 1997).

It is also advisable to avoid immunization for at least 6 months after the diagnosis of ADEM as relapse into MDEM has occurred following routine vaccinations (Bennetto & scolding, 2004).

- **Corticosteroids**

In addition to immunosuppression, steroids also have anti-inflammatory and anti edema actions, and the immediate improvement following administration of steroids is likely to be due to reduction in cerebral edema. The role of corticosteroids in patients presenting late in the course of the disease is questionable (Dale et al., 2000).

Corticosteroid therapy is widely accepted as first line therapy for ADEM. The recommended treatment regime is intravenous methylprednisolone 1g daily with a cumulative dose of 3g to 5g followed by a 1 month to 2 month oral prednisolone taper (Bennetto & scolding., 2004; Menge et al., 2007).

Intravenous steroids are often instituted for patients with acute TM. Although no randomized placebo controlled study supports this approach, evidence from related disorders and clinical experience supports this treatment (Kalita & Misra., 2001; Krishnan et al, 2004).

The optic neuritis treatment trial (ONTT) administered high-dose steroids consisted of methylprednisolone 250 mg administered intravenously every 6 hours for 3 days, followed by oral prednisone 1 mg/kg daily for 11 days (Beck et al., 2004).

The study showed that intravenous methylprednisolone (IVMP) accelerates the recovery of vision in terms of visual acuity, contrast sensitivity, and visual field by 2 weeks in patients with acute ON. There was no effect of IVMP on the final visual outcome at 6 months or 10 years compared with placebo or oral prednisolone (Beck et al., 2004).

Attacks of NMO are often severe and disabling, and usually require treatment. First-line treatment is intravenous corticosteroids (1000 mg methylprednisolone intravenously for 5 consecutive days) Followed by a brief oral steroid taper (Wingerchuk et al., 2005).

- **Plasmapharesis**

Plasma exchange is another therapeutic modality, and its role in the management of demyelinating disorders that are nonresponsive to corticosteroids has been established in one randomized control trial. In most studies, 1-1.4 plasma volumes were exchanged by continuous flow centrifugation and 70% of volume was replaced by 5% serum albumin, fresh-frozen plasma, or hydroxyethyl starch (Keegan et al., 2002).
Patients received 2-20 exchanges, depending on the severity of illness and clinical response. It is likely to be effective in patients of ADEM not responding to corticosteroids, especially when given early in the course of the disease (Keegan et al., 2002).

Additionally, the use of plasma exchange in ADEM has been reported in only a small number of severe cases, usually refractory to corticosteroid or IVIG treatment (Khurana et al., 2005; Newton et al., 2005).

Plasma exchange is used because serum antibodies directed against MBP and galactocerebroside are found in patients with post-rabies inoculation ADEM, as well as intrathecal synthesis of these antibodies (Bennetto & Scolding, 2004).

In a small randomized controlled trial (crossover of true versus sham plasmapheresis) of patients with paraplegia or quadriplegia due to idiopathic CNS demyelinating diseases, 42% of patients treated with plasmapheresis showed a meaningful benefit compared with 6% of the sham treated group (Weinshenker et al., 1999).

Among this heterogeneous group of inflammatory CNS disorders, the NMO patients were most likely to respond to treatment. A retrospective review of 59 consecutive Mayo Clinic patients treated with plasmapheresis for acute, severe attacks of CNS demyelination revealed that male sex, preserved reflexes, and early initiation of treatment were associated with a greater likelihood of improvement (Keegan et al., 2002).

Improvement generally occurred rapidly following plasmapheresis (75% first noted improvement within three exchanges) and improvement was sustained. Ten of the 59 patients had NMO, and 60% of these had marked or moderate improvements in myelitis-associated paraparesis within days of commencing plasmapheresis. Plasmapheresis may also have a role in the treatment of steroid refractory optic neuritis, because the underlying pathogenic mechanisms of myelitis and optic neuritis are likely similar (Keegan et al., 2002).

Plasmapheresis is often initiated 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 within 5 to 7 days of intravenous steroids. Plasmapheresis has been shown to be effective in adults with TM and other inflammatory disorders of the CNS (Weinshenker, 1999).

Predictors of good response to plasma exchange include early treatment (less than 20 days from symptom onset), male sex, and a clinically incomplete lesion (ie, some motor function in the lower extremities, intact or brisk reflexes) (Keegan et al., 2002).

In a subsequent small case series, 7 of 10 patients with severe steroid resistant ON showed improvement in visual acuity after plasma exchange (Ruprecht et al., 2004).

- **Immunoglobulin (IVIG).**

The use of IVIG has proven effective with particular subgroups of patients showing both CNS and peripheral nervous system (PNS) involvement and some authors have proposed that in patients with evidence of polyradiculopathy, IVIG should be considered as first line therapy (Marchioni et al., 2005). The usual total dose of IVIG is 1-2 g/kg, administered over 2-5 days (Pittock et al., 2001).

IVIG is reserved for ADEM that fails to respond to corticosteroid treatment and where plasma exchange is contraindicated or difficult to access. IVIG may be preferred to plasma exchange in
cases of post-vaccination encephalomyelitis (Bennetto& scolding, 2004).

Several small studies have suggested that IVIG may have a beneficial effect in patients with optic neuritis and severe visual deficits (Noseworthy et al., 2001). However a double-blinded, randomized clinical trial did not confirm these results (Roed et al., 2005).

The use of intravenous immunoglobulin (IVIG) has been reported in several case studies as well, either alone or in combination with corticosteroids (Straussberg et al., 2001).

- **Other Immunomodulatory Treatment**

In ADEM several other therapies have been tried and used with anecdotal success. These include intravenous cyclophosphamide and mitoxantrone (Bennetto& scolding., 2004; Menge et al., 2007).

No controlled information currently exists regarding the use of other treatment strategies in patients with acute TM. Some clinicians consider pulse-dose IV cyclophosphamide (500 mg/m2 to 1000 mg/m2) for patients with TM that continues to progress despite IV steroid therapy. 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 (Krishnan et al., 2004).

CSF filtration is a new therapy, in which spinal fluid is filtered for inflammatory factors (including cells, complement, cytokines, and antibodies) prior to being reinfused into the patient. In a randomized trial of CSF filtration versus plasma exchange for acute idiopathic demyelinating radiculoneuropathy (AIDP), CSF filtration was better tolerated and was at least as effective (Wollinsky et al, 2001).

**DISCUSSION**

Postinfectious demyelinating neurological disorders are a group of neurological disorders that are characteristically Postinfectious, post vaccination in nature; they are a white matter demyelinating monophasic pathological process characterized by abrupt neurologic deficits associated with inflammatory cell infiltrates and demyelination (Metwally, 2009).

For many years after the original descriptions of post-infectious encephalomyelitis, the question of whether this was an "allergic" reaction or a direct (but delayed) CNS invasion by the infecting pathogen remained contentious. A more complicated residual question of whether CNS invasion at some time in the course of infection was a necessary precipitant of postinfectious demyelination has only more recently been answered, careful studies confirming the absence of viral invasion of the CNS in these disorders. Thus, simple systemic infection in susceptible individuals appears sufficient for the development of these disorders (Bennetto& scolding, 2004).

The spectrum of neuroinflammatory CNS conditions varies based on regional involvement of the CNS, ranging from monofocal involvement (eg, TM involving the spinal cord and isolated ON involving the optic nerve) to multifocal involvement (eg, ADEM involving the brain and spinal cord and NMO involving the optic nerve and spinal cord) (kaplin et al., 2005).

What accounts for this regional specificity is a subject of considerable research interest, for which there is no current consensus explanation. Presumably, this regional specification could result from differences inherent in CNS tissue at different sites (such as varying threshold for injury or distinct localization of signal transduction machinery or antigens) or from differential access to distinct regions of the CNS by exogenous pathogenic mechanisms (kaplin et al., 2005).
Myelin basic protein (which is the main antigen that is targeted in the immune mechanism that ends in myelin destruction) is different in different parts of the CNS. The myelin basic protein in the peripheral nerves is different from that of the CNS and this might explain why the demyelinating process may preferentially involve some parts of the CNS and spare other parts in different patients (depending upon the antigenic properties of the myelin basic protein of the involved sites) resulting in a protean clinical presentations of the same disease in different patients (Metwally, 2009).

The disease is better termed cerebral ADEM (Acute disseminated encephalitis), Spinal ADEM (acute postinfectious transverse myelitis), Cerebellar ADEM (acute postinfectious cerebellitis), Optic ADEM (Optic neuritis in children)...etc. ADEM is probably the clinico-pathological category under which all other subtypes are filed (Metwally, 2009).

Postinfectious demyelinating disorders must be differentiated from the more malignant and progressive post infectious neurological disorders such as SSPE (sub acute sclerosing pan encephalomyelitis) and other viral encephalitis (Metwally, 2009).

Subacute sclerosing panencephalitis is slowly progressive and fatal encephalitis. The disease usually occurs 3-10 years following a measles infection and is believed to be caused by this virus. Pathologically both gray and white matters are involved. In the gray matter, gliosis and perivascular infiltration by lymphocytes are found. Demyelination of variable degrees and gliosis are usually seen in the white matter (Metwally, 2009).

Because of the current widespread administration of measles vaccine, the incidence of acute measles infection has been dramatically reduced and SSPE has been virtually eliminated and forgotten. However, measles, with the associated risk for SSPE in late childhood remains a recurrent public health hazard in developing nations (Metwally. 2009).

Herpes simplex encephalitis commonly presents with abnormal behavior and focal/secondary generalized seizures, which are more frequent and difficult to treat than in ADEM. MRI, EEG, and CSF polymerase chain reaction for Herpes simplex virus help in confirmation of the diagnosis (Hahn et al., 2007).

Japanese encephalitis presents with acute encephalopathy. MRI may show bilateral thalamic lesions, akin to ADEM. History, EEG findings, and CSF evidence of antibodies to the virus are useful for differentiation (Hahn et al., 2007).

Other infections such as bacterial meningitis and brain abscess can be ruled out by relevant investigations such as imaging and lumbar puncture. Complicated tuberculous meningitis may sometimes mimic ADEM and can be excluded if CSF sugar is normal and cultures are sterile (Hahn et al., 2007).

Acute haemorrhagic leucoencephalomyelitis, or Weston- Hurst disease, is a rare, more severe (indeed commonly fatal) disorder than ADEM that probably represents a gradient of severity in the same disease. The course is more rapid, with pronounced systemic features; seizures are frequent and coma usual. Cerebrospinal fluid (CSF) analysis often reveals a raised intracranial pressure, and a pleomorphic cellular reaction with lymphocytes, neutrophils, and significant numbers of red cells, reflecting the micro-haemorrhagic process (Bennetto& scolding.,2004).

Connective tissue diseases can be characterized by central nervous system (CNS) involvement, in some patients manifested by demyelination areas in the white matter of the brain and spinal cord, which are difficult to differentiate from multiple sclerosis (MS) and other demyelinating processes, such as transverse myelitis and optic neuritis. Demyelinating process may be the feature
of nervous impairment in systemic lupus erythematosus, Behcet's disease (BD), Sjögren's syndrome (SS), systemic sclerosis (SSc) or very rarely other systemic autoimmune diseases (Cikes., 2008).

Patients with Behcet's disease may present with multifocal neurological signs due to brain and spinal cord involvement. Clinical and imaging features may resemble ADEM, and the history of recurrent mucocutaneous ulcers of the mouth and genitalia will be essential to establish the diagnosis (Cikes, 2006).

Antiphospholipid antibody syndrome may also mimic the clinical and MRI features of ADEM and should be ruled out by measuring the specific antibodies (Lockshin et al., 2000). Immune-mediated disorders such as systemic lupus erythematosus, Sjögren syndrome, and sarcoidosis may present with neurological dysfunction and multifocal white matter changes and can be diagnosed by history and relevant blood tests (Theodoridou & Settas., 2008).

In a patient presenting with neurological dysfunction and MRI showing multiple white matter lesions, the most important differential diagnosis is MS. Distinguishing between ADEM and MS is a diagnostic challenge and has important therapeutic and prognostic implications. There are several clinical, imaging, and laboratory parameters that may be useful to distinguish between the two (Brinar, 2004).

The degree of similarity with MS varies a little according to different authors. Myelin is lost, but whether this mainly represents primary rather than secondary demyelination is not wholly clear. Areas of necrosis may be found (though some authors would suggest such change indicates a diagnosis of acute haemorrhagic encephalomyelitis rather than ADEM), and the presence of meningeal inflammation may also provide some distinction from MS. An astrocytic response is common to both disorders (Bennetto & Scolding, 2004).

In general ADEM is an autoimmune meningo-encephalitic process that is associated with disturbed level of consciousness, seizures and meningeal irritation signs (multiple sclerosis is not an encephalitic process) (Brinar., 2004).

Multiple sclerosis is characterized by dissemination in time and space, but not defined by it. Its distinctive feature is the plaque with sharply defined borders. Other inflammatory demyelinating diseases such as DEM may share the characteristic dissemination but not the defining feature. Relapsing DEM, while more frequent in children, unquestionably occurs in adults. The reality of its existence is strongly bolstered by experimental evidence. The clinical manifestations of DEM, especially in children, are valuable clues, as the characteristic symptoms rarely are seen in MS (Poser & Brinar., 2007).

The clinical history, aided by MRI is the most reliable means of distinguishing between acute DEM and the initial bout of MS, or between recurrent DEM and relapsing- remitting multiple sclerosis (RRMS). The lesion load is heavy, gray matter is frequently affected, the lesions are much larger than those commonly seen in MS, and in the early stages of the disease, most of the lesions enhance with gadolinium. Both brain and spinal cord imaging should be obtained in every case of clinically isolated syndrome (CIS). Spinal cord MRI is particularly valuable in that the long lesion of DEM is essentially never seen in MS (Brinar, 2004).

- **Conclusion**

Benign regressive postinfectious neurological disorders (BRPIND) comprises a group of poorly understood inflammatory/demyelinating white matter disorders of cerebrum, cerebellum and spinal cord. that is characteristically postinfectious in nature. It is unclear what are the triggers
and effector mechanisms resulting in white matter insult, though tantalizing clues have emerged. These disorders exist on a continuum of postinfecitious neuroinflammatory and white matter demyelinating background that includes Guillain-Barre syndrome (GBS), acute disseminated encephalomyelitis (ADEM), Neuromyelitis Optica (NMO), optic neuritis, transverse myelitis and postinfecitious cerebellitis. Each of these disorders differs in the spatial and temporal restriction of inflammation within the nervous system. However, clinical and pathologic studies support the notion that there are many common features of the inflammation and white matter demyelination that is postinfectious or postvaccinal in nature.

These disorders might coexist in various combinations in the same patient or might present clinically as an isolated disease. It looks like that the division between these postinfectious disorders is indistinct, which is suggestive of a clinical continuum. These disorders simply represent a single disease with different clinical presentations. Myelin basic protein (which is the main antigen that is targeted in the immune mechanism that end in myelin destruction) is different in different parts of the CNS. The myelin basic protein in the peripheral nerves is different from that of the CNS and this might explain why the demyelinating process may preferentially involves some parts of the CNS and spare other parts in different patients (depending upon the antigenic properties of the myelin basic protein of the involved sites) resulting in a protean clinical presentations of the same disease in different patients. Different areas of the white matter within the CNS and the peripheral nervous system are targeted by the inflammatory demyelinating pathological process in various combinations in different patients depending upon the antigenic properties of the myelin basic protein in these areas resulting in some patients having their optic nerves, cerebrum, and spinal cord involved (acute disseminated encephalomyelitis), other patients having their optic nerves and spinal cord involved (neuromyelitis optica) and so on. [27]

Myelin destruction and inflammatory white matter demyelination is an immune-mediated mechanism in Benign regressive postinfectious neurological disorders (BRPIND) that is triggered by antecedent infection. The immune mechanisms include antibody-mediated complement dependant myelinolysis, T-cell mediated lysis of Schwann cells and T-cell mediated induction of an immune reaction with release of cytokines and recruitment of inflammatory cells including macrophages.

References


25.


40. Ishizu T, Minohara M, Ichiyama T. CSF cytokine and chemokine profiles in acute


76. Lalive PH, Menge T, Delarasse C. Antibodies to native myelin oligodendrocyte glycoprotein are serologic markers of early inflammation in multiple sclerosis. Proc Natl Acad Sci U SA 2006; 103:2280-2285.


80. Lana-Peixoto1 Marco Aurélio, Cardoso de Andrade2 Gustavo. the clinical profile of childhood optic neuritis Arq Neuropsiquiatr 2001; 59:311-317.


119. Sejvar JJ, Kohl KS, Bilinsky R. Encephalitis, myelitis, and acute disseminated


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