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# Autoimmunity – Multiple Sclerosis

## Chapter 45

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Dreams are nothing but incoherent ideas, occasioned by partial or imperfect sleep.

Benjamin Rush (1746–1813)

### EPIDEMIOLOGY

MS is a common cause of neurological disability in middle-aged adults. This disease affects over one million people worldwide and is very common within the USA (Minden et al., 1993; Pugliatti et al., 2002; O'Connor et al., 2002). Age, sex, race, geographical latitude, genetics and environmental exposure are risk factors for developing MS.

The median age of onset of MS is approximately 24 years of age (Minden et al., 1993) with a female to male ratio of two to one (O'Connor et al., 2002). The mean age of death of MS patients is 58 years old, compared to the general national average in the USA of 72 years old (Minden et al., 1993). Within the USA, MS is observed more often in Caucasians compared to African-Americans (Minden et al., 1993). However, the typical clinical course is more severe within African-Americans who are affected (Pugliatti et al., 2002). In regard to geographical patterns, a higher incidence of MS occurs when moving either more north or south of the equator, especially in countries with colder climates (Pugliatti et al., 2002). This latitude effect is also present within the USA as the incidence of MS is highest within the upper Midwest and Northeast compared to the South (Minden et al., 1993).

Family studies have shown that genetic factors contribute to MS (Sadovnick, 2002; Herrera and Ebers, 2003;

Kenealy et al., 2003; Willer et al., 2003). The risk for developing MS within dizygotic twins is the same as for other siblings (3–5 per cent). However, the risk for monozygotic twins is greater than 30 per cent (O'Connor et al., 2002; Willer et al., 2003). A greater than 10-fold increased risk of developing MS exists within individuals having certain human leukocyte antigens (HLA) genotypes (O'Connor et al., 2002; Sadovnick, 2002; Herrera and Ebers, 2003; Kenealy et al., 2003). The major predisposing associated haplotype is HLA-DR2 in cellular typing nomenclature (DR15,DQ6 by serology and DRB5\*0101-DQA1\*0102-DQB1\*0602 by sequence-based terminology) (Haegert and Francis, 1993; Hillert, 1994). Even though an association between HLA class II DRB1\*15 and DRB1\*17 alleles and MS has been seen in individuals of northern European and Mediterranean descent, the presence of these haplotypes does not preclude the development of MS (Sadovnick, 2002; Herrera and Ebers, 2003; Kenealy et al., 2003). Genetic interactions may also occur between certain haplotypes and certain T cell receptors, immunoglobulins and tumor necrosis factors which may lead to an increased chance of developing MS (O'Connor et al., 2002; Alizadeh et al., 2003).

Not only genetic but also one or more exogenous or environmental factors may influence the development of MS (O'Connor et al., 2002). Although twin studies have provided strong evidence for genetic factors in the development of MS, the concordance rate for monozygotic twins has never been demonstrated to be greater than 40 per cent (Compston and Ebers, 1990; Sadovnick, 2002;

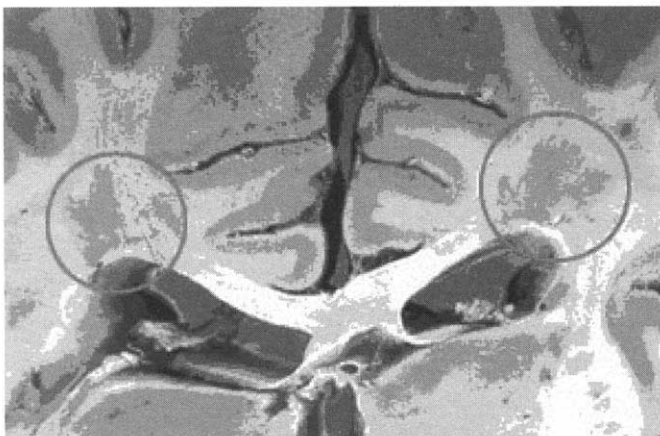
Willer et al., 2003). Thus, at least 60 per cent of persons with an identical twin who has MS will not develop the disease.

Certain foods, toxins, psychological stress, anesthesia, surgery and physical trauma have been implicated in the development of MS (O'Connor et al., 2002). However, no direct causal relationships have been proven to date. Overall, it is believed that both genetic and environmental factors are responsible for the subsequent development of MS within a susceptible individual (O'Connor et al., 2002). The resulting disability that results from MS leads to a major burden not only to the affected individual but also to the health care system and society (Whetten-Goldstein et al., 1998).

## PATHOPHYSIOLOGY

Loss of myelin due to inflammation with limited subsequent remyelination are the two cardinal features of MS (Noseworthy et al., 2000). Breakdown of the blood–brain barrier is typically observed with early inflammatory changes (Smith et al., 1993). Immunocytochemical studies of active MS lesions have shown damage to vascular walls with intramural deposition of complement on smooth muscle components as well as protein-rich leakage (Noseworthy et al., 2000). These abnormalities can occur within hours to days of an acute attack and slowly resolve over subsequent weeks to months (Poser, 1986).

Typical pathological findings seen in MS are plaques containing inflammatory cells scattered throughout the affected parenchyma and arranged in cuffs around blood vessels (Figure 45.1). Inflammatory cells that are stimulated during an acute flare include macrophages, lymphocytes, large mononuclear cells and plasma cells (Prineas and Wright, 1978; Tourbah et al., 1993). In MS macrophages are immunologically active and can stimulate T cells leading to the subsequent production of large quantities of cytokines and inflammatory mediators (Hafler and Weiner, 1995; Hohlfeld et al., 1995; Martin and McFarland, 1995;



**Figure 45.1** Circles surround periventricular plaques seen on pathology.

O'Connor et al., 2000). These cytokines can be either pro- or anti-inflammatory in nature (Hafler and Weiner, 1995) with a T cell either stimulatory or inhibitory depending on surrounding environment factors (Hafler and Weiner, 1995; McFarland, 1995; Hohlfeld, 1997).

Axonal loss has also shown to be a key factor in the pathogenesis of MS and is responsible for part of the irreversible clinical impairment and disability (O'Connor et al., 2002). Axonal loss could stem from:

- 1 direct autoimmune attack against axons
- 2 a 'bystander injury' due to exposure of axons to immune attack following demyelination
- 3 degeneration of axons as a result of chronic demyelination
- 4 primary degeneration of axons, stimulating a secondary inflammatory response (Trapp et al., 1999; Lassmann, 2003).

The importance of these potential associated mechanisms remains to be determined.

## ETIOLOGY

The exact etiology of MS remains unknown, but it is believed that this disease most likely results from a viral infection. These organisms can induce disturbances within a previously competent or compromised immune system (Allen and Brankin, 1993; Cook et al., 1995; O'Connor et al., 2002). MS may either be due to infection by viruses that directly induce neurological dysfunction from the onset or result from reactivation later in life. A number of organisms or their nucleic acids have been observed within the CSF or brain parenchyma of patients with MS (Booss and Kim, 1990; O'Connor et al., 2002). These organisms include mycoplasma (Cavassut, 1930), protozoa (Bequignon, 1956), spirochetes (Ichelson, 1957), as well as a number of both DNA and RNA viruses, such as herpes simplex viruses types 1, 2 and 6 (Sanders et al., 1996), rabies virus (Bychkova, 1964), parainfluenza virus type I (ter Meulen et al., 1972), coronavirus (Talbot et al., 1996), canine distemper virus (Rohowsky-Kochan et al., 1995), measles virus (Haase et al., 1981), human immunodeficiency virus type 1 (HIV-1) (Berger et al., 1989) and human T lymphotropic virus type I (HTLV-I) (Salmi et al., 1983; Greenberg et al., 1989). However, none of the above organisms have been successfully isolated from large groups of clinically definite MS patients. Furthermore, within MS patients infected with these organisms, levels did not correlate with disease activity (O'Connor et al., 2002).

Despite the lack of definitive evidence of a viral source for MS, it is commonly believed that one or more viruses may be responsible for the development of MS within certain genetically susceptible individuals (Allen and Brankin, 1993; Cook et al., 1995). One hypothesis for the

mechanism in which viruses cause MS has been proposed which involves both direct and indirect pathways (Clausen, 2003). Viruses could directly damage and lead to functional alterations within oligodendrocytes, resulting in demyelination. Because a single oligodendrocyte can send processes to many neighboring axons, impairment can cause demyelination within a large volume of brain tissue (Silberberg, 1986). Viral invasion may also directly damage endothelial cells within blood vessels and lead to a disruption of the blood–brain barrier. This may subsequently allow for indirect mechanisms in which immunocompetent or activated T lymphocytes can gain entry into the CNS. Demyelination could develop due to the release of cytokines from these activated cells (Poser, 1986; Noseworthy et al., 2000).

Another theory has suggested that viral infection leads to demyelination due to repeated constant exposure of certain antigens to the immune system (Clausen, 2003). An inappropriate immune sensitivity results with antibodies cross-reacting against the oligodendrocyte and/or vascular endothelial cells (Allen and Brankin, 1993; Cook et al., 1995). Alternatively, viral infection might cause a disorder of immunoregulation and secondary demyelination (Salonen et al., 1982). Myelin may not be the primary focus of attack but instead may be an ‘innocent bystander’ with the large-scale destruction that occurs resulting from the interaction of the immune system and reactivated viral infection (Silberberg, 1986; Clausen, 2003).

## CLINICAL MANIFESTATIONS

There are no clinical findings that are unique to MS (Kurtzke, 1983; Lisak, 2004). Symptoms and signs that result from MS can include neurological, neuro-ophthalmologic and psychiatric features.

### Neurological signs and symptoms

Neurological signs and symptoms of MS are caused primarily by both demyelination and axonal loss that can occur within the cerebral hemispheres, cerebellum, brain stem and spinal cord. Demyelination and destruction of axons produce a variety of somatosensory, motor, cerebellar symptoms and signs (Miller, 1990; Matthews et al., 1991; Kinkel and Rudick, 2002; Lisak, 2004).

Sensory symptoms are the most common clinical manifestations of MS and present as the initial manifestation of the disease in over 70 per cent of MS patients (Kurtzke, 1970; McAlpine, 1972). The anatomic distribution of sensory symptoms often does not correspond to a recognized dermatome, peripheral nerve or homuncular pattern. Some patients may complain of numbness, whereas others are bothered by sensations of tingling, burning or tightness.

Up to 40 per cent of cases of MS will initially present with motor symptoms and signs (Mueller, 1949; Miller,

1990; Matthews et al., 1991; Kinkel and Rudick, 2002; Lisak, 2004). Patients with motor dysfunction may complain of heaviness, stiffness and/or pain in one or more extremities. Typically these symptoms are present in the legs more often than within the arms. Spasticity can also develop and often produces significant discomfort or frank pain (Hooge and Redekop, 1992, 1993).

Cerebellar symptoms and signs can sometimes be seen on initial presentation but typically occur in patients with well-established MS. Cerebellar signs usually manifest as gait ataxia, limb dysmetria and intention tremor (Kurtzke, 1970; McAlpine, 1972). Many patients develop a non-specific impairment of articulation leading to a speech disturbance called ‘scanning speech’.

A Lhermitte’s sign, sudden electric-like sensations that radiate down the spine or extremities upon neck flexion, can also be observed. This sign results from a demyelinating lesion in the cervical spinal cord. However, it is not pathognomonic for MS and can be observed within patients with cervical pathology, neck trauma, radiation myelopathy and subacute combined degeneration of the spinal cord (Matthews et al., 1991).

Fatigue can also be seen within MS patients and is usually present in greater than 80 per cent of individuals eventually diagnosed with MS (Tartaglia et al., 2004; Racke and Hawker, 2004; Fisk et al., 1994; Vercoulen et al., 1996; Kinkel and Rudick, 2002; Lisak, 2004). This symptom is particularly bothersome for those with mild to moderate disease. Many patients will complain of a complete lack of motivation. These symptoms can be so severe that they are unable to carry out even the most simple activities of daily living (Miller, 1990; Kinkel and Rudick, 2002). Typically these patients experience fatigue in the setting of motor difficulties (Vercoulen et al., 1996).

### Neuro-ophthalmologic manifestations

Optic neuritis (ON) may be the initial presentation of MS (Leibowitz and Alter, 1968; Kuroiwa and Shibasaki, 1973; McDonald and Barnes, 1992). ON usually presents as acute or subacute unilateral eye pain (about 2/3 of the time) accentuated by retro-orbital pain with eye movements. A variable degree of visual loss within the central vision can be observed (Leibowitz and Alter, 1968; Kuroiwa and Shibasaki, 1973). Often the patient with ON will complain of a loss of color vision (red desaturation). Physical examination can reveal a relative afferent pupillary defect. Most often the lesion in ON is retrobulbar with the fundoscopic examination normal during the acute stages (Nordmann et al., 1987). Later, as the disease progresses, the optic disc can become pale as a result of axonal loss and resultant gliosis with temporal pallor present. Typically acute ON will get worse over a time period of several days to 2 weeks, with subsequent visual recovery slowly occurring over 2–4 weeks (Beck et al., 1994). Improvement from ON can continue to progress for up to 1 year after the initial onset of visual symptoms (Beck et al., 1993c).

The Optic Neuritis Treatment Trial (ONTT) was a multicenter trial that attempted to assess the benefit of treatment with corticosteroids on visual recovery in acute optic neuritis (Optic Neuritis Study Group, 1991, 2004; Beck et al., 1993a; Jacobs et al., 2000; Liu, 2000; CHAMPS Study Group, 2001). The ONTT enrolled 457 patients, aged 18–46 years, with acute unilateral optic neuritis. Patients in the ONTT were randomized to one of three treatment protocols:

- 1 oral prednisone (1 mg/kg/day) for 14 days with a 4-day taper
- 2 intravenous (IV) methylprednisolone sodium succinate (250 mg every 6 h for 3 days) followed by a course of oral prednisone (1 mg/kg/day) for 11 days with a 4-day taper
- 3 oral placebo for 14 days (Beck et al., 1992; Trobe et al., 1996).

The major findings of the ONTT were:

- 1 IV methylprednisolone hastened the recovery of visual function in acute optic neuritis, but had no long-term benefits in visual outcome at either 6 months or at 10 years when compared to placebo or oral prednisone. This medication was most beneficial if given within the first 15 days of presentation
- 2 treatment with oral prednisone alone was associated with an increased rate of recurrent optic neuritis in not only the affected eye but the contralateral eye as well at both 6 months and at 10 years
- 3 monosymptomatic patients in the IV methylprednisolone group had a reduced rate for the subsequent development of MS during the first 2 years of follow up, but this benefit was not observed beyond 2 years (Optic Neuritis Study Group, 1991, 2004).

These results suggest that no effective treatment exists for preventing patients who develop acute ON from subsequently developing long-term visual disability (Söderström, 2001; Biousse and Newman, 2002; Foroozan et al., 2002).

The average interval from initial presentation of ON symptoms until subsequent development of MS can vary but typically occurs within 5–7 years (Optic Neuritis Study Group, 1991, 2004). Brain MRI is a powerful technique for predicting subsequent events in MS patients with acute ON (Optic Neuritis Study Group, 1991, 2004; Beck et al., 1993b). The presence of even a single characteristic brain MRI lesion at the time of acute ON is associated with a significantly increased risk (Optic Neuritis Study Group, 2004). More than one lesion on MRI does not substantially increase this risk. Patients with no lesions on MRI and with atypical ON have a very low risk of developing MS.

Internuclear ophthalmoplegia (INO) refers to abnormal horizontal ocular movements with loss or delayed adduction and horizontal nystagmus of the abducting eye due

to a lesion in the medial longitudinal fasciculus on the side of diminished adduction (Reulen et al., 1983; Müri and Meienberg, 1985; Gass and Hennerici, 1997). The adduction weakness may be manifest as:

- 1 complete inability to adduct the eye beyond the midline
- 2 a mild limitation of adduction associated with decreased velocity of adduction or
- 3 a mild decrease in the velocity of adducting saccades without any limitation of adduction (Meienberg et al., 1986).

Patients with a unilateral INO can also have a skew deviation with the higher eye on the side of the lesion (Thömke et al., 1992).

### Psychiatric manifestations

Neuropsychiatric manifestations may appear at any time of the disease and commonly precede definitive neurological manifestations by months to years (Schiffer and Babigian, 1984; Herndon, 1990; Hutchinson et al., 1993). Overall, cognitive changes can be observed in almost 50 per cent of MS patients (Patti et al., 2003; Benedict et al., 2004). Symptoms tend to progress as the disease worsens (Hutchinson et al., 1993). The most common neuropsychiatric signs and symptoms are disturbances in cognition especially within recent memory, information processing, abstraction and conceptual reasoning (Herndon, 1990; Miller, 1990; Ron and Feinstein, 1992; Benedict et al., 2000; Patti et al., 2003; Lisak, 2004).

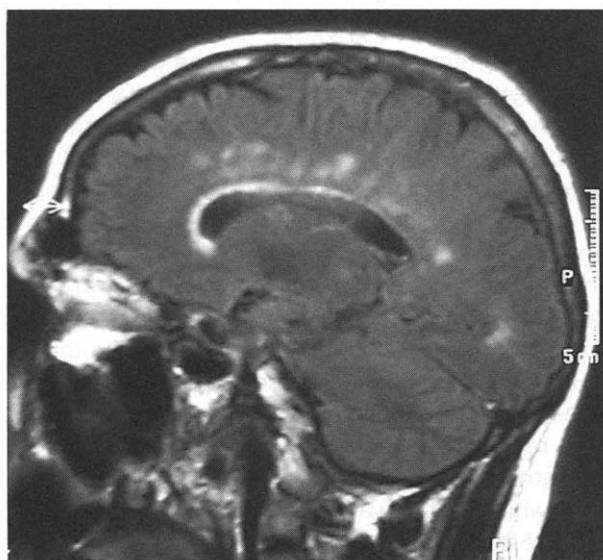
Depression can also be a common finding in MS patients with up to 75 per cent experiencing some form of depression during their illness (Schiffer and Babigian, 1984; Kinkel and Rudick, 2002; Patti et al., 2003; Lisak, 2004). The degree of depression can range from mild to severe (Patti et al., 2003; Lisak, 2004) and typically develops after other clinical manifestations. This progression suggests that depression may result within individuals from a greater understanding and knowledge of their disease process rather than due to a direct reaction to the illness. Depression may be quite difficult to identify in some patients, as symptoms can overlap with other disease features, including fatigue, diminished attention and concentration and pain (Kinkel and Rudick, 2002).

### GUIDES TO THE DIAGNOSIS OF MS

MS is clinically diagnosed with additional support coming from neuroimaging and paraclinical sources, such as cerebral spinal fluid and evoked potentials. A detailed clinical history requires documentation of at least two discrete episodes within time affecting the CNS (Poser et al., 1983). The McDonald criteria have been developed to assist in the diagnosis of MS. Based on the extent to which the diagnostic criteria are fulfilled for a particular

clinical presentation, patients can be categorized as 'MS' (diagnostic criteria fulfilled), 'possible MS' (criteria not completely met – patient at risk but diagnostic evaluation is equivocal) or 'not MS' (criteria fully explored and not met) (McDonald, et al., 2001). The McDonald criteria have successfully been shown to accurately diagnose MS in patients with recent onset of a clinically isolated syndrome. At least two studies have evaluated the sensitivity and specificity of these criteria. One study prospectively evaluated 50 patients at 3 months, 1 year and 3 years of follow up and demonstrated a sensitivity and specificity of 83 per cent (McDonald, et al., 2001). A second study analyzed 139 patients using a retrospective analysis found similar results (Dalton et al., 2004).

The diagnosis of MS is assisted by neuroimaging findings that show evidence of dissemination of lesions within time and space. MRI is particularly sensitive for detecting lesions in the brain stem, cerebellum and spinal cord (Cutler et al., 1986; Ormerod et al., 1986; Grossman and McGowan, 1998; Fazekas et al., 1999; Arnold and Matthews, 2002; Bot et al., 2004) (Figure 45.2). Gadolinium (Gad) can be injected and assists in the diagnosis of newly active plaques. Gad enhancement diminishes or disappears after treatment with corticosteroids due to restoration of the blood–brain barrier. Lesions that are more suggestive of MS include those that are 6 mm or more in diameter, ovoid, abutting the lateral ventricles and infratentorial (Arnold and Matthews, 2002). Usually lesions will be observed within the periventricular region, corpus callosum, centrum semiovale and, to a lesser extent, within deeper white matter structures and the basal ganglia. Lesions seen on MRI in MS patients often will fluctuate over time (Grossman and McGowan, 1998; Arnold and Matthews, 2002) with some lesions disappearing, some reappearing, some enlarging, some decreasing and some remaining unchanged (Grossman and



**Figure 45.2** MRI of patient showing multiple demyelinating plaques.

McGowan, 1998; Arnold and Matthews, 2002). However, the extent of MRI abnormalities may not correlate with the degree of clinical disability.

Despite these advances in neuroimaging, lesions that are observed may not always be MS (Arnold and Matthews, 2002). Healthy patients over 50 years of age can have similar lesions due to atherosclerotic and hypertensive cerebrovascular disease, CNS vasculitis, migraine, sarcoidosis, venous angiomas and both primary and metastatic brain tumors (Paty, 1990; Boppa and Zagzag, 1993; Arnold and Matthews, 2002). Therefore neuroimaging findings alone cannot be used in the diagnosis of MS.

In addition to demyelinating lesion burden and activity, neuronal and axonal loss are likely to have a crucial role in the development of neurological and visual impairment in MS (Raine and Cross, 1989; Ferguson et al., 1997). Proton MR spectroscopy (MRS) can also provide information on phospholipid metabolism as well as other metabolic components, such as N-acetyl aspartate (NAA) (an exclusively neuronal marker), creatine phosphate (Cr) (a marker of energy metabolism), choline (a cell membrane component), and lactic acid (LA) (Larsson et al., 1991; DeStefano et al., 1995; Kimura et al., 1996; Matthews et al., 1996). Acute MS lesions can have a decrease in NAA and an increase in LA. Chronic MS brains have a reduced amount of NAA as well as a reduced NAA/Cr ratio due to loss of neurons or axons (DeStefano et al., 1995).

### Cerebrospinal fluid analysis

Examination of CSF can also assist in the diagnosis of MS (McDonald et al., 2001). Typically glucose and protein levels in the cerebrospinal fluid (CSF) are normal in MS. A few mononuclear cells per cubic millimeter may also be observed. Often a significant elevation of the CSF immunoglobulin level relative to other protein components is present. This immunoglobulin increase is predominantly IgG with an excess primarily in lambda and kappa light chains (Whitaker et al., 1990; Fukazawa et al., 1993). The IgG level may be expressed as a percentage of total protein (normal < 11 per cent), as a percentage of albumin (normal < 27 per cent) or by the use of the IgG index (normal value < 0.66) (Whitaker et al., 1990). CSF IgG production abnormalities, as measured by the IgG index, are found in more than 75 per cent of clinically definite MS patients (Miller et al., 1983; Zeman et al., 1993, 1996; Lowenthal and Karcher, 1994). An elevation in oligoclonal bands can also be observed and is seen in more than 80 per cent of patients with clinically definite MS (Zeman et al., 1993, 1996). More recently, the presence of serum anti-myelin basic protein (MBP) antibodies can predict progression to MS after a clinically isolated event. MBP is one of the major components of myelin and is normally negligible in the CSF. During an acute MS flare it rises and falls quickly (Warren and Catz, 2003).



### Visually evoked potentials (VEPs)

VEPs are electric potentials or voltages evoked by brief sensory stimuli. These signals are delayed, attenuated or absent within regions of demyelination. An abnormal VEP is seen in 85 per cent of clinically definite MS cases (Brooks and Chiappa, 1982). However, almost any patho-physiologic process that damages the optic nerve can affect VEP results (Asselman et al., 1975; Wilson, 1978). In addition, even though VEPs are considered an 'objective' test and are used in the McDonald criteria they may be affected by the patient's age, attention and concentration (Regan, 1972; Regan et al., 1977; Hawkes and Stow, 1981).

## TREATMENT

Although some patients with MS have an illness that is slowly progressive from onset (primary progressive MS, or PPMS) and others have an acute, rapidly progressive disease (acute MS), most cases of MS begin with a relapsing-remitting course (RRMS). While not all patients with RRMS develop a progressive course, secondary progressive MS (SPMS) is a long-term sequela of RRMS for many patients (Lublin et al., 1996). While patients with RRMS have clearly defined relapses with a lack of disease progression during inter-relapse intervals, SPMS is characterized by disease progression and worsening of neurologic baseline following an initially relapsing-remitting course. Treatments must therefore be targeted not only toward reducing inflammatory responses and numbers of exacerbations in patients with MS, but ideally should minimize disease progression and axonal loss (Noseworthy et al., 2000; O'Connor, 2002).

Corticosteroids are often used in acute attacks. Treatment usually consists of a short course of IV methylprednisolone, 500 to 1000 mg daily for 3–5 days, with or without a taper. As demonstrated by the ONTT, oral steroid therapy alone should probably not be offered to patients with acute optic neuritis. Patients treated with oral prednisone alone are more likely to suffer recurrent episodes of optic neuritis than those treated with methylprednisolone followed by oral prednisone taper (Optic Neuritis Study Group, 1991, 2004).

Treatment for RRMS consists of starting disease modifying medications, including the interferons or glatiramer acetate. These medications can lead to a decrease in the frequency of relapses and reduce disability in patients with RRMS.

### Interferon-beta-1b (Betaseron)

This drug is a cytokine that modulates immune responsiveness, although its precise mechanism of action in MS is unknown. Interferon-beta-1b is administered every other day subcutaneously by self-injection (Arnason, 1993). The efficacy of interferon-beta-1b was demonstrated in a

double blind, placebo-controlled trial of patients with RRMS who were randomly assigned to either interferon-beta-1b or placebo (Paty and Li, 1993). After 2 years, the exacerbation rate was significantly lower for patients receiving interferon-beta-1b compared to placebo. The INCOMIN study (*independent comparison of interferons*) compared interferon-beta-1b (Betaseron) with intramuscular interferon-beta-1a (Avonex) in 188 patients with relapsing-remitting MS and found the former to be more effective on both clinical and MRI outcomes. Over a 2-year period, patients had more relapse free periods as well as developing fewer new MRI lesions on interferon-beta-1b compared to those assigned to interferon-beta-1a (Durelli et al., 2002).

### Interferon-beta-1a (Avonex)

Like interferon-beta-1b this drug is a cytokine that modulates immune responsiveness. Interferon-beta-1a is given by weekly intramuscular injections. The efficacy of interferon-beta-1a in patients with RRMS was demonstrated in a randomized, double blind study comparing interferon-beta-1a to placebo (Jacobs et al., 1996). Over a 2-year period, patients treated with interferon-beta-1a had a reduction in the annual exacerbation rate, a decrease in MRI lesion volume burden and less disability compared to patients receiving placebo. In a subsequent study, the Controlled High-Risk Avonex MS Prevention Study (CHAMPS), patients newly diagnosed with MS (those who suffered a first acute clinical demyelinating event and who also had evidence of prior subclinical demyelination on brain MRI) were treated with either Avonex or placebo after initial treatment with corticosteroid therapy. Treatment with Avonex led to a significantly lower probability of developing clinically definitive MS during the subsequent 3 years of follow up compared to patients who were treated with corticosteroids followed by placebo (Jacobs et al., 2000; Galetta, 2001; CHAMPS Study Group, 2002). An extension study of the CHAMPS with all patients on active interferon beta-1a therapy, the Controlled High-Risk Avonex MS Prevention Surveillance (CHAMPIONS) has provided additional data in support of early use of Avonex for the treatment of MS (Kinkel et al., 2003).

Interferon-beta-1a at higher doses (Rebif) has also been shown to be beneficial in RRMS. This medication is given subcutaneously three times a week. The efficacy of interferon-beta-1a was shown through the Prevention of Relapses and Disability by Interferon-beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) study. In this study RRMS patients were given placebo or Rebif three times per week for 2 years. Treatment with Rebif also led to a significant reduction in the MRI lesion burden. Approval for Rebif in the USA arose from results from the EVIDENCE trial in which Rebif was compared directly to Avonex (PRISMS Study Group, 1998). Relapse rate was less frequent and the mean number of active MRI lesions was lower for patients on Rebif compared to those on Avonex.

The main side effects of interferons are flu-like symptoms and depression that tend to diminish with time. Periodic laboratory evaluations including liver enzymes, complete white blood cell counts and thyroid function tests should be performed every 3–6 months. All of the interferons are capable of stimulating the production of neutralizing antibodies that can limit the efficacy of these agents (Sorensen et al., 2003). The risk of antibody formation over 18 months of treatment is highest with Betaseron, intermediate with Rebif and lowest with Avonex (Bertolotto et al., 2003).

### Glatiramer acetate (Copaxone)

Glatiramer acetate (Copaxone), a daily subcutaneous injectable synthetic polymer, has been shown to have some positive effects in a small double-blind trial of RRMS (Bornstein et al., 1987). Studies have shown a lower relapse rate and a significant reduction in the number of new T2 lesions compared to placebo. Side effects can include local injection site reactions and transient systemic post-injection reactions such as chest pain, flushing, dyspnea, palpitations and/or anxiety. No laboratory monitoring is necessary and no neutralizing antibodies have been detected.

There are now a number of medications approved by the US Food and Drug Administration for the treatment of RRMS. There are no clear guidelines, nor is there strong evidence for choosing one drug versus another (Galetta et al., 2002). After making a diagnosis of MS the patient should be started on one of the medications listed above. MS patients should be notified that these therapies primarily slow the disease course but are not a cure. These drugs are typically continued indefinitely unless side effects are intolerable or the patient begins to fail in terms of response, after which use of another agent can be considered.

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