Keywords Multiple sclerosis; experimental allergic encephalomyelitis; central nervous system; virus; cerebrospinal fluid; T-cell receptor; acute disseminated encephalomyelitis; lymphocyte; immune system

18.1. Introduction

Multiple sclerosis (MS) is the most common idiopathic demyelinating disease of the central nervous system (CNS). Although partially effective treatments are now available, MS represents a major target for research into the development of disease-modifying therapies that specifically focus on the neuroimmune pathways of myelin and tissue damage that currently are incompletely understood. Multiple sclerosis is considered to be an example of development of autoimmunity to self-antigens within the CNS through multiple initiating events that include infections and other environmental factors. The direct or indirect induction of immune responses against CNS antigens includes chemotaxis of T cells, B cells, and monocytes, and production of immunoglobulin responses, each of which can act as an effector of myelin damage that occurs in distinct histological patterns. Because a specific cause for MS has not been identified, much MS research has focused on CNS immune responses triggered by unidentified insults that in turn trigger inflammation-mediated cascades of myelin and cellular damage that are likely relevant to other neurodegenerative diseases. This chapter discusses current the epidemiology, etiology, pathophysiology, animal models, virus models and recent advances in the neuroimmunology of MS from the perspective of the potential for development of newer therapies for MS and other inflammatory CNS diseases.

18.2. Clinical Features and Diagnosis of Multiple Sclerosis

Multiple sclerosis (MS) is a disease of unknown etiology that primarily affects the myelin membrane and/or the oligodendroglia (myelin-producing cells) within the central nervous system (CNS). The clinical features are highly variable, but they consistently reflect dysfunction due to inflammation, local edema, and destruction of the “central myelin” of the brain, spinal cord, and/or optic nerves (reviewed in Miller, 1996).

Symptoms generally present with gradually increasing severity (days to weeks), followed by gradual resolution (weeks), which may be complete or partial. The frequency of different types of symptoms in MS is difficult to accurately establish, in part due to their highly variable severity and duration (Matthews, 1998). The most common neurological symptoms are focal sensory disturbances including numbness/tingling sensations, dysesthesia (sensation), paresthesia (abnormal sensation), L’hermitte’s sign (sudden electric-like sensations radiating into the arms or legs while flexing one’s neck), and occasionally burning pain. Such sensory disturbances occur in up to 70–80% of individuals during the course of MS (Miller, 1996; Matthews, 1998). Motor manifestations attributable to corticospinal tract dysfunction occur in up to 60% of patients, and often involve the lower extremities. Motor symptoms generally include dyscoordination and weakness that is often described as “heaviness” of an extremity, which may present unilaterally or bilaterally, in the case of spinal cord involvement. Optic nerve involvement, manifested as optic neuritis (inflammation of the optic nerve associated with visual loss) presents as the initial symptom in about 20% of MS patients, but its prevalence during the course of MS is thought to be much higher (Matthews, 1998).

The clinical course of the disease (reviewed in Ebers, 1998) is also variable, with approximately 70–85% of patients starting with a relapsing remitting disease pattern in which remissions are associated with complete or nearly complete recovery (Coyle, 2000). The disease typically gradually progresses (over years) so that remission periods are shorter and neurological recovery is incomplete. In the chronic phase, neurological dysfunction increases without significant improvement. Approximately 15% of patients have primary progressive MS, most commonly expressed as a progressive myelopathy. Other clinical courses have been described including an acute form with rapid neurologic deterioration and sometimes death within a few months, a progressive form
without defined remissions and relapses, and a benign form with a few exacerbations associated with complete recovery. A subclinical form has also been described based upon autopsy findings in asymptomatic individuals. MS can be viewed as a disease with multiple phenotypic presentations that are superimposed over pathological components that range from pure inflammation to gliosis.

Diagnostic criteria intended originally for the purposes of classifying patients for research protocols are now considered standard criteria for clinicians making the diagnosis of MS. The original clinical criteria of Schumacher (Schumacher et al., 1965) (reviewed in Coyle, 2000), were expanded by Poser (Poser et al., 1983) to incorporate paraclinical tests (MRI, cerebrospinal fluid analysis, and evoked potential testing) to increase the certainty of the diagnosis. The MRI typically demonstrates multifocal areas of demyelination surrounding the brain ventricles and within the spinal cord (Figure 18.1). The Poser criteria include the categories of clinically definite, laboratory-supported definite, probable, and possible multiple sclerosis. Previously, practicing clinicians generally attempted only to diagnose cases of definite MS (clinically definite or laboratory-supported definite) because of early recommendations for treatment of definite MS with the first FDA-approved immunomodulating medication, Interferon beta-1b/Betaseron. However, because recent clinical trials in individuals with single, clinically-apparent demyelinating events who did not meet Poser criteria for definite MS demonstrated that Interferon beta-1a (Avonex) greatly reduced the likelihood of development of definite MS over a 2-year period (Kinkel et al., 2006) clinicians have been advised to diagnose and treat patients with such isolated demyelinating events (Frohman et al., 2006b).

These diagnostic criteria, were again modified (Table 18.1) to include specific numbers and locations of MRI-defined lesions that can confirm the diagnosis of MS with a clinically monosymptomatic event or an insidious neurological progression suggestive of MS (McDonald et al., 2001; Polman et al., 2005). Included in Table 18.1 are the Poser criteria (Poser et al., 1983), McDonald criteria (McDonald et al., 2001) and the revised McDonald criteria (Polman et al., 2005). By the Poser criteria (Table 18.1, top two clinical presentations) “definite” multiple sclerosis requires objective evidence of central nervous system (CNS) dysfunction in ≥2 sites of involvement, predominantly in the white matter, relapsing-remitting or chronic progressive (>6 months) in patients between the ages of 10 to 50 years at onset of symptoms. Importantly, there must be no better explanation of the symptoms. These “attacks” may be motor, sensory, visual, or coordination deficits and must last more than 24 h (typically days to weeks). They may be subjective and amnestic (i.e. recalled historically by the patient) or demonstrable by a physician, and separate attacks must be separated in time by at least 30 days of significant improvement to be classified as distinct attacks. In addition, if a physician can demonstrate objective dysfunction in two anatomically separate regions of the CNS, criteria are met for clinically definite multiple sclerosis, assuming no better explanations of the symptoms.

18.3. Epidemiology and Etiology of MS

MS is the most common inflammatory disease of the CNS, affecting an estimated 2,500,000 people worldwide and 350,000 in the United States alone (Johnson, 1994) (Kantarci