The Spectrum of Multiple Sclerosis

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Multiple sclerosis (MS) is the most common cause of chronic neurologic disability in young people. Genetic susceptibility and unidentified environmental triggers appear to be necessary in order to result in disease. MS is an extraordinarily complex trait with evidence of heterogeneity at clinical, pathologic, and therapeutic levels. Recent studies have not resolved the important question whether at a mechanistic level MS is a single disease with a wide spectrum of clinical expression, or whether it encompasses a group of separate diseases that share certain pathologic final common pathways. This question is important not only for helping to understand the causes of MS but also for designing and applying better treatments.

Introduction

For many reasons, multiple sclerosis (MS) is one of the most challenging diseases to study, understand, and treat. Underlying them is a degree of complexity that is evident at clinical, radiologic, pathologic, and perhaps mechanistic levels. Therapeutic response to the currently available treatments is also variable, even within single phenotypic subgroups. For some time many investigators and particularly clinical neurologists have believed it likely that the phenotypic spectrum is so wide that MS may not be a single disease. Genetic and pathologic advances have supported this idea, the extreme position being that any similarities common to the various inflammatory demyelinating diseases result from a limited capacity of the central nervous system (CNS) white matter to respond to disparate pathologic insults. However, there is a strongly held opposing opinion that the phenotypic variation of MS is due to a spectrum of expression by a single disease entity, and this concept has recently gained currency from detailed analysis of the natural history of MS through interrogation of large clinical databases.

Clinical Heterogeneity

The term *multiple sclerosis* embraces several distinct phenotypes, and other related conditions are also considered to be primary inflammatory demyelinating disorders (Table 1). In the absence of any proven biomarker for MS the diagnosis is usually made on the basis of a variety of clinical, laboratory, and imaging criteria. Often a diagnosis can be suspected but remain unconfirmed for years.

Different clinical phenotypes can be defined on grounds of clinical features (clinical course, severity, age of onset, rate of progression), anatomic localization, MRI appearance, and presence of family history [1,2].

Clinical course

The name *multiple sclerosis* refers to the many lesions that accumulate in the CNS during the course of the disease. Very often the early stages are characterized by the abrupt appearance of some new symptom, which later fully or partially recovers. There may be an interval of months or years between these relapses, but it is well known that periods of clinical remission do not necessarily indicate pathologic quiescence, because MS is typically active in most patients most of the time. Inflammation is the hallmark of these new emerging lesions. Many new lesions occur in regions of the CNS where they result in no detectable neurologic symptoms, and only a small proportion of them are clinically eloquent, giving rise to typical symptoms and hence described as relapses. This form of MS is termed *relapsing remitting multiple sclerosis* (RRMS) and approximately 85% of patients first experience this form of the disease [3]. A relapse is defined as a focal neurologic deficit lasting at least 24 hours (in order to exclude various paroxysmal symptoms that can occur in MS) but more typically recovery occurs over 2 to 6 weeks.

As the disease progresses, relapses may continue to occur but often begin to lessen in frequency. At the same time, recovery from individual relapses may be incomplete and permanent disability results. Disability often begins to increase in the absence of identifiable clinical relapses, and this form (or stage) of MS is termed *secondary progressive multiple sclerosis* (SPMS). About 50% of patients with early relapsing MS will have entered a secondary progressive phase 10 years after diagnosis and 30% to 40% of patients overall will have SPMS. The main feature of SPMS is gradual and inexorable progression of disability without relapses; although inflammatory activity may

Table 1. Classification of major phenotypic variants of MS and related primary demyelinating conditions

Clinical course
Relapsing remitting MS (RRMS)
Secondary progressive MS (SPMS)
Progressive relapsing MS (PRMS)
Primary progressive MS (PPMS)
Clinically isolated syndrome (CIS)
Age at onset
Childhood MS
Late onset MS
Severity
Subclinical MS
Benign MS
Aggressive or fulminant MS (Marburg)
Anatomic involvement
Neuromyelitis optica (NMO)
Optico-spinal (Asian-type) MS (OMS)
Other distinct conditions
Baló concentric sclerosis (BCS)
Acute disseminated encephalomyelitis (ADEM)
Acute hemorrhagic leukoencephalopathy (AHLE)

continue to occur, the chief pathologic phenomenon now is neuronal degeneration and white matter volume loss.

Approximately 10% of patients have a clinical course that appears to progress from its earliest stages, either never experiencing a defined relapse, or with a single relapse-like presentation followed by steady worsening. This form of the disease is called *primary progressive multiple sclerosis* (PPMS). These patients often develop MS later in life; males and females are affected more equally; and much of the disability is caused by spinal cord involvement. MRI shows that patchy inflammatory lesions occur in the brain, but are often less frequent than in RRMS and SPMS. Perhaps 5% of patients will have a clinical course that is progressive from onset but punctuated by clear relapses, so-called *progressive relapsing multiple sclerosis* (PRMS) [4].

The term *clinically isolated syndrome* (CIS) refers to patients who present with a single monophasic neurologic syndrome caused by a focal inflammatory CNS lesion. The most commonly affected regions are the optic nerve (causing optic neuritis), spinal cord (transverse myelitis), brainstem, or cerebellum. Commonly a CIS heralds the appearance of a relapsing clinical course (RRMS), but this is far from inevitable. MRI has proved useful in predicting which patients with a CIS are likely to develop RRMS; if brain imaging is normal the risk of developing MS is relatively low, and conversely if MRI is abnormal the patient is at higher risk of developing MS [5].

Age at onset

MS most commonly appears in the third or fourth decade but can occur anytime between early childhood and the seventh decade. Traditionally MS and optic neuritis have been considered uncommon in children but the incidence is increasing, as it is in the adult population also. It has been reported that MS often carries a more benign outlook when it occurs in children, but it has also been shown that childhood optic neuritis carries a high risk of conversion to MS, particularly when cerebral MRI is abnormal [6]. Overall it seems that RRMS has a similar natural history in both children and the more typical adult population.

Late-onset MS (LOMS) is a clinically defined subgroup in which diagnosis is made after the age of 50. This category includes between 3% and 12% of patients. It has commonly been held that LOMS is associated with a poor prognosis; however, recent analysis of a large Canadian database has shown that this is not necessarily the case, and again this age-defined subgroup appears to have a natural history similar to typical MS in patients under the age of 50 years [7].

Severity

Neurologists are daily confronted with a wide range of severity in MS. Severity cannot easily be predicted; neither are there reliable biomarkers for severity. For example, severity of disease does not always correspond closely with the severity of MRI abnormalities. Apart from the range of severity seen in patients who nonetheless are considered to have "typical" MS, extreme variants deserve comment. First, it appears that MS may remain asymptomatic or subclinical in some patients. This has become apparent from autopsy studies and from MRI studies of asymptomatic relatives of MS patients [8•]. Asymptomatic MS is difficult to study but may not be uncommon. "Benign MS" is a term applied to a subset of RRMS patients who experience fewer than typical relapses and recover well each time with little permanent disability accrued, even after many decades. Acute (or aggressive, also termed Marburg variant) MS is fortunately uncommon. Patients develop severe, destructive white matter disease that may be mistaken on MRI for a tumor. Recovery is limited and the course is relapsing and progressive usually over several months.

Anatomic site

Although single anatomic sites define the nature of a CIS, anatomic predilection can also define relapsing and progressive disease syndromes. Neuromyelitis optica (NMO) is a severe demyelinating syndrome that has traditionally been considered a variant of MS. It is often monophasic but is now recognized as a relapsing condition [9]. The hallmark is involvement of both the spinal cord and optic

nerves. MS-like brain lesions on MRI have been considered to not occur in NMO but recently proposed criteria allow for CNS involvement outside the two index regions. As we have already seen, optic neuritis and transverse myelitis can occur as isolated monosymptomatic events that may, but do not necessarily, herald the subsequent development of typical relapsing multiple sclerosis. These and other less common inflammatory demyelinating diseases such as longitudinally extensive myelitis (LETM), acute disseminated encephalomyelitis (ADEM), Baló concentric sclerosis (BCS), and acute hemorrhagic leukoencephalopathy (AHLE) all share certain clinical, imaging, and pathologic features with the more commonly seen forms of MS, which is the archetypal CNS demyelinating disease, but are nonetheless phenotypically distinct on other counts.

Evidence for Etiologic Heterogeneity

Therefore, the important question is whether MS is a single disease with a wide spectrum of clinical expression, or whether several different etiopathologic processes culminate in a series of final common pathways in which there are varying degrees of inflammation, myelin damage, and neuronal loss with similar clinical features. The cause (or causes) of MS remain unknown. It is accepted that a complex genetic susceptibility is important but also that various undefined environmental triggers or insults are also necessary. The most important genetic susceptibility maps to the HLA-DRB1*1501 class II allele on chromosome 6, indicating that genetic control of immune mechanisms is involved in permitting the development and persistence of damaging autoimmunity [10,11]. A variety of viruses have been suggested as possible contributors to risk of MS but no single infective agent has yet been confirmed, and it seems unlikely that this is about to change [12]. Our understanding of the causes of MS is too sketchy to provide any reassurance that we are dealing with a single nosologic entity, and the question remains debated and unresolved, with evidence supporting both possibilities.

Pathology of the MS lesion

The most convincing evidence for heterogeneity within the MS phenotype has come from recent detailed pathologic studies of acute MS lesions. The pathology of the acute MS lesion is well described [13,14]. Localized breakdown of the blood-brain barrier permits ingress of a range of inflammatory cells. T cells produce inflammatory cytokines such as interferon (IFN)-γ and interleukin (IL)-2. An inflammatory cascade is induced by local secretion of IL-1β, IL-6, and tumor necrosis factor (TNF)-α. Macrophages participate in oligodendrocyte damage, myelin sheath breakdown, and ingestion of myelin components. Humoral mechanisms are known to be involved locally. Other cytokines are thought to have a direct neurotoxic effect. Local and systemic mechanisms appear which exert anti-inflammatory effects, a range of neurotrophins and nerve growth factors are secreted, and the majority of acute MS lesions in early stage MS are able to remyelinate within a few weeks [15].

An important contribution has been made by Luchinetti et al. [16,17] in a series of studies in which acute demyelinating lesions from a large number of patients were studied in detail. These authors concluded that four distinct patterns could be identified. All four showed myelin loss associated with T cell and macrophage infiltration. Pattern I showed neither immunoglobulin (Ig) G nor complement deposition. Pattern II, in contrast, showed both these features. Both patterns I and II had sharply defined lesion borders and showed some surviving oligodendrocytes within the plaques with evidence of remyelination occurring. Pattern III showed inflammatory lesions with a preferential loss of the myelin component known as myelin-associated glycoprotein (MAG), apoptotic oligodendrocytes, limited remyelination, and ill-defined lesion borders. Pattern IV showed complete loss of oligodendrocytes.

A most important observation was that although the patterns seen varied between patients, only a single pattern was ever observed in multiple lesions within any single patient at the time of autopsy or biopsy. Furthermore, different patterns of demyelination correlated to some extent with clinical phenotypes. Pattern II was the most commonly seen, followed by pattern III. Both were present about equally in patients with acute MS, but pattern III was rare in chronic MS and found mostly in patients with MS of less than 2 months' disease duration. Patterns I and II, but not III, correlated with gadolinium enhancement on MRI and pattern II was associated with a good therapeutic response to plasma exchange. Pattern IV was uncommon and was seen in patients with advanced progressive MS. These findings support pathogenic heterogeneity in immune effector mechanisms involved in MS lesion formation and would be consistent with the hypothesis of etiologic heterogeneity.

Unfortunately, other equally detailed pathologic studies have suggested there are common features seen in the very earliest stages of development of an MS lesion [18].

Biomarkers

One of the most interesting findings recently has been that a serum IgG autoantibody may be a specific biomarker for NMO. It has been observed previously that NMO, often an extremely severe disease, can respond to plasma exchange. Lennon et al. [19••] have been able to identify the putative target autoantigen in NMO by showing selective binding of the NMO-IgG to the aquaporin-4 water channel, a component of the dystroglycan protein complex found in astrocytes adjacent to the blood-brain barrier. This finding establishes NMO as a humoral-mediated demyelinating disease with distinct differences from typical MS. Other studies [20] have suggested that

NMO-IgG defines a spectrum of demyelinating diseases including recurrent transverse myelitis without optic neuritis and recurrent optic neuritis without myelitis as well as typical NMO.

Does this make NMO a separate disease entity, or could it still be part of a continuum that also includes MS? This finding has stimulated considerable interest in the possibility that other autoantibodies might be discovered to serve as biologic markers for the diagnosis, classification, disease activity, and phenotype of MS [21]. Thus the recent finding of antibodies to soluble Nogo-A is potentially of great importance [22•]. Nogo proteins are potent inhibitors of axonal growth and regeneration. The authors found a small soluble Nogo-A product in the CSF of 96% of patients with MS but not in any patients with other inflammatory neurologic diseases [22•]. If this finding is confirmed it will be a second example of a specific humoral immune mechanism involved in MS. The likelihood that the MS spectrum will be dissected further by findings of this type is considered by many to be high.

Evidence That MS Is a Single Disease

An even more challenging question to address is whether MS is a single disease. The most convincing evidence that MS is best regarded as a single disease with a spectrum of phenotypic expression has come from recent detailed analyses of large, long-established databases. Confavreux and Vukusic [23•] have studied the natural history of MS in nearly 2000 patients. RRMS and SPMS cases shared similar age at onset, initial symptoms, degree of recovery from the first episode, and interval between first and second relapses. PRMS and PPMS were essentially similar in clinical characteristics. In patients with progressive disease, the age at onset of progressive disability was the same in the SPMS and PPMS cases. The proportion of cases with superimposed relapses was about 40% in each category. Finally, RRMS and PPMS patients showed the same rate of disability accumulation from any given disability score. The authors suggest that RRMS is multiple sclerosis that has not had enough time to convert to SPMS; that SPMS is late-stage RRMS; and that PPMS is similar to SPMS but without the preceding relapsing phase. The rate of disability accrual and time to reach disability milestones are not influenced by superimposed relapses, despite these being the clinical events that are so prominent in the early years of the disease in a majority of patients. This is consistent with the reliable finding from clinical trials that disease-modifying treatments may suppress inflammation and relapses, but have no impact on disability progression [24]. These observations lead to a unifying hypothesis in which relapsing and progressive forms of MS are essentially similar.

Conclusions

MS is a complex trait that most likely develops as a result of interplay between genetic and environmental factors. Based on our present knowledge, it is reasonable to expect that in order to develop MS it is necessary to have inherited a particular polygenic pattern of susceptibility and then to be exposed to one or a series of environmental triggers. This interaction is likely to be quite complex and various mathematical models have been proposed [25]. The result may be a spectrum of pathology that at one end becomes expressed as a variety of demyelinating phenotypes. It now appears likely that these phenotypes will be further dissected as new biomarkers are discovered, but the natural history of MS shows that there are sufficient common features to indicate that we probably are dealing with a single, albeit protean, disease.

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