Epidemiology and natural history of multiple sclerosis: new insights

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Purpose of review

The cause of multiple sclerosis remains elusive. We review recent epidemiological studies of genetic and environmental factors that influence susceptibility to the disease and its clinical course.

Recent findings

Genetic advances strengthen the association of multiple sclerosis with the human leukocyte antigen (HLA)-DRB1 allele and interferon-γ polymorphisms and suggest that apolipoprotein E alleles play an important role. In the environmental realm, nested case–control studies show that prior Epstein–Barr virus exposure is overrepresented in multiple sclerosis. Smoking has been associated with both risk of multiple sclerosis and progressive disease. Vitamin D deficiency might tie together environmental clues with higher multiple sclerosis prevalence rates; dietary vitamin supplementation is also associated with reduced multiple sclerosis risk. Natural history studies demonstrated dissociation between relapses and disease progression, facilitated the ability to distinguish neuromyelitis optica and related syndromes from typical multiple sclerosis, and spawned the exploration of large datasets to model long-term disease activity.

Summary

Our understanding of the contributions of specific genetic and environmental factors that contribute to multiple sclerosis has improved. Further refinements will eventually allow powerful longitudinal studies to assess genetic and environmental interactions with implications for prediction of individual disease susceptibility, clinical course, and response to therapy.

Keywords

environmental factors, epidemiology, genetic factors, longitudinal studies, multiple sclerosis, natural history

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Abbreviations

APOE	apolipoprotein E
EDSS	Expanded Disability Status Scale
HLA	human leukocyte antigen
IIDD	idiopathic inflammatory demyelinating disease
MRI	magnetic resonance imaging
MS	multiple sclerosis
NMO	neuromyelitis optica

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Introduction

Multiple sclerosis (MS) is part of a spectrum of idiopathic inflammatory demyelinating diseases (IIDDs) of the central nervous system that vary from each other by lesion size and number, pathology, and clinical outcome; a recent review highlights pathological aspects of IIDDs [1••]. Diagnosis is achieved using consensus clinical and magnetic resonance imaging (MRI) criteria that document white matter disease disseminated in time and space [2]. The clinical manifestations, temporal course, and pathology of MS are heterogeneous, in part because it results from complex interactions of multiple genetic and environmental factors. We review recent advances in understanding the genetic and environmental epidemiology and the natural history of MS.

Epidemiology of multiple sclerosis

MS affects approximately 1 000 000 people between 17 and 65 years old worldwide. In 2000, the projected prevalence rate of MS for the white US population was 191 per 100 000 and the incidence rate was 7.3 per 100 000 person years at risk [3]. MS is twice as common in women then men. Men have a tendency for later disease onset with worse prognosis, supporting gender-dependent factors in etiology and phenotypic variability [4]. In 1994, the annual cost of MS in the USA in terms of direct care and lost productivity was estimated at $6.8 billion and total lifetime cost per patient was $2.2 million [5]. Despite the introduction of disease-modifying treatments with modest effects on overall disease outcome [6–8], current costs are certainly much higher.

Genetic epidemiology of multiple sclerosis

Susceptibility to MS is 'complex', with evidence supporting genetic and environmental factors [9]. Factors supporting genetic effects include excess occurrence in Northern Europeans relative to indigenous populations from the same geographic location, familial aggregation

Table 1 Risk of developing multiple sclerosis according to the relationship to a multiple sclerosis patient [10,11,12••]

Relative with multiple sclerosis	Chance of developing multiple sclerosis (%)
Monozygotic twin	25–30
Dizygotic twin	3–5
First-degree relative (child or full sibling)	2–4

(MS is 20–40 times more common in first-degree relatives, dropping off rapidly with the degree of relatedness), and lack of excess of MS in adopted relatives of patients with MS [10,11]. Monozygotic twin studies suggest that up to 25–30% of MS risk is genetically determined and the risk rapidly drops to 3–5% with dizygotic twins, supporting the complex susceptibility to MS [12••] (Table 1). Phenotypic heterogeneity in MS also has a genetic basis; relative pairs with MS in family studies have greater similarity of clinical course than expected by chance [13].

Genetic epidemiology studies can be classified as hypothesis-independent whole-genome studies (linkage or association) or hypothesis-driven candidate-gene association studies. In complex disorders, whole-genome studies are limited by the sample size necessary to study a sufficient number of markers with power to uncover small effects, particularly after correcting for multiple comparisons [14]. On the other hand, hypothesis-driven candidate gene-association studies require an understanding of the biology of the disease to identify reliable candidates.

Other than the well-defined human leukocyte antigen (HLA)-DRB1*1501-DQB1*0602 haplotype on chromosome 6p21, multiple genetic factors likely have small individual contributions to the etiology of MS [15,16,17••]. Recent studies showed that HLA locus association is with HLA-DRB1 rather than the DQ allele [18,19•]. There was also suggestive linkage with MS on chromosomes 5q33, 17q23, and 19p13 [17••]. In another hypothesis-independent association study, an additional candidate locus was identified on chromosome 1 [20•].

Two promising candidate genes have emerged from the multitude of individual candidate gene studies. Polymorphisms of the regulator cytokine interferon-γ and the haplotypes formed between them are associated with MS susceptibility, likely in a gender-dependent fashion [21–23,24••]. This association has not been confirmed in all tested populations [25–28]. Apolipoprotein E (APOE) is linked to prevention of neurotoxicity and repair processes in a variety of neurological disorders [29,30]. APOE genotype has been associated with MS disease severity but consensus is lacking [13]. APOE e3 and e4 alleles have been associated with neuronal loss as measured by magnetic resonance spectroscopy [31]. The APOE e2 allele is associated with lesser disease severity in patients with familial MS [32]. This association is present in women but not men with MS in population-based sporadic cases [33]. APOE e4 allele is associated with progressive disease in women and cognitive impairment in men with MS [34,35]. The studies in interferon-γ and APOE suggest the presence of non-sex-chromosomal yet gender-specific genetic contributions to MS etiology and phenotype.

Environmental epidemiology of multiple sclerosis

Environmental influence upon MS etiology is suggested by variation in disease incidence and prevalence according to geography (including distance from the equator), mutable risk of developing MS with migration from both low-to-high and high-to-low prevalence areas, presence of rare clusters and epidemics of MS (e.g. Faroe Islands and Iceland), and incomplete concordance in monozygotic twins. [11,12••].

Quantification of environmental exposure in epidemiology studies is difficult due to reliance on retrospective data from case–control studies in which all subjects are exposed to the same environment. A practical, albeit limited, design is a nested-cohort study in which a population cohort already identified for exposure to given factor(s) for another disease is exploited for excess of MS occurrence after sufficient follow-up. Many recent studies have taken this approach [36].

The environmental epidemiology of MS is poorly understood but recent advances implicate factors such as viral exposure (e.g. canine distemper virus, Epstein–Barr virus, and human herpes virus-6), dietary fatty acids, vitamin D, solar ultraviolet radiation exposure, organic solvent exposure, and cigarette smoking. We concentrate on recent advances subsequent to publication of comprehensive reviews [36,37].

The role of early infections in MS remains unproven [36,37]. The absence of a relationship between MS risk and birth-order position makes the hypothesis of early exposure to infections from siblings an unlikely etiology [38]. A recent report documented lack of active canine distemper virus in MS lesions [39]. In a small nested case–control study of nurses, presence of Epstein–Barr virus in plasma was associated with a trend for increased risk of MS even after adjusting for smoking, ancestry, and latitude of residence at birth [40]. In a more recent nested case–control study conducted among more than 3 million US military personnel, anti-Epstein–Barr virus antibody titers among cases compared with controls were already significantly elevated 5 or more years before the onset of MS [41••]. Further studies are needed to explore the role of Epstein–Barr virus in MS susceptibility.

Past sun exposure and vitamin D supplementation have been associated with decreased risk of MS [36,37,42•,43•]. These studies suggest a role for vitamin D metabolism as a potential explanation of the increased risk of MS as a factor of distance from the equator. These findings justify vitamin D supplementation trials in MS [44•].

The risk of MS has been linked to organic solvent or trace metal (e.g. zinc) exposure, although the evidence remains unconvincing [36,37,45–47]. A recent study found no evidence of increased prevalence of MS in a population living near an oil refinery where crude oil and other chemical product (e.g. benzene, xylene, and toluene) spills and leaks were documented on site and subsurface soils were contaminated off-site; a groundwater plume had migrated into a neighboring residential area [48].

The risk of MS was 1.8-fold higher among tobacco smokers compared with those who had never smoked in one study [49]. A nested case-control study confirmed this finding and also determined that the risk of secondary progression is 3.6-fold higher among smokers compared with those who had never smoked [50•]. These data further underline the necessity of advising patients with MS to quit smoking [51].

There are no unifying hypotheses that encompass each of the identified environmental risks. However, Hawkes [52•] put forth an interesting conjecture that people with MS might be 'risk-takers' prone to behavior patterns that make them more likely to smoke, disregard health matters, and increase their exposure to infections (e.g. through higher sexual partner number). Though unlikely to be validated, this paper at least demonstrates the need for expanding our current hypotheses beyond the current immunological paradigm.

Natural history of multiple sclerosis

Natural history of MS has to be considered as part of the natural history of IIDDs. In this review we will concentrate on heterogeneity in MS and isolated syndromes with specific attention to risk of conversion to MS and other IIDDs.

Heterogeneity in multiple sclerosis

Relapsing-remitting MS ultimately evolves into a progressive disease in most but not all patients (secondary progressive MS). Some cases present with insidious neurological dysfunction from onset without any acute clinical relapses (primary progressive MS). While relapses and new inflammatory lesions detected on MRI become less frequent over time, an insidious course of worsening neurological function ensues, characterized by progressive axonal loss. Axonal dropout begins at least in some patients at a very early stage when the clinical course appears relapsing-remitting [1••]. During and between clinical relapses, demyelination and axonal loss evolves even in white matter regions that appear normal on conventional MRI studies. Four patterns of demyelination in early active MS lesions suggest discrete pathways that lead to the common endpoint of myelin injury in MS [53]. While all patterns have infiltrating macrophages and T cells, the more common patterns I and II, are characterized by oligodendrocyte survival and remyelination. Patterns I and II suggest myelin as the primary target of an inflammatory mechanism of myelin injury and resemble the experimental autoimmune encephalomyelitis model of MS. In contrast, patterns III and IV show very little remyelination due to depletion of oligodendrocytes, suggesting oligodendrocytes as the target of injury and resemble toxic, viral, and/or ischemic models of MS. This heterogeneity complicates prediction of long-term outcome and treatment effects in MS. Therapeutic plasma exchange appears to specifically benefit fulminant demyelinating attacks with underlying pattern II immunopathology [1••,54••].

Isolated idiopathic inflammatory demyelinating diseases and risk of conversion to multiple sclerosis

Some initially isolated IIDDs, such as optic neuritis, acute transverse myelitis, and tumefactive demyelinating lesions, have the potential to convert to relapsing-remitting MS. Intervention with disease-modifying treatments at onset of disease promises the benefit of delaying recurrence of symptoms and delaying a diagnosis of MS [55]. After an acute episode of optic neuritis associated with one or more lesions typical of MS on MRI scanning, 44% of patients do not develop clinically definite MS in 10 years [4,56]. Partial myelitis, which is more characteristically associated with MS than acute transverse myelitis, portends a 20–60% risk for clinical MS within 3 years [57,58]. Complete acute transverse myelitis may be monophasic or evolve into a relapsing disorder. 'High-risk' syndromes for development of neuromyelitis optica (NMO) include recurrent optic neuritis with a normal brain MRI or the occurrence of longitudinally extensive transverse myelitis (with spinal MRI lesion extending over three or more vertebral segments). NMO is probably identical to Japanese optic-spinal MS and is distinguished from typical 'Western' MS by preferential involvement of optic nerves and spinal cord, relative sparing of the brain, lack of cerebrospinal fluid oligoclonal banding, relatively worse prognosis, and association with the serum autoantibody NMO-IgG [59,60•]. This autoantibody, which targets the water channel aquaporin-4, is about 75% sensitive for NMO but does not occur in typical MS [61,62••]. This is the first specific immunological marker that can help sort the part of the clinical heterogeneity in IIDDs. Furthermore, detection of NMO-IgG after presentation of acute transverse myelitis with a longitudinally extensive spinal cord lesion is strongly predictive of relapse of myelitis or optic

Table 2 Time to major disability milestones (Expanded Disability Status Scale)

Median time for multiple sclerosis patients to reach major disability milestones in a population-based study [75]	Median (years)
EDSS 3 (fully ambulatory)	9
EDSS 6 (unilateral assistance with canes, crutches, or braces required to walk 100 m)	16
EDSS 8 (restricted to bed, retains many self-care functions and generally has effective use of arms)	33
Percentage of patients with multiple sclerosis reaching major disability milestones 15 years from onset of symptoms in a hospital-based study [77]	Patients (%)
EDSS ≥ 3	66
EDSS ≥ 6	41

EDSS, Expanded Disability Status Scale.

neuritis within 1 year [63]. Identification of such cases is imperative because NMO and related disorders appear to require immunosuppressive therapy rather than standard MS immunomodulatory drugs (e.g. interferon-β and glatiramer acetate).

Assessment of disease severity in multiple sclerosis

Kurtzke's Expanded Disability Status Scale (EDSS) [64] has long been the standard impairment instrument in MS epidemiological and therapeutic studies. However, the EDSS has a bimodal distribution, is disproportionately affected by ambulation, and does not adequately emphasize upper-extremity dysfunction and cognitive defects that contribute substantially to disability [13]. The MS functional composite (MSFC) attempts to address these deficiencies, has been validated concurrently with the EDSS [65,66], has excellent intra- and interrater reliability [67], and correlates with quality-of-life measures [68]. There are three components of this scale: the timed 25-foot walk (for leg function and ambulation) [69], the nine-hole peg test (for upper-extremity function) [70], and the Paced Auditory Selective Addition Test (PASAT; for cognitive evaluation) [71]. While verbal fluency and verbal learning are impaired earlier, impairment in attention and information processing speed correlate better with a disease duration longer than 7 years in MS [72•]. However, another recent study documented that cognitive impairment, mainly affecting attention, information processing speed, memory, inhibition, and conceptualization is common even in the early stages of MS and the severity of these deficits reflects the extent of the lesions and the severity of tissue disorganization outside lesions [73•].

Assessment of disease severity in the absence of longitudinal data poses a significant problem. For such situations where the patient assessment is done cross-sectionally but where disease duration information is available, patients may be stratified into 5-year cohorts based on disease duration and EDSS score. Each group is then assigned a ranked severity score and a new ordinal measure of severity is generated which yields a normal distribution of scores as long as no systematic bias in ascertainment exists. This approach has been successfully used in several population-based studies [13]. A recent study expanded this approach by generating a cross-sectional Multiple Sclerosis Severity Score with EDSS scores from 9892 patients in 11 countries [74•]. These data may be used as a benchmark for cross-sectional hospital-based studies.

Long-term outcome in multiple sclerosis

About 50% of MS patients become at least dependent on a walking aid after 15 years of disease [75,76] whereas 10% remain free of major disability after 25 years, even without treatment [77] (Table 2). A population-based study found that there is 90% chance that MS patients remain stable if their EDSS scores were 2 or lower for 10 years or longer [77]. This ambulatory 'benign' group constituted 17% of MS patients [78]. Existence of benign MS was previously well known but this study documents the absolute prevalence of this subgroup. The biological basis of this variability in long-term clinical outcome is poorly understood and clinical predictors are inadequate at the individual level [4]. Nevertheless, several factors have been consistently associated with poor long-term prognosis: male sex; older age at onset ($>$ 40 years); motor, cerebellar, or sphincter symptoms at initial presentation; polyregional onset; relatively frequent attacks especially within the first 5 years; short interval between the first two attacks; relatively short time to reach EDSS level 4; and a progressive course [4] (Table 3). However, none of these early assessable clinical variables significantly influences the subsequent progression of irreversible disability after moderate disability is reached

Table 3 Prognostic factors in multiple sclerosis [4,77]

Favorable	Unfavorable
Early age at onset	Older age at onset ($>$ 40 years)
Female gender	Male gender
Optic neuritis or sensory symptoms at onset	Motor, cerebellar, or sphincter symptoms at onset
Relapsing disease course	Frequent attacks within the first 5 years
	Short relative interval between the first two attacks
	Short relative time to reach EDSS level 4
	Progressive disease course

EDSS, Expanded Disability Status Scale.

(EDSS 4), suggesting that long-term behavior of ambulatory disability is established early in MS [79]. The progressive phase in MS, regardless of the presence (secondary progressive) or absence (primary progressive) of initial relapses, behaves similarly [77]. An unfavorable outcome in primary progressive MS is predicted by rapid early progression of disability and involvement of three or more systems [80]. Men tend to have older age of onset, tendency for a more progressive course, more frequent onset of disease with motor, cerebellar, or sphincter symptoms [77]. A recent study confirmed the above findings as well as the lack of female preponderance in primary progressive MS, independent of age of onset [81].

There is a need for reliable surrogates that predict course and outcome of MS to individualize existing and future treatment strategies. This will ensure better efficacy and help avoid side effects and unnecessary health care costs.

Assessment of treatment effects on natural history of multiple sclerosis

It is difficult to prove long-term benefit of therapy in chronic diseases characterized by individual variability and unpredictability and there exists no study that convincingly establishes a long-term improvement over natural history for any MS therapy. Long-term extension studies are usually hampered by attrition bias. A preliminary report outlined plans to evaluate 16-year clinical, cognitive, and MRI outcomes in 372 patients treated in the pivotal interferon-β1b clinical trial and compare them with natural history cohorts from Canada and the UK [82]. Early analysis of 234 patients showed that 89% of the cohort is alive and about 20% require a wheelchair. Patients originally randomized to 250 μg of interferon-β1b were more likely to report continued ability to ambulate compared to those who were randomized to placebo. Although still subject to biases, this study offers some advantages over earlier observational studies, including the effort to evaluate all patients rather than only those who continued their treatment.

An alternative strategy worthy of exploration exploits meta-analytic modeling of pre-treatment-era natural history datasets (and placebo groups from controlled trials) as comparison groups for detecting any long-term, large-impact effects of current therapies. Although such observational approaches also have inherent potential for bias, it is worth exploring whether cohorts of patients being treated for very long intervals with one therapy behave clearly differently than one would expect from benchmark untreated groups. A variety of attempts are being made in this area [83].

Conclusion

Focused efforts over the past two decades have resulted in development of powerful longitudinal databases that allow assessment of the contribution of individual genetic and environmental influences on MS susceptibility and disease course. Advances in genetic techniques allow for completion of association studies using different approaches such as whole-genome screening or hypothesis-driven evaluation of individual candidate genes. Longitudinal population-based studies represent the best opportunity to apply valid clinical epidemiological techniques to evaluate environmental factors. For both genetic and environmental researchers, the next frontier in causative research must include collaborative assessments that have the power to evaluate genetic and environmental interactions, since these appear to underlie MS susceptibility and probably influence disease course. Such discoveries will be of great clinical importance as they will likely allow refinement of risk assessment for individuals deemed at risk for MS, facilitate the development of preventive therapies, and identify factors that influence treatment decisions such as prediction of response to a specific therapy.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 320–321).

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