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Multiple Sclerosis Overview

[*MS*]

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Summary

Disease characteristics. Multiple sclerosis (MS) is an inflammatory, demyelinating, neurodegenerative disorder of the central nervous system (CNS) of unknown etiology. The peak onset is between 20 and 40 years of age; it may develop in children and has also been identified in persons age 60 years and older. Women are affected approximately twice as often as men. The most common clinical signs and symptoms, occurring in isolation or in combination, include sensory disturbance of the limbs (~30%), partial or complete visual loss (~15%), acute and subacute motor dysfunction of the limbs (~13%), diplopia (7%), and gait dysfunction (5%). The course may be relapsing-remitting or progressive, severe or mild, and may involve the entire neuroaxis in a widespread fashion or predominantly affect the spinal cord and optic nerves. The three clinical phenotypes of MS are relapsing-remitting MS (RR-MS) (occurring in more than 80% of individuals with MS), primary-progressive MS (PP-MS) (occurring in10-20% of individuals with MS), and progressive relapsing MS (PR-MS) (a rare form).

Diagnosis/testing. Multiple sclerosis is diagnosed clinically. The RR-MS phenotype is diagnosed in individuals who have at least two clinical attacks, each lasting at least 24 hours and separated by at least one month, or a slow, progressive course for at least six months, and who have lesions in more than one area or functional system of the brain or spinal cord. Diagnostic criteria for PP-MS include a minimum period of clinical progression of at least 12 months and onset between 25 and 65 years of age; three proposed categories include definite PP-MS, probable PP-MS, and possible PP-MS.

Management. Agents used to treat MS decrease the clinical relapse rate and accompanying inflammation within the CNS. These agents include interferon beta-1b, interferon beta-1a, glatiramer acetate, and mitoxantrone. Various medications are utilized for symptomatic treatment of pain, muscle spasms, fatigue, depression, sexual dysfunction, and bladder and bowel dysfunction. Surveillance includes periodic neurological examination to track disease progression and periodic brain and spinal cord MRIs to monitor disease activity; additional examination techniques include the ambulation index, the 25-foot timed walk, and the 25-foot walk combined with the nine-hole peg test and the paced serial auditory addition test. Possible febrile infections require vigilance as they may exacerbate MS. Pharmacotherapy is typically discontinued in women planning to become pregnant. Potential exacerbations during the postpartum period can often be managed by initiating immunomodulatory therapy soon after delivery.

Genetic counseling. Available data suggest that multiple sclerosis is inherited as a complex multifactorial disorder that results from the interaction of genetic and environmental factors. Estimated risk to the sibs of a proband is 3.0-5.0%, increasing to 29.5% if one or both parents have MS. Risk to the offspring of a person with MS is 2.0-3.0% and higher if both parents have MS.

Definition

Clinical Manifestations of Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory, demyelinating, neurodegenerative disorder of the central nervous system (CNS) of unknown etiology [Noseworthy et al 2000].

The peak age of onset is between 20 and 40 years of age [Kurtzke et al 1992, Liguori et al 2000]. Less commonly, MS may develop in children [Duquette et al 1987, Bauer et al 1990, Ghezzi et al 1997]. MS has also been identified in older individuals, e.g., age 60 years and older, although it is sometimes difficult to ensure that clinical signs or symptoms were not present previously [Martinelli et al 2004]. It must be noted that age of clinical onset does not coincide, at least in the majority of cases, with age of acquisition.

Women are affected approximately twice as often as men [Sadovnick & Baird 1982, Wallin et al 2004].

The most common clinical signs and symptoms at presentation include sensory disturbance of the limbs (~30%), partial or complete visual loss (~16%), acute and subacute motor dysfunction of the limbs (~13%), diplopia (7%), and gait dysfunction (5%).

These signs and symptoms may occur in isolation or in combination, and have to be present for a minimum of 24 hours to be considered a "clinical attack." As any anatomical location of the CNS may be affected, the clinical presentation of individuals with MS is extremely variable.

The course may be relapsing-remitting or progressive, severe or mild, and may involve the entire neuroaxis in a widespread fashion or predominantly affect spinal cord and optic nerves. Very little is known about the underlying cause of disease course variability in MS. Individuals can be stable for many months or years, while suddenly experiencing a devastating clinical attack. Currently, no biological markers can assist the clinician in predicting the clinical course and/or the accumulation of disability. Within families, the clinical course of MS among affected relatives can span the entire spectrum of possibilities — the clinical course does not run true to type in families [Dyment et al 2002].

Clinical disease progression is assessed by recording the accumulation of neurological disability with valid methodological tools, including the expanded disability status scale (EDSS) [Kurtzke 1983]. One particular cohort of more than 1000 individuals with MS evaluated for over 25 years has been the subject of numerous scientific reports [Weinshenker et al 1989a, Weinshenker et al 1989b, Weinshenker 1998]. These data have demonstrated that temporal accumulation of disability accelerates with disease duration. Other groups studying other cohorts reported similar results.

The three clinical phenotypes of MS:

Relapsing-remitting MS (RR-MS). Initially, more than 80% of individuals with MS experience a relapsing-remitting disease course with defined clinical exacerbations of neurological symptoms, followed by complete or incomplete remission [Lublin & Reingold 1997].

Approximately ten years after disease onset, an estimated 50% of individuals with RR-MS convert to a progressive clinical course called secondary progressive (SP) MS, which is no longer characterized by clinical attacks and remissions, but by insidious progression of clinical symptoms [Confavreux et al 1980, Lublin & Reingold 1997].

Primary-progressive MS (PP-MS). Another 10 to 20% of individuals with MS are diagnosed with primary-progressive MS, clinically defined as a disease course without any clinical attacks or remission from onset [Lublin & Reingold 1997].

Demographic characteristics of PP-MS are distinct from those of other clinical MS phenotypes:

- The age of onset is typically around 40 years of age and thus significantly later than that of RR-MS [Confavreux et al 1980, Weinshenker et al 1989a, Andersson et al 1999, Bashir & Whitaker 1999].
- In contrast to RR-MS, PP-MS does not show a sex predilection in most studies [Weinshenker et al 1989a].

Progressive relapsing MS (PR-MS). A significantly rarer form is progressive relapsing MS, which initially presents as PP-MS; however, during the course of the disease, these individuals develop true neurologic exacerbations [Tullman et al 2004]. Individuals with SP-MS who have clinical exacerbations followed by incomplete remission are included in this category [Lublin & Reingold 1997].

The life expectancy of individuals with MS in developed countries approaches that of the general population [Sadovnick et al 1992].

Histopathology. Traditionally, the histopathological correlate of clinical disability was thought to be loss of myelin within the plaque, resulting in exposure to ion channels and impaired propagation of action potentials across the demyelinated region of the axon. However, the early literature on MS already described substantial axonal damage in actively demyelinating lesions. It is not known whether this process is independent or a consequence of demyelination, but renewed interest in MS pathology has focused considerable attention on the neurodegenerative aspects of this disease. Studies confirm that partial or total axonal transection begins early in the disease process and suggest that the cumulative axonal loss may ultimately determine neurological disability [Ferguson et al 1997, van Waesberghe et al 1999]. Histopathologic studies reveal abundant transected and dystrophic axons in sites of active inflammation and demyelination [Trapp et al 1998]. Axonal loss in MS is perhaps the principal contributor to CNS atrophy and clinical disability, although demyelination may also decrease tissue volume.

Establishing the Diagnosis of MS

Multiple sclerosis (MS) is a clinical diagnosis.

Relapsing-remitting MS (RR-MS). The RR-MS phenotype can be diagnosed by commonly used diagnostic criteria if dissemination in time and dissemination in space are present.

- **Dissemination in time:** Defined as at least two clinical attacks, each lasting at least 24 hours, separated by at least one month, or a slow, stepwise progressive course for at least six months.
- **Dissemination in space:** Defined as lesions in more than one area or functional system of the brain or spinal cord white matter.

Revised diagnostic criteria that specifically integrate MRI with clinical and paraclinical methods facilitate the diagnosis in individuals with monosymptomatic disease, relapsing-remitting disease, and progressive disease [Polman et al 2005].

Primary-progressive MS (PP-MS). No diagnostic criteria are universally accepted for PP-MS; however, the following specific diagnostic criteria were formulated by a panel of MS specialists:

- **Definite PP-MS:** Reserved for individuals in whom adequate clinical and investigative evidence is present to render the diagnosis definite enough for inclusion in research protocols and clinical trials.
- **Probable PP-MS:** Strong clinical suspicion of the diagnosis, but insufficient evidence to be definite.
- **Possible PP-MS:** Limited evidence is required to suggest the diagnosis:
  - Evidence of intrathecal immunoglobulin IgG antibody production.
  - One of three MRI patterns: (1) nine brain lesions; (2) two spinal cord lesions; or (3) four to eight brain lesions and one spinal cord lesion

Differential Diagnosis of Multiple Sclerosis

Because MS is clinically a heterogeneous disorder, the differential diagnosis includes the following [Gasperini 2001]:

Inflammatory and infectious diseases

- Systemic lupus erythematosus
- Sjögren syndrome
- Behget syndrome
- Sarcoidosis
- Lyme disease
- Antiphospholipid antibody syndrome
- Neurosyphilis
- Acquired immune deficiency syndrome (AIDS)
- Whipple disease
- Human T lymphocyte virus (HTLV)-I-associated myelopathy

Cerebrovascular diseases

- Recurrent strokes
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Vascular malformations
- Moyamoya disease

Others

- Cerebral lymphoma
- Mitochondrial diseases (see Mitochondrial Diseases Overview.)

- Funicular myelopathy
- Adrenoleukodystrophy with adult onset
- Other genetic leukodystrophies with occasional adult onset [Natowicz & Bejjani 1994, Van der Knaap et al 1999]

Prevalence

The worldwide prevalence of MS is estimated to be between 1.1 and 2.5 million cases of MS [Pugliatti et al 2002].

The geographical distribution of physician-diagnosed MS is uneven. A greater frequency is observed between 40 and 60 degrees north and south latitude. Thus, areas with a high MS prevalence of 50-120/100,000 population are:

- **Western Europe** [Sutherland 1956, Koch-Henriksen & Hyllested 1988]
- **Northern Europe**
- **Canada** [Warren & Warren 1993]
- **Russia** [Boiko et al 1995]
- **Israel** [Alter et al 1978]
- **Parts of northern US, New Zealand**
- **South-East Australia** [Barnett et al 2003]

Zones with a very low disease frequency of 5/100,000 population are:

- **Asia** [Araki et al 1987, Hou et al 1992]
- **Sub-Saharan Africa**
- **South America** [Callegaro et al 1992]. Data continues to emerge on prevalence in S. America.

A reported increase in the prevalence of MS in some of the latter regions over the last decades may represent a real increase or better ascertainment [Callegaro et al 2001, Itoh et al 2003].

Causes

Environmental Causes

Epidemiological and genetic methods have suggested a role of infectious pathogens in MS. At least four lines of evidence support an environmental contribution to MS etiology:

- Geographical
- Seasonal [Koziol & Feng 2004]
- Socioeconomic variations in the incidence and prevalence of MS [Hammond et al 1996]
- Migration studies [Alter et al 1978, Kurtzke et al 1985]

In addition, a concordance rate of only about 30% among monozygotic twin siblings of index cases confirms an etiologic role for non-genomic factors.

Despite evolving and ever more sensitive detection techniques, not a single agent (virus, bacteria, toxin) has gained acceptance as the causal agent in MS. The expectation that a single

agent would have enough specificity and universality to account for all cases of MS is unrealistic.

Heritable Causes

Recurrence risk estimates in families combined with twin data predict that the MS-prone genotype results from multiple independent or interacting polymorphic genes, each exerting a small or moderate effect; however, no gene mutation has been specifically associated with MS pathogenesis.

Some studies have reported intrafamilial concordance for disease course, disease severity, and age of onset [Robertson, Clayton et al 1996; Oturai et al 2004], but others have not. Concordance for age at onset may be greater among identical female twins.

The clinical course and severity of MS may also differ among ethnic groups [Osuntokun 1971, Cabre et al 2001, Houzen et al 2003, Cree et al 2004]. Conceivably, this phenotypic aggregation is a result of genetic sharing. Several reported studies examining the influence of genes *(HLA, fIL-1R, TNF, APOE, CTLA4,* and *CCR5* among others) on MS disease course and severity await confirmation.

Equally significant is the likelihood of genetic heterogeneity, meaning that specific genes influence susceptibility and pathogenesis in some affected individuals, but not in others. Genes affecting susceptibility are probably different from those affecting clinical outcome.

The identification of specific genetic determinants has been difficult; the only strong and consistent linkage finding has been at chromosome 6p21, the location of the major histocompatibility complex (MHC) [Ebers et al 1996, Haines et al 1996, Kuokkanen et al 1996, Sawcer et al 1996]. For individuals of Northern European origin, there is consensus that one copy of the common HLA allele, *DRB1*1501* increases the risk of MS by an odds ratio of about three. The *HLA-DRB1*1501*, allele is common, occurring in 15-30% of persons of North European origin.

Much of the genetic effect in MS remains to be explained: While some loci may be involved in the initial pathogenic events, others could affect the progression of the disease.

Evaluation Strategy

Once the diagnosis of multiple sclerosis has been established in an individual, it is appropriate to determine if it appears to be heritable. A three-generation family history with attention to other relatives with neurologic signs and symptoms should be obtained. Documentation of relevant findings in relatives can be accomplished either through direct examination of those individuals or review of their medical records including laboratory test results, neuroimaging studies, and the results of autopsy examinations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

While evidence implicates a genetic component in the pathogenesis of MS, a simple model of inheritance is unlikely. Available data suggest a complex multifactorial etiology, including interactions of genetic and environmental factors.

- A nonlinear decrease in disease risk in families with increasing genetic distance from the index case has been observed.
- Recurrence risk estimates in twin data and multiplex families predict that a genotype predisposing to the development of MS results from multiple independent and/or interacting polymorphic genes, each of which may exert a minor or moderate effect [Dwosh et al 2003a, Dwosh et al 2003b].

Risk to Family Members

Considering a lifetime prevalence of MS in the general population of 0.2%, the age-adjusted recurrence risk estimates (in %) of family members vs the general population is summarized in Table 1.

Table 1. Risk Estimates for Multiple Sclerosis in First-Degree Relatives of a Probanf

Relationship to Proband	Age-Adjusted Risk Estimate vs the General Population [1]
Parents	2.0 - 3.0%
Sibs	3.0 - 5.0% If one or both parents have MS, the risk can increase to 29.5% [2]
Offspring	2.0 - 3.0% [3]

1. Sadovnick et al 1988; Robertson, Fraser et al 1996; Montomoli et al 2002
2. Sadovnick et al 1999
3. Higher if both parents have MS

Management

Treatment of Manifestations

Disease-modifying agents. Evidence from controlled randomized clinical trials suggests that all currently approved agents for the treatment of MS decrease the clinical relapse rate and accompanying inflammation within the CNS [IFNB MS Study Group 1993, Johnson et al 1995, Jacobs et al 2000, Hartung et al 2002].

Interferon beta (IFNβ)

- The first agent to be approved in 1993 for the treatment of RR-MS was IFNβ-1b (Betaseron®). This agent reduced the rate of exacerbations of RR-MS in a multi-center trial [IFNB MS Study Group 1993]. In addition, IFNβ-1b reduced the number and frequency of lesions on brain MRI [IFNB MS Study Group 1993]
- In 1996, another multi-center placebo-controlled trial demonstrated that IFNβ-1a (Avonex®), administered intramuscularly once weekly to individuals with RR-MS, delayed the time to sustained clinical disability and decreased the exacerbation rate [Jacobs et al 1996].
- Another IFNβ-1a (Rebif®) preparation reduced the number of clinical attacks, the percentage of MRI T2-weighted lesions, and sustained disease progression. A more recent phase IV clinical trial demonstrated that Rebif®, given at 44 µg subcutaneously three times weekly, was significantly more effective than Avonex®, given at 30 µg intramuscularly once weekly, in reducing relapses and magnetic resonance imaging (MRI) activity in persons with relapsing-remitting multiple sclerosis at 24 and 48

weeks of therapy. This trial led to the approval of Rebif® in the United States [Panitch et al 2002].

The role of interferon beta in clinical phenotypes other than RR-MS is less clear. In 1999, a European double-blinded, placebo-controlled trial demonstrated that IFNβ-1b treatment resulted in a highly significant delay in progression in SP-MS [European Study Group 1998]. These results could not be reproduced in a North American study (unpublished data). Currently, IFNβ-1b is only approved in Europe for treatment of individuals with SP-MS.

Glatiramer acetate (GA). A multi-center, randomized study showed that GA (Copaxone®) decreased the frequency of clinical exacerbations by 29% [Johnson et al 1995]. In a subset of individuals, MRI studies showed that GA treatment significantly decreased the percent annual MRI lesion volume and brain atrophy.

Mitoxantrone. In 2002, Mitoxantrone (Novantrone®) was the first agent to be approved for treatment of SP-MS with worsening relapsing and progressive relapsing disease course [Hartung et al 2002]. In a placebo-controlled randomized trial, mitoxantrone reduced sustained disease progression by 64% and the number of treated relapses by 69% [Hartung et al 2002].

Symptomatic treatment. Various medications are utilized for symptomatic treatment of pain, muscle spasms, fatigue, depression, sexual dysfunction, and bladder and bowel dysfunction [Krupp & Rizvi 2002].

Surveillance

Assessment with a periodic neurological examination continues to be the most important means of tracking changes in disease manifestations and hence progression. The interval recommended for follow-up ranges from once a month to every two years, depending on clinical disease activity.

In addition to the clinical neurological examination, brain and spinal cord MRIs are now routinely obtained in regular intervals to monitor disease activity. Currently no consensus exists regarding the frequency at which imaging studies should be performed nor is there a generally accepted imaging protocol. It is conceivable that with improvement in imaging techniques, new recommendations will emerge regarding the interval for follow-up imaging studies.

Additional examination techniques may be added, including the ambulation index (AI), EDSS [Kurtzke 1983], the 25-foot timed walk, the MS functional composite (MSFC) [Cutter et al 1999] that combines a timed 25-foot walk (T-25), the nine hole peg test (a measure of upper extremity function), and the paced serial auditory addition test (PASAT; a measure of cognitive capabilities) [Hobart et al 2004]. Many of these tests are useful as outcome measures in clinical trials. However, time restraints limit their application in daily clinical practice.

Agents/Circumstances to Avoid

Two circumstances associated with clinical MS exacerbations:

- **Febrile infections** [Gilden 2002]. Physicians should be vigilant about possible infections; the threshold for paraclinical diagnostic tests should be low.
- **Postpartum period** [Confavreux et al 1998, Vukusic et al 2004]. In women who are planning to become pregnant, pharmacotherapy is typically discontinued because of the potentially teratogenic and abortifacent properties of many experimental and approved agents [Hughes 2004]. In addition, the last two trimesters of pregnancy convey protection from clinical attacks [Runmarker & Andersen 1995, Confavreux et al 1998, Vukusic et al 2004]. Potential exacerbations during the postpartum period

can often be managed by initiating immunomodulatory therapy soon after delivery [Achiron et al 2004, de Seze et al 2004]. Treatment strategies for this period, and their potential implications for mother and child, should be discussed closely with affected individuals and their families.

Testing of Relatives at Risk

Early pharmacological intervention with immunomodulatory agents may be clinically beneficial [Jacobs et al 2000, Comi et al 2001, PRISMS 2001].

Currently, numerous experimental therapies and diagnostic procedures are being evaluated in MS. Search ClinicalTrials.gov for access to information on clinical studies for multiple sclerosis.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

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Multiple Sclerosis

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

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