

Ministry of Defence

Synopsis of Causation

Multiple Sclerosis

Author: Dr David Jenkins, Medical Author, Medical Text, Edinburgh
Validator: Dr Paul Jarman, The National Hospital for Neurology and Neurosurgery, London

September 2008

Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

The Ministry of Defence accepts full responsibility for the contents of this synopsis, and for any claims for loss, damage or injury arising from the use of this synopsis by the Ministry of Defence.

1. Definition

- 1.1. Multiple sclerosis is a disease of the central nervous system caused by inflammatory [demyelination](#) of nerve fibres in the brain, brainstem and spinal cord.
- 1.2. Nerve fibres have an outer layer of [lipoprotein](#) forming the [myelin](#) sheath which is essential for normal transmission of nerve impulses within the nervous system.
- 1.3. The process of demyelination involves the breakdown of the myelin sheath, with resulting disruption of nerve impulse transmission. This produces a variety of functional effects depending on the particular part of the brain or nerve tracts that are affected. Demyelination can occur in early life as a result of inherited or congenital metabolic disorders. In later life it can occur in a variety of conditions including the syndrome of multiple sclerosis. What typifies multiple sclerosis is the development of localised areas of inflammation and demyelination which arise unpredictably in different parts of the nervous system over a period of time. It usually runs a course of relapse and remission and may lead to gradually increasing disability over a period of years.
- 1.4. Synonyms include:
 - Disseminated sclerosis
 - Focal sclerosis
 - Insular sclerosis
 - Sclerosis in plaques
 - MS
- 1.5. The usual age of onset is between 18 and 50 years with a peak age of onset of 24 years but it can occur in any age group including childhood.
- 1.6. Multiple sclerosis is 1.6-2 times more common in females and this ratio is higher (3:1) where onset is before age 15 years. Primary progressive forms are more common in older males. It is estimated that 85 000 people in the United Kingdom have multiple sclerosis, with a prevalence of approximately 1/1000 of the population.¹

2. Clinical Features²

- 2.1. Multiple sclerosis is one of the more common disabling neurological conditions affecting younger people.
- 2.2. The typical pathological lesion is of infiltration by [lymphocytes](#) and [macrophages](#) around the vascular areas of the myelin sheath forming [indurated](#) inflammatory plaques. These can occur in the white matter of the brain, the brain stem and the spinal cord. Areas affected by the plaques have impaired ability to conduct nerve impulses, with significant functional effect on the areas supplied by the nerve pathway.
- 2.3. The clinical features and presentation vary considerably depending on the location of demyelination within the nervous system. The condition has been described as being ‘dynamic’, with plaques developing and resolving with progress of time. Severity and progress of disease depends to some extent on the relative rate of development and regression of the inflammatory lesions.
- 2.4. There are variable symptoms and signs of central nervous system dysfunction which can remit fully, remit partially or persist. Relapses may occur infrequently, sometimes with many years between episodes, or can occur at regular intervals with increasing frequency. Rate of progression of disability depends to some extent on frequency of relapse, the duration of the attack, whether it fully resolves in remission and the particular area affected. Clinical variants can be summarised as following the forms:³
 - Primary progressive
 - Relapsing remitting
 - Relapsing progressive
 - Secondary progressive
- 2.5. Physical and/or mental health symptoms can occur.
 - 2.5.1. **Physical signs and symptoms** may include:
 - [Paraesthesia](#) in one or more parts of the limbs, the trunk or the face
 - Clumsiness or weakness of an upper and/or lower limb
 - Stiffness, pain or fatigue in a limb
 - Gait disturbance
 - Partial or complete loss of vision or visual field, usually in one eye
 - Pain in the eye from optic neuritis
 - [Ocular palsy](#)
 - Loss of bladder control
 - [Dysarthria](#) - speech difficulties (slurred speech)
 - 2.5.2. **Mental health symptoms** may include:
 - Apathy, lack of judgement
 - Emotional lability
 - Euphoria
 - Depressed mood
 - [Dysphasia](#) - difficulty finding words, speech hesitancy

- 2.6. As the disease progresses and more areas are affected, multiple problems appear with significant disability due to weakness, spasticity (stiffness), ataxia, loss of balance, loss of sensation with subsequent injury from burns or cuts, difficulty feeding, swallowing, dressing, and managing personal hygiene. The disease may run a course lasting many years and, despite the severity of disability, life expectancy is around 25 years. Mortality is often due to complications, such as infection in immobile patients, rather than the condition itself. In severe cases early death may be due to respiratory failure from involvement of the medulla or massive cerebral demyelination. The symptoms can present in three phases – relapse with full recovery, relapse with persisting deficit and secondary progression. Some patients may spend several years or possibly decades in one phase whereas others may progress rapidly between phases. Around 25% have little or no disability from the condition. Patients who present with sensory or visual symptoms seem to have longer periods of remission and less disability than those with early motor deficit.^{2,3}
- 2.7. **Diagnosis.** There is no specific test for multiple sclerosis. Diagnosis is based on the history and presentation, pattern and type of symptoms. Early diagnosis can be difficult as presentation may be non-specific with vague symptoms. A particular problem is the difficulty in making a firm diagnosis after a first ever attack of symptoms compatible with demyelination – a so-called ‘clinically isolated syndrome’. Diagnosis may be delayed until a further clinical episode occurs or until a follow-up MRI scan demonstrates new areas of demyelination not present on the initial scan at the time of presentation. The reluctance to come to a conclusion on the diagnosis in the early stages, coupled with a long period between relapses can add to this delay. MRI scan is essential for showing plaques, particularly in the brain. The number and pattern of lesions found on MRI gives some indication of prognosis with regard to disease severity.⁴ Cerebrospinal fluid usually shows raised [IgG](#) levels with [oligoclonal](#) band pattern on [electrophoresis](#).² Lymphocytes numbers and protein levels in CSF are sometimes elevated.
- 2.8. **Differential diagnosis.** The following conditions may need to be eliminated in coming to a diagnosis of multiple sclerosis:
- Amyotrophic lateral sclerosis
 - Syringomyelia
 - Spinal nerve root pressure
 - Tumours of the nervous system
 - Hereditary ataxia
 - Lyme disease
 - Cerebral infarction
 - Systemic Lupus erythematosus
 - Pernicious anaemia
 - Guillain-Barré disease

A diagnosis of multiple sclerosis has a significant impact on the life of a patient and family members, and a conjectural diagnosis or treatment based on speculation should be avoided. Not every incidence of demyelination necessarily means a diagnosis of multiple sclerosis and other conditions within the differential should be considered before this diagnosis is made.

3. Aetiology

- 3.1. The cause of multiple sclerosis is not fully understood. The condition has an autoimmune basis that appears to be mainly affected by genetic and environmental factors.
 - 3.1.1. An autoimmune disease is one where the immune system produces antibodies to an antigen that arises within the body rather than from external sources and the subsequent immune reaction causes injury to the body's own tissues.
- 3.2. **Genetic factors**
 - 3.2.1. The apparent autoimmune nature of multiple sclerosis has long been considered to be associated with genetic predisposition.⁵
 - 3.2.2. No specific genetic abnormality has yet been identified as causing the disease but extensive research continues to try to identify such an abnormality. Risk of multiple sclerosis is 2%-5% in first degree relatives of sufferers and this represents about a 20-40 fold increase in risk compared with the general population. Studies in twins have shown concordance rates of around 30% in monozygotic twins with lower rates in dizygotic twins giving further indication of a genetic predisposition.^{2,6}
 - 3.2.3. Twenty percent of patients with multiple sclerosis have at least one affected relative. About 4% of first degree relatives of patients develop the disease.⁷ A study of rates of multiple sclerosis in adopted relatives of patients showed that familial distribution is due to genetic rather than environmental factors.⁸
 - 3.2.4. Genes found in the general population are subject to variation in their make up (polymorphism). Predominance of a variation that influences immune reactivity may give an exaggerated immune response to certain antigens that can lead to autoimmunity. Research has focused particularly on genes that promote antigen formation such as the human leukocyte antigens (HLA) which are highly polymorphic and have been shown to play a role in multiple sclerosis susceptibility. Linkage with genetic areas where such genes occur supports the contention that genetic factors predispose to the disease. Factors influencing the activation of T cells in the mediation of the immune response have also been implicated. However, with the exception of HLA association, genetic studies have failed to find a consistent association with specific genetic abnormalities.^{9,10}
- 3.3. **Distribution of multiple sclerosis.** Multiple sclerosis is not rare and affects millions worldwide. Prevalence varies depending on geographical factors and higher levels are encountered with increasing distance from the equator. It has a predilection for Caucasians, and Northern Europe and North America have a high prevalence of the disease. At least 350,000 people in Europe have the condition and around 350,000 in the United States alone. However, wide variations occur between different countries. It is rare among Chinese, Japanese, the African black population and New Zealand Maoris. One review of over 400 publications dealing with prevalence of multiple sclerosis emphasised that comparison of prevalence remains difficult because of problems caused by variability in surveyed population sizes, age structure and ethnic background. An

updated review of the distribution of multiple sclerosis in Europe gives many exceptions to the previously described north/south variation suggesting that genetic and environmental factors may play as much part as geographical location.¹¹

- 3.3.1. One meta-analysis of prevalence studies between 1980 and 1998 looked at standardising incidence and prevalence rates by age and sex. This showed that the apparent latitudinal effect on incidence of multiple sclerosis was significantly less remarkable when figures standardised for age and sex are analysed than when crude rates were used.¹² A study in year 2000 looked at the prevalence of multiple sclerosis in the Australian-born population in five areas of Australia and compared this with rates for the immigrant population from UK and Ireland (UKI). Prevalence in both groups showed a close correlation with latitude, with higher rates to the south. The figures were confounded somewhat by a particularly high rate in Hobart but for those who immigrated before age 15 years from areas of high prevalence in UKI to low prevalence parts of Australia there was no significant difference in risk from that of the local population.
- 3.3.2. Although the latitudinal gradient of incidence of multiple sclerosis is still referred to in many formal texts, this effect is not consistent. There are geographic areas where the incidence of multiple sclerosis is high but it is not possible to relate either the area of origin or where one currently lives as a specific explanation for developing multiple sclerosis. Geographic variability could be related to the genetic make-up of the population or to some feature in the local environment, either of which may be dependent upon latitude.
- 3.3.3. While evidence of a genetic predilection to multiple sclerosis is strong, no single gene has been identified as the cause. It seems that several genetic variants may interplay to give this effect.

3.4. **Environmental factors**

- 3.4.1. Geographical variation in prevalence and the autoimmune nature of multiple sclerosis suggests that environmental factors play a part in causation. Agents such as bacteria or viruses as well as a variety of potential environmental toxins have been suggested as possible causes.
- 3.4.2. The changing risk of multiple sclerosis with migration suggests effects of environmental factors on development of the disease. Immigrant populations tend to acquire the risk of the new location. Migration from high to low risk areas before age 15 lowers the overall risk of developing multiple sclerosis. Clusters of the disease such as those in Iceland and the Faroe Islands further suggests an environmental factor, possibly due to exposure of the local population to some agent brought in during the influx of non-indigenous people.⁷
- 3.4.3. The pattern of disease suggests that multiple sclerosis is triggered by an environmental factor in persons who are genetically susceptible and the pattern of familial distribution implies that several genes contribute to the susceptibility. The potential environmental agents that trigger the effect have been subject to much speculation and research. Infection, cold climate, type of

soil, peat level in soil, toxic chemicals, head injury and trauma have all been investigated at some time.

3.5. Infection

- 3.5.1. Relapses can occur in 9% of patients following infection with common upper respiratory viruses and there can be a history of preceding infection in up to 27% of cases.³ It has been hypothesised that an infectious agent may be responsible for triggering multiple sclerosis. A review of the evidence in support of this hypothesis concluded it is based on the findings of different geographic gradients in frequency among Caucasians, changes in prevalence due to migration, clustering of cases in small communities, and low degree of concordance in monozygotic twins. The hypothesis is confounded by the lack of evidence of a specific agent and weaknesses in the analytical studies that have tested the association. Viral infection due to measles, minor respiratory infection, herpes simplex virus, papilloma virus, canine distemper, Epstein-Barr virus, adenovirus, mumps and rubella have all been investigated as potential causes. Infection from other organisms such as *Chlamydia* and *Mycoplasma pneumoniae* have also been implicated. No direct causal relationship has been established between any of these infections and multiple sclerosis.¹³

Some more specific features of consideration of the effects of infection relate to:

- 3.5.2. **Epstein-Barr virus (EBV).** [Mononucleosis](#) is a common infection of childhood and adolescence. Evidence shows that in areas of high prevalence of multiple sclerosis, one-third of the population has no evidence of previous infection by Epstein-Barr virus at puberty. In contrast, areas of low prevalence have almost complete seroconversion to EBV by adolescence. Childhood immunity to EBV appears to confer protection against multiple sclerosis whereas infection by EBV in adolescence appears to be associated with greater incidence in later life in those with other predisposing genetic factors.¹⁴ Despite this, no direct causative link is established.
- 3.5.3. [Herpes virus.](#) Human herpesvirus 6 (HHV-6) and other herpes viruses have the ability to invade all types of nerve tissue and their ability to periodically reactivate leads to speculation about an influence on relapse and remission of multiple sclerosis. HHV-6 has been isolated from plaques in multiple sclerosis and can also induce demyelination in experimental animals. A recent review of studies showing reported associations between herpes virus and multiple sclerosis concluded that the association was not confirmed and remains controversial.^{15,16}
- 3.5.4. **Hepatitis B vaccine.** Vaccination against hepatitis B virus has also been implicated as a factor in predisposition to multiple sclerosis. A review of evidence for this in 2001 followed a decision by the French government to compensate three recipients of hepatitis B vaccine preceding the onset of multiple sclerosis. That decision presumed a causal link between the two events but the review concluded that available evidence either does not support a causal link or is at most equivocal. It advised that larger and longer randomised trials were needed before such a link could be accepted. A further review in 2002 concluded that there is only weak evidence to support an association

between hepatitis B vaccine and multiple sclerosis, and epidemiological studies have shown that hepatitis B vaccine does not increase the risk of multiple sclerosis. The US Institute of Medicine has concluded that current evidence supports rejection of a causal link between hepatitis and multiple sclerosis.^{17,18}

- 3.5.5. **Other viral infections.** Common childhood illnesses such as measles, rubella and [varicella](#) form a substantial background of immune challenge in childhood. This has led to speculation that these viruses are a potential cause or exacerbating factor of multiple sclerosis. A review of data relating to the link between vaccinations and multiple sclerosis in 2001 concluded that current evidence shows that vaccinations do not increase the risk of multiple sclerosis. A further review in 2001 covering the association between multiple sclerosis and varicella-zoster virus concluded that there was large variability in the quality of evidence and no substantive evidence could be found to link infection to causation of multiple sclerosis. Indeed, the five studies within the review that had the best methodology failed to show an increased risk of multiple sclerosis from varicella-zoster virus infection.^{19,20}

3.6. Other environmental considerations

- 3.6.1. **Allergy.** Epidemiological studies have shown that autoimmune and allergic diseases are more common in 'developed' countries with an inverse association with frequency of childhood infections. There is recent evidence that allergy may influence the development of autoimmunity. Those who are more likely to have been exposed to a greater degree to infection in early life are less likely to develop allergic conditions and also less likely to develop multiple sclerosis.
- 3.6.2. **Toxic Chemicals.** The multifactorial nature of multiple sclerosis has led to speculation that toxicity due to a variety of chemical substances may be a causative factor. Organic solvents are known to cause several types of neurotoxicity. Many studies have examined the possible association between exposure to solvents and later development of multiple sclerosis. Results have been variable with some showing a positive association and others not making a link. An extensive cohort study from Finland compared incidence of multiple sclerosis in twin pairs where one had been exposed to solvents and one had not. Twenty-one cases fulfilled criteria for diagnosis of multiple sclerosis and detailed occupational history showed exposure to a mixture of solvents in six cases, trichloroethylene in one and lead in another. Of these, two cases in a twin pair had multiple sclerosis but in the rest the co-twins were healthy. The report concluded that the findings did not support a causal association between occupational exposure to chemicals and multiple sclerosis.²¹ Overall the evidence of a causal link with solvents has been at best equivocal with results being based on retrospective recall and small numbers.
- 3.6.3. **Mercury and other metals.** There has been a great deal of interest in the possible link between multiple sclerosis and the use of mercury amalgam in dentistry. There is a hypothesis that suggests that retrograde seepage of ionic mercury from root canals, coupled with recurrent caries and erosion can lead to multiple sclerosis.²² Lead absorption has also been considered as a cause, as has the effect of zinc but all of these remain unproven and require further investigation.

- 3.6.4. **Trauma.** The role of injury in causing multiple sclerosis or initiating exacerbations has been investigated. An American study looked in detail at the possible link between multiple sclerosis and physical and psychological trauma. This reviewed a large number of papers on the topic and concluded that on the basis of generally strong evidence there was no support for an association between trauma, particularly head trauma, and the onset or exacerbation of multiple sclerosis. Neither was there any strong evidence to link psychological stress causally with multiple sclerosis.²³ Another prospective study followed 170 cases of multiple sclerosis and 134 controls prospectively over eight years. The results published in 1991 concluded there was no evidence of a relationship between trauma and exacerbation of multiple sclerosis.²⁴ Sufferers do have an increased incidence of injuries from falls and burns due to loss of sensation, weakness and poor coordination but there is no support for a causal link with onset or exacerbation of the disease.
- 3.6.5. **Diet.** Factors in diet have been claimed to affect both onset and exacerbation of multiple sclerosis, including the effects of 'junk food', synthetic additives, food contamination and allergies. There is no compelling scientific evidence to support this association and it remains an anecdotal view. It has been suggested that a high fibre diet or a diet rich in lipoproteins helps to reduce the effects of multiple sclerosis but again there is no compelling evidence to support this. Maintenance of a nutritious, balanced diet is encouraged as helpful in maintaining physical wellbeing but not with the expectation of modifying the course of the illness.
- 3.7. Despite the extensive research into causation, no specific factor has been established and it remains likely that the aetiology of multiple sclerosis is a complex mix of genetic and environmental factors with several of these coming together to initiate the immune reaction that leads to demyelination.

4. Prognosis

- 4.1. Clinical progression and outcome depend on the type of presentation, frequency and severity of acute exacerbations, the areas of the central nervous system affected and response to treatment.
- 4.2. The **primary progressive** form affects 10-15% from onset, tends to present more commonly in middle aged men and progresses steadily without remission. In the **relapsing remitting** type of multiple sclerosis, variable periods of remission lasting sometimes several years occur most commonly. A significant proportion of patients with relapsing remitting multiple sclerosis will go on to develop the **secondary progressive** form, usually after several years, with gradually progressive disability in the absence of relapses. The **relapsing progressive** form, where residual disability persists after an exacerbation accounts for a smaller proportion of cases.
- 4.3. Around 80% of cases are of the relapsing remitting type and, of this group, about 50% develop the secondary progressive form within 10 years. Ultimately 75-80% of cases are likely to enter the secondary progressive stage. In 5% of cases the disease pursues a relentless course, with rapid progression, severe disability and early death. Around 25% of cases may have persistent mild symptoms with no effective disability.⁴ Prognosis is relatively good where sensory or visual symptoms predominate with almost complete recovery between attacks.
- 4.4. Some patients may go for many years between episodes but about 15% may become very disabled in the shorter term. Prognosis is poorer when the onset of disease occurs in the fifth decade of life. Apart from the small proportion of rapidly progressive cases, life expectancy is not significantly reduced. A large proportion of patients die from other intercurrent conditions. Death from multiple sclerosis in advanced stages is usually from gross debility, malnutrition and respiratory failure due to postural difficulties, problems swallowing and weakness of respiratory musculature.
- 4.5. The Kurtzke Expanded Disability Status Scale (EDSS) is widely used as a measure of the severity of disability. This uses a score of 1-10 based on the clinical status, where 1 represents no disability and 10 represents death due to multiple sclerosis. Although this does not correspond to disease progression in a linear way it is useful as a measure to attempt to standardise disability and measure progression.
- 4.6. Treatment is aimed at:
 - Reducing the duration and severity of an acute attack
 - Preventing or slowing the frequency of relapses and slowing rate of progression in progressive disease
 - Minimising secondary symptoms
 - Minimising the effects of residual disability
- 4.7. In the UK, the National Institute for Health and Clinical Excellence (NICE), has developed guidelines for all aspects of clinical management of multiple sclerosis, including provision of diagnostic, support and therapeutic measures.²⁵

- 4.8. Treatment regimes are complex depending on the type of presentation and stage reached. Drug treatment falls into three broad categories - treatment of the acute attack, treatment that may alter disease progress, and management of specific symptoms.
- 4.8.1. The acute attack is managed by treatment with corticosteroid drugs either orally or intravenously and this is helpful in abbreviating the acute episode.
- 4.8.2. Drugs which alter the immune response such as β interferons, glatiramer acetate and others are used to ameliorate the acute episode and reduce frequency of relapses. The use of combination treatment with several interferons and glatiramer acetate has been shown to reduce the rate of development of new lesions. The use of β interferon has been shown to give a 30% reduction in relapse rate over a two-year period.^{2,26}
- 4.8.3. Symptoms such as muscle cramps or spasm, spasticity, pain, fatigue, and constipation are treated by drugs used generally for these symptoms. Urinary frequency and incontinence requires appropriate specialist treatment. The role of cannabis alkaloids in managing pain and spasticity is currently under investigation.
- 4.9. Physical therapy such as physiotherapy and occupational therapy can help to minimise the effects of disability and are an important part of neurological rehabilitation for patients with MS.

5. Summary

- 5.1. Multiple sclerosis is a common disorder of the central nervous system affecting around 1 in 1000 people in the United Kingdom. Prevalence tends to increase with increasing latitude and there are some localised areas of increased prevalence.
- 5.2. The disease generally runs a variable course of relapse and remission with attacks affecting widespread and variable areas of the nervous system. Severity of disability also depends on the frequency and duration of exacerbations and the pattern of progression but the disease often takes years to reach an advanced stage. Approximately 5% of cases progress continuously with no remission.
- 5.3. The cause is not known but the underlying pathological lesion is an inflammatory demyelination occurring in localised plaques throughout the brain and spinal cord that is probably due to an autoimmune reaction.
- 5.4. Autoimmune reaction is associated with a variety of factors including genetic and environmental features. Factors such as viral or bacterial infection, chemical toxicity of various sorts, trauma, allergy and diet have all been considered as precipitants but no reliable relationship with any of these has been established.
- 5.5. Treatment is aimed at reducing the local effects of an exacerbation, reducing frequency and duration of relapse, and symptomatic management of progressive disability. Current treatment options are not curative and no preventative measures are available.
- 5.6. At present this condition appears to be due to the effect of an environmental trigger on a genetically susceptible individual. Methods of identifying and screening for susceptibility and trigger factors are still subjects of ongoing research. In view of there being no identified specific factor and the wide range of potential associations with causation, it would be difficult to attribute causation to a specific exposure or experience in individual cases.

6. Related synopses

Motor Neurone Disease

Parkinson's Disease

7. Glossary

autoimmune disease	Illness which occurs when the tissues are attacked by the body's own immune system.
demyelination	Destruction or breakdown of the fatty sheath lining a nerve fibre.
dysarthria	A problem with speech due to difficulty with articulation resulting from a disorder of muscle control or structural damage to the organs of speech.
dysphasia	A problem with speech due to difficulties with recall and use of words resulting from a disorder of the areas of the brain that deal with language.
electrophoresis	A test where a body fluid is applied to a gel and an electrical voltage is passed across it. Proteins in the fluid migrate across the gel in different proportions according to their molecular type.
herpes virus	Common viral infection that causes "cold sores" and other superficial infections of the skin and genital areas.
IgG	Abbreviation for "immunoglobulin G" – one of the circulating blood proteins involved in the immune response.
indurated	Abnormally hardened or thickened.
lipoprotein	A complex substance formed of protein with a fatty component that helps transport insoluble fats in the blood stream and forms part of the myelin (<i>q.v.</i>) in nerve sheaths.
lymphocytes	Circulating white blood cells that are associated with functions conferring immunity.
macrophages	Circulating white blood cells that play an important part in organisation and repair of damaged body tissue by killing micro-organisms and ingesting dead tissue.
mononucleosis	Infectious disease, most common in young adults and adolescents, caused by the Epstein-Barr virus and commonly known as glandular fever.
myelin	A white fatty substance that forms the outer layer of a nerve fibre known as the myelin sheath.
ocular palsy	Paralysis of the muscles controlling eye movement.
oligoclonal band	A pattern of bands of immunoglobulin protein that show up on electrophoresis (<i>q.v.</i>) of the cerebrospinal fluid in multiple sclerosis.

paraesthesia

An abnormality of sensation commonly described as tingling, numbness or “pins and needles”.

varicella

Chicken pox, an infectious disease caused by the varicella-zoster virus.

8. References

- ¹ Department of Health UK. Neurological conditions outline. [Online]. 2004 [cited 2004 Jul]. Available from: URL:<http://www.dh.gov.uk/publications/>
- ² Dangond F. Multiple sclerosis. [Online]. 2004 [cited 2004 Jul 12]. Available from: URL:<http://www.emedicine.com>
- ³ Multiple sclerosis. In: Warrell D, Cox T, Firth J, et al, editors. Oxford textbook of medicine. 4th ed. Oxford: Oxford University Press; 2004.
- ⁴ Brex PA, Ciccarelli O, O'Riordan JI et al. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med* 2002;346(3):158-64.
- ⁵ Compston A. The genetics of multiple sclerosis. *J Neurovirol* 2000;6 Suppl 2:S5-9.
- ⁶ Ebers GC, Bulman DE, Sadovnick AD et al. A population-based study of multiple sclerosis in twins. *N Engl J Med* 1986;315(26):1638-42.
- ⁷ Pirko I, Noseworthy JH. Demyelinating disorders of the central nervous system: multiple sclerosis. In: Goetz CG, editor. Textbook of clinical neurology. 2nd ed. Philadelphia PA: WB Saunders; 2003. p. 1060-6.
- ⁸ Ebers GC, Sadovnick AD, Risch NJ. A genetic basis for familial aggregation in multiple sclerosis. Canadian Collaborative Study Group. *Nature* 1995;377:150-1.
- ⁹ Kenealy SJ, Pericak-Vance MA, Haines JL. The genetic epidemiology of multiple sclerosis. *J Neuroimmunol* 2003;43(1-2):7-12.
- ¹⁰ Eoli M, Pandolfo M, Amoroso A et al. Evidence of a linkage between susceptibility to multiple sclerosis and HL-class II loci in Italian multiplex families. *Eur J Hum Genet* 1995;3(5):303-11.
- ¹¹ Rosati G. The prevalence of multiple sclerosis in the world: an update. *Neurol Sci* 2001;22(2):117-39.
- ¹² Zivadinov R, Iona L, Monti-Bragadin L et al. The use of standardised incidence and prevalence rates in epidemiological studies on multiple sclerosis. A meta-analysis study. *Neuroepidemiology* 2003;22(1):65-74.
- ¹³ Granieri E, Casetta I, Tola MR, Ferrante P. Multiple sclerosis: infectious hypothesis. *Neurol Sci* 2001;22(2):179-85.
- ¹⁴ Haahr S, Plesner AM, Vestergaard BF et al. A role of late Epstein-Barr virus infection in multiple sclerosis. *Acta Neurol Scand* 2004;109(4):270-5.
- ¹⁵ Enbom M. Human herpesvirus 6 in the pathogenesis of multiple sclerosis. *APMIS* 2001;109(6):401-11.
- ¹⁶ Simmons A. Herpesvirus and multiple sclerosis. *Herpes* 2001;8(3):60-3.
- ¹⁷ DeStefano F, Verstraeten T, Chen RT. Hepatitis B vaccine and risk of multiple sclerosis. *Expert Rev Vaccines* 2002;1(4):461-6.
- ¹⁸ Jefferson T, Heijbel H. Demyelinating disease and hepatitis B vaccination: is there a link? *Drug Saf* 2001;24(4):249-54.
- ¹⁹ Sievers EJ, Heyneman CA. Relationship between vaccinations and multiple sclerosis. *Ann Pharmacother* 2002;36(1):160-2.
- ²⁰ Marrie RA, Wolfson C. Multiple sclerosis and varicella zoster virus infection: a review. *Epidemiol Infect* 2001;27(2):315-25.
- ²¹ Juntunen J, Kinnunen E, Antti-Poika M et al. Multiple sclerosis and occupational exposure to chemicals: a co-twin study of a nationwide series of twins. *Br J Ind Med* 1989;46(6):417-9.
- ²² Ingalls TH. Epidemiology, etiology and prevention of multiple sclerosis. Hypothesis and fact. *Am J Forensic Med Pathol* 1983;4(1):55-61.
- ²³ Goodin DS, Ebers GC, Johnson KP et al. The relationship of MS to physical trauma and psychological stress. *Neurology* 1999;52:1737-45.
- ²⁴ Sibley WA, Bamford CR, Clark K et al. A prospective study of physical trauma and multiple sclerosis. *J Neurol Neurosurg Psychiatry* 1991;54:584-9.
- ²⁵ National Institute for Clinical Excellence. Management of multiple sclerosis in primary and secondary care. Clinical Guideline 8. [Online]. 2003 Nov [cited 2004 July]. Available from: URL:<http://www.nice.org.uk/nicemedia/pdf/cg008guidance.pdf>
- ²⁶ Jacobs LD, Beck RW, Simon JH et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Eng J Med* 2000;343(13):898-904.