

MODULE 1

Understanding Multiple Sclerosis

English Version

★★★★★
professional
msnurse
A Project of the European Multiple Sclerosis Platform



CME Module Title Understanding Multiple Sclerosis

Learning Objectives

After completing this activity, the participant should be better able to:

- Appreciate the importance of understanding the pathophysiology of MS as a foundation for making decisions concerning the management of MS.
- Identify the various types of MS and know their natural history and progression.
- State the genetic, race, gender and environmental factors which affect the incidence of MS.
- Describe the structure of the nervous system and how its function is altered by MS.
- Explain the function of the immune system and how its role is disrupted by MS.
- Describe the underlying pathophysiological causes of the most common symptoms associated with MS.
- Recognise that central to this is the inflammation and demyelination of axons which disrupts neural conduction.
- Appreciate that cortical pathology, that is, inflammatory focal lesions (cortical lesions) and atrophy (cortical thickness), may determine cognitive disability in MS.

Target Audience

This activity has been developed to meet the educational needs of nurses who have an interest in optimising the management of people with MS.

Accreditation

This e-learning training curriculum is accredited by the Royal College of Nursing Accreditation for the award of continuing professional development credits.

This continuing education activity has been approved by the International Council of Nurses (ICN) for the award of International Continuing Nursing Education Credits (ICNECs).

Credit Designation

The Royal College of Nursing and the International Council of Nursing designates this module of the e-learning training curriculum for a maximum of 5 credits. On completion of the course (i.e. all 5 modules) you will be able to download a Virtual College certificate.

Estimated time to complete this module: 5 hours

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Method of Participation

There are no fees for participating and receiving CME credit for this activity. During the period of TBC, 2013, through TBC, 2015, participants must; (1) read the learning objectives and faculty disclosures, (2) participate in the entire educational activity, consisting of 5 core modules, (3) complete the post-test for each module by recording the best answer to each question, and (4) complete the online evaluation form for each module. Upon successful completion of all 5 post-tests (75% or better) and online evaluation forms, you will be provided with a statement of credit which you can download, save and print.

Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this activity should not be used by nurses without evaluation of their patient's conditions and possible contraindications on dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Grant Statement

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MODULE 1: Understanding Multiple Sclerosis



1 Why Understanding the Pathophysiology of Multiple Sclerosis (MS) Will Improve Patient Care

Intro

It is important for MS Nurses to have an appreciation of the pathophysiology contributing to the development of MS. This will provide the essential concepts and information required to answer patients' questions about what causes their disease and how the disease will affect their future life. This education and counselling will help patients, their family and carers to develop a realistic picture of disease progression, assess the benefits of treatment and set appropriate expectations related to its management.

The pathophysiology also helps to explain the multiple symptoms that people with MS typically experience, and it underpins the identification of therapeutic targets and the optimisation of current and emerging therapies. In addition, an understanding of the pathophysiology of MS may help to anticipate the way a person with MS will respond to treatment. It will also provide a valuable insight into identifying and managing possible side effects that might arise from therapies.

2 MS Demographics

2.1 Learning Objectives

After review of this section, you should be better able to:



- Appreciate the importance of understanding the pathophysiology of MS as a foundation for making decisions concerning the management of MS.
- Identify the various types of MS and know their natural history and progression.
- State the genetic, race, gender and environmental factors which affect the incidence of MS.

2.2 Overview of MS

The distribution of MS varies throughout the world and appears to be related to geographical location and genetic background. Worldwide, it is estimated that up to 2.5 million people are affected by MS and it is more common in cooler climates¹. Globally, the median estimated incidence of MS is 2.5 per 100,000 (with a range of 1.1–4)². Regionally, the median estimated incidence of MS is greatest in Europe (3.8 per 100,000), followed by the Eastern Mediterranean (2), the Americas (1.5), the Western Pacific (0.9) and Africa (0.1). Twice as many women are affected with the disease than men (lifetime risk of MS: 2.5% for women and 1.4% for men)³. The incidence appears to be highest between the ages of 35 and 64 years⁴.



The mean European MS incidence rate is estimated to be 4 cases per 100,000 population per year, with twice as many women with the disease than men.

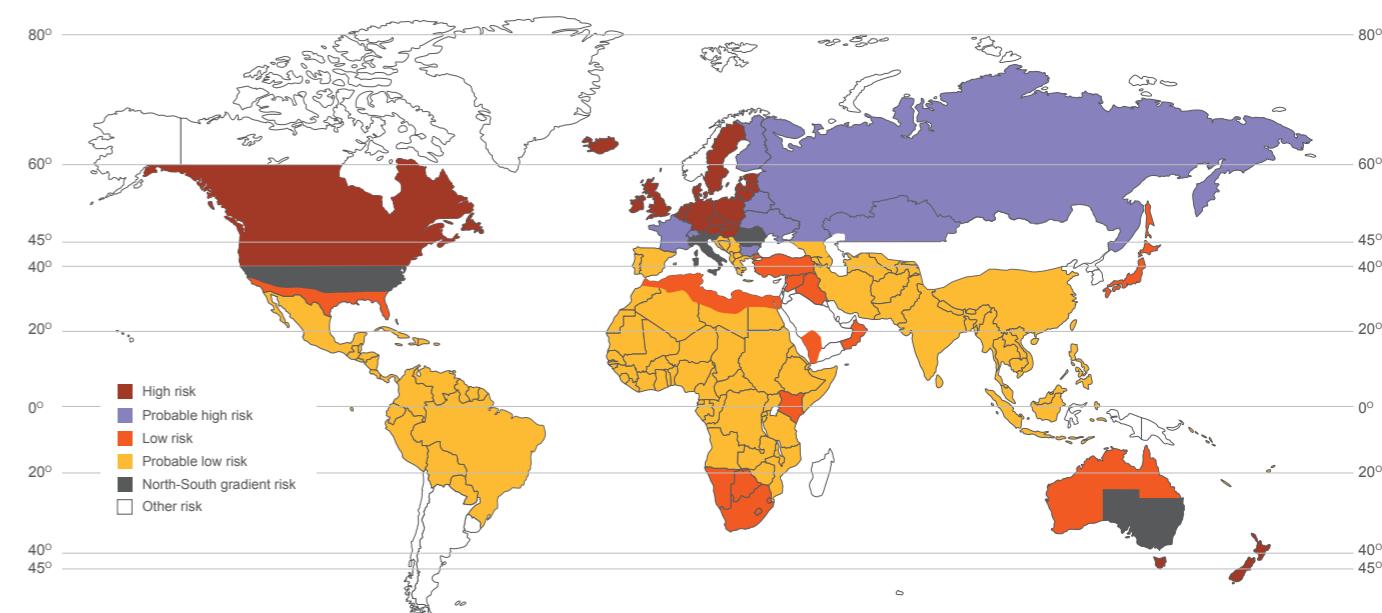


Figure 1 – The geography of multiple sclerosis

European countries reporting the highest estimated incidence of MS include Croatia (29 per 100,000), Iceland (10), Hungary (9.8), Slovakia (7.5), United Kingdom (6), Lithuania (6), Denmark (5.9), Norway (5.5) and Switzerland (5) (Figures 2 and 3)².

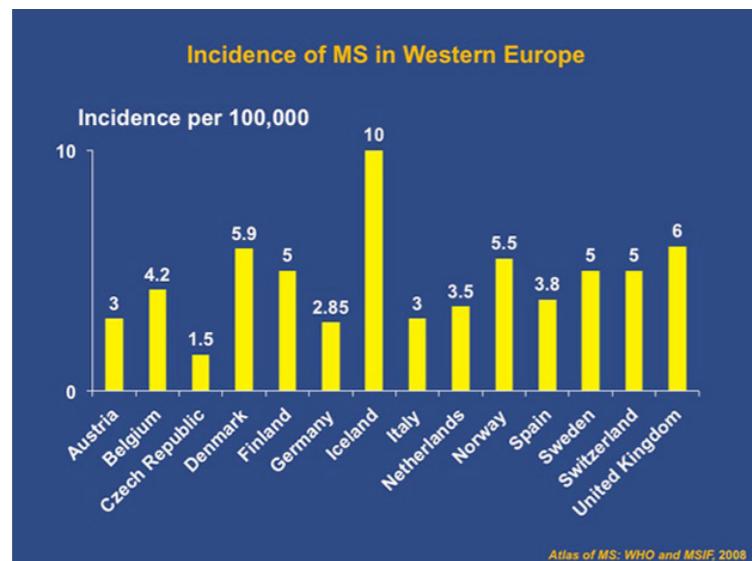


Figure 2 – Incidence of MS in Western Europe

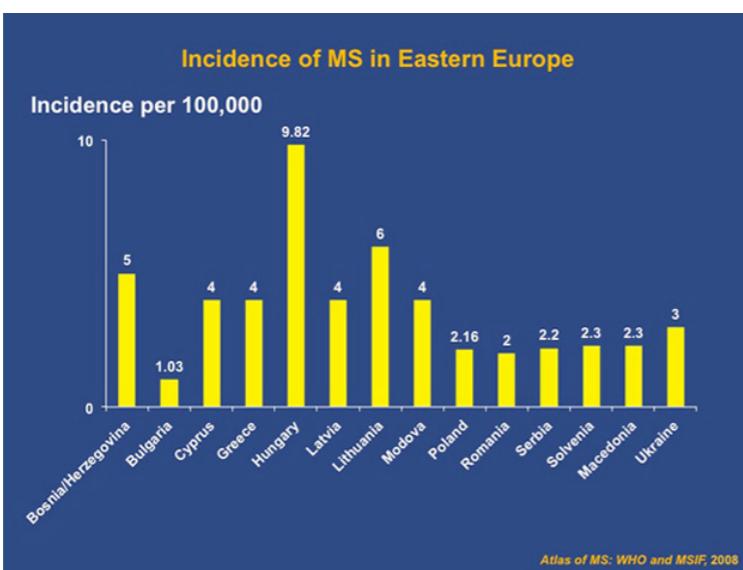


Figure 3 – Incidence of MS in Eastern Europe

MS is the most common serious, chronic neurological disorder in young adults⁵. It is a progressive, autoimmune, degenerative disease, and is characterised by neuro inflammation of the central nervous system (CNS), mainly of the white matter, which results from a mix of clinical, pathological and immunological components, together with an interaction between genes and the environment⁶. The disease usually begins between the ages of 20 and 40 years and is more common in young females than males. However, men often have a later onset of disease and a worse prognosis⁷. In either gender, it is often diagnosed at a time when family and job responsibilities are at their most demanding and this results in a serious socioeconomic impact on the family^{8,9}.

MS can cause an unpredictable and diverse range of neurological impairments that are unique to each individual. Since neurological damage can affect any part of the CNS, MS can cause a variety of distressing symptoms, including fatigue, visual impairment, urinary and bowel incontinence, mobility problems, spasticity, tremor, pain, sexual dysfunction, depression and cognitive dysfunction. Many people with MS experience multiple symptoms concurrently and 90% of people with MS experience these at an early stage. The majority will go on to develop progressive disability⁸. It is this diversity of symptoms, and the unpredictable nature of MS, that makes it one of the most difficult neurological diseases with which to cope.

Reported survival times among people with MS have varied considerably in the past, but more recent studies have demonstrated some reproducible statistics. For instance, British people with MS were recently reported to have a 3.5-fold increase in mortality compared with the general population¹⁰. Smoking and respiratory diseases were reported as the major factors associated with the increased mortality. In a Norwegian study, the median survival time from onset of MS was 41 years compared with 49 years in the corresponding population, and mortality was increased 2.5 fold¹¹. Median survival times were longer amongst relapsing-remitting MS (43 years) than in patients with primary-progressive (PP) disease (49 years), and the relative mortality risk (RMR) was higher in PPMS (RMR = 1.55). According to death certificates, 57% died from MS. Similarly, a large Canadian study involving 6,917 patients with MS found an overall standardised mortality ratio of 2.89 in people with MS and MS patients survived approximately 6 years less than expected relative to the general population¹².



MS is the most common serious, chronic neurological disorder in young adults. Men often have a later onset of disease and a worse prognosis. MS can cause an unpredictable and diverse range of neurological impairments that are unique to each individual.



Reflective learning point

How will my ability to discuss MS with my patients be improved through a better appreciation of the underlying causes?

2.3 Definition and Classification of Multiple Sclerosis

In clinical practice it can be difficult to identify a particular disease category or classification, as MS shows considerable individual variability. As a consequence, it is essential to take care when discussing disease patterns and to ensure that patients realise that their type of MS will have a lifetime course that is unique to them. Moreover, not all people with MS will reach the same level of disability, and there can be wide variations in prognosis and functional difficulties between individuals. There are several well defined stages and types of MS which are described below.



Ensure that patients realise that their type of MS will have a lifetime course that is unique to them.

The four categories of disease courses are briefly defined below¹³. They are described in greater detail in Module 2. Briefly, the categories are classified as:

2.3.1 Relapsing-remitting MS (RRMS)

RRMS is the most common form of MS and accounts for 85% of MS cases at onset¹⁴. It is characterised by clearly defined relapses (a period in which a person with MS experiences an acute worsening of function that lasts for at least 24 hours, usually lasting for several days or weeks, followed by an improvement that lasts for at least one month) that generally evolve over days to weeks, followed either by complete remission or with some residual deficit following recovery.



RRMS is the most common form of MS and accounts for 85% of MS cases at onset.

2.3.2 Secondary-progressive MS (SPMS)

SPMS is the long-term outcome of RRMS, occurring when the clinical course of RRMS changes so the patient experiences a steady decline in function; the period between relapses becomes progressively longer and there is a steady deterioration in function¹.

2.3.3 Primary-progressive MS (PPMS)

PPMS is diagnosed in ~10–15% of the MS population. In contrast to RRMS, in both genders with this form of MS, symptoms develop faster and the disease is progressive from the outset without any discernible relapses or remissions.



PPMS is diagnosed in ~10–15% of the MS population.

2.3.4 Progressive-relapsing (PRMS)

PRMS accounts for ~5% of MS. Like those with PPMS, patients with PRMS experience a steady deterioration in their condition from disease onset, but like those with SPMS, they experience occasional acute attacks superimposed upon their progressive course.



PRMS accounts for ~5% of MS.

Disease severity varies considerably between people with MS, no matter the type of disease ascribed to them at the time of diagnosis¹⁵.

2.4 The Clinical Course of MS Over Time

Despite the unpredictable nature of MS, results of cohort studies have provided general prognostic markers.

(i) Factors pointing to a more favourable prognosis include:

- younger age at onset.
- female gender.
- monosymptomatic presentation (particularly optic or sensory presentation).
- complete recovery between relapses.
- long intervals between relapses and a low number of relapses.

(ii) Factors pointing to a poor prognosis include:

- male gender.
- older at disease onset (>40 years).
- motor, cerebellar or sphincter symptoms at presentation.
- polysymptomatic presentation.
- frequent attacks in the first 5 years.
- short interval between the first two attacks.
- short time to reach an Expanded Disability Status Scale (EDSS) of 4.

Please see Module 2, Section 6 for more detailed information about prognosis of MS.

2.5 Factors Contributing to MS

Both environmental and genetic factors contribute to the aetiology of MS, and genetic factors also contribute to MS susceptibility. MS is particularly prevalent in populations from Northern Europe and their descendants, including those living in Australia, New Zealand and North America. It has been suggested that MS is more frequent in areas settled by Vikings and Goths, and that migrants from these areas took this susceptibility throughout Europe, the New World, South Africa, Australia and New Zealand¹⁶. Other prevalence rates are as follows^{17,18}:

- United Kingdom: 80–250 per 100,000.
- Scandinavia: 32–93 per 100,000.
- Northern United States (above 37°N): 69 per 100,000.
- Asia, Africa, South America: 5 per 100,000.
- Canada: 150–200 per 100,000.
- Orkney and Shetland Islands, and South East Scotland: 250 per 100,000 population – this is the highest prevalence rate in the world.

The prevalence of MS significantly increases for each degree of northern latitude, by 1.5% in men ($p = 0.013$) and 1% in women ($p = 0.015$). Equatorial countries are usually the areas of low risk, while the northernmost and southernmost countries tend to be areas of high risk⁷.



Both environmental and genetic factors contribute to the aetiology of MS, and genetic factors also contribute to MS susceptibility.

People will often enquire why they have MS. There is no one cause and the disease is multifactorial – including genetic susceptibility, environmental factors, viral exposure and possibly hormonal interplay.

MS nurses need to have an understanding of the current concepts of MS etiology and the pathological changes that are characteristic of the disease, so that they are better able to address the concerns of their patients and their families.

2.5.1 Race

MS affects Caucasians more than other races¹⁹. MS was virtually unknown among black Africans, although, of late, there are increasing reports amongst these races. Indeed, while MS has a higher incidence in Caucasian Americans than in African Americans, the latter may have a more aggressive disease course and experience greater disability²⁰. Migration studies are particularly interesting when studying the cause of MS. The potential for developing MS may be established in early life. Thus, if a person is born in a high risk area (e.g. Northern

Europe, Northern USA, Southern Canada, Southern Australia or New Zealand) but moves to a low risk area (e.g. Asia, Latin America, Middle East) before the age of 15 years, he or she will assume the low risk potential. Equally, people of Japanese origin living in the USA are more likely to develop MS than those living in Japan²¹.

Some ethnic groups show disproportionately low frequencies of MS, e.g. Maltese, Innuits, Lapps, Siberians, Hungarian Gypsies and Central Asians¹⁵.



MS affects Caucasians more than other races. The potential for developing MS may be established in early life.

2.5.2 Age

Although MS can occur at any age, the average age at diagnosis is approximately 30 years worldwide. Childhood MS is uncommon (~5% of cases), and paediatric presentation is generally one of relapses of sensory symptoms. More than 90% of the paediatric MS population have RRMS. Disease course is usually slower than in adults, but significant disability may still occur by early adulthood. It is not clear at the onset of symptoms which children will go on to develop MS²².



The average age at diagnosis is approximately 30 years worldwide.

2.5.3 Gender

Like the majority of other autoimmune diseases, MS predominately affects women. The ratio of women to men with MS is approximately 2:1. This is consistent with the phenomenon that women, especially during childbearing years, are more likely to have autoimmune diseases. Women in high risk areas have a lifetime risk of 1 in 200²³. Moreover, MS symptoms are affected by the normal ebb and flow of hormones during the menstrual cycle²⁴. The only exception to this is PPMS, in which the female preponderance is absent. However, when present, MS tends to be more severe in men and the male gender is typically associated with a poor prognosis²⁵.



MS tends to be more severe in men and the male gender is typically associated with a poor prognosis.

Sex hormones are known to play a central role as modulators of the immune response in autoimmune diseases. Use of hormone replacement therapy may be associated with a lower risk of MS – suggesting that sex hormones may have a role in the decrease in relapse rates observed during pregnancy and the increase seen following delivery. More studies are needed to determine the precise relationship between MS and hormonal imbalances.

2.5.4 Genetics

Some of the geographic variation of this disease may result from genetic predisposition. Family studies and [twin studies](#) have shown that there is a strong genetic component underlying the etiology of multiple sclerosis. The rate of MS among family members of an individual affected by the disease is higher than would be expected by chance. The prevalence of this disease among first-degree relatives of affected individuals is 20 to 40 times higher than the overall population²⁶. However, this cannot be entirely attributed to genetics, as most family members share a similar environment and lifestyle.



20% of people with MS have a positive family history.

One of the most common questions a newly diagnosed person with MS will ask is “[Is MS inherited?](#)” When counselling people with MS and their relatives it should be explained that the risk for first-degree relatives of people with MS is greater than the risk for second-degree relatives. Overall, siblings have the highest age-adjusted risk, followed by parents, then children, then uncles, aunts and cousins²⁶ (*Figure 4*).

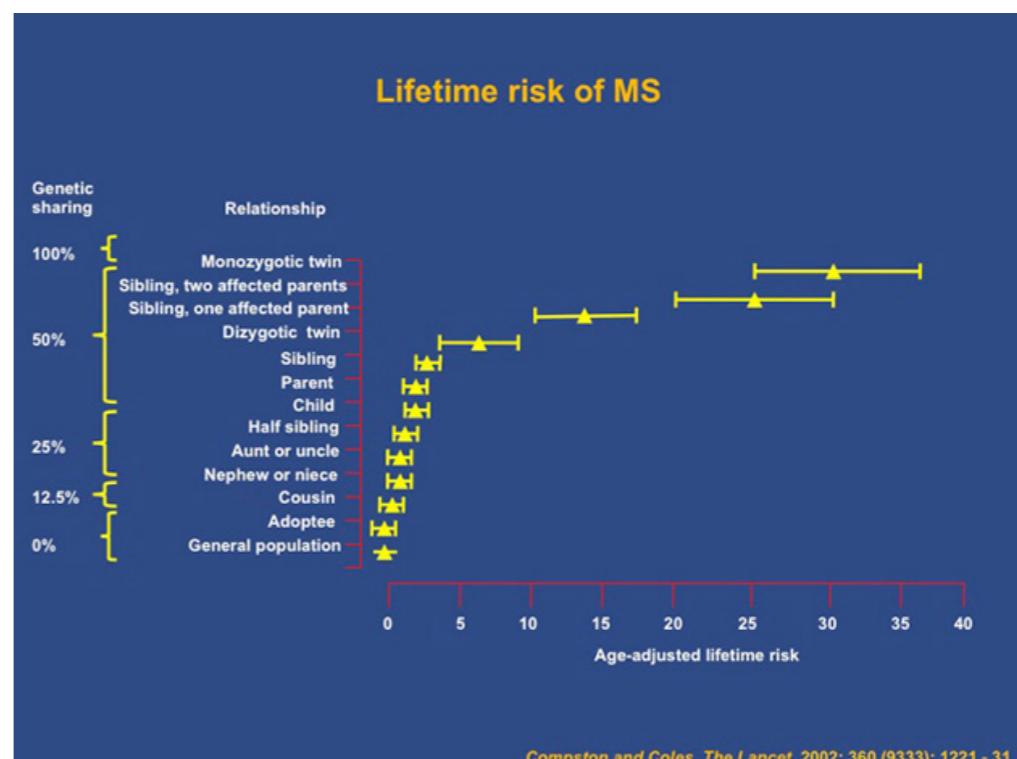


Figure 4 – Incidence of MS in Eastern Europe

Twin studies

In theory, if genes were solely responsible for determining the risk of the development of MS, then it would follow that if one monozygotic twin were diagnosed with MS, then there would be a 100% chance of the other twin also developing the disease. In fact, this is not the case. In a Canadian study of twin pairs, Sadovnick and colleagues followed up their study group for 7.5 years³⁰. They discovered the concordance rate is approximately 30% in monozygotic twins, which contrasts with the rate in dizygotic twins of approximately 4.7%. The rate in the latter group is roughly the same risk as in non-twin siblings.

Recent studies have highlighted the fact that monozygotic twins might not actually be genetically or epigenetically identical³¹. Baranzini and colleagues sequenced the genome from a pair of monozygotic twins discordant for multiple sclerosis, and also examined DNA methylation and gene expression across the genome³². No consistent difference in DNA sequence, DNA methylation or gene expression was found between affected and unaffected twins. This result suggests that the environment is the key driver of twin discordance.

This has led to the conclusion that up to 75% of MS cases must be due to non-genetic factors^{33,34}.

“Is MS inherited?”

One UK study examined the risks of developing MS in both first- and second-degree relatives of an MS patient and reported the following figures²⁷:

- Sister = 4.4%
- Brother = 3.2%
- Parent = 2.1%
- Child = 1.8%

Where both parents have MS, the risk to their children is higher, approaching 20%.



The risk for first-degree relatives of people with MS is greater than the risk for second-degree relatives.

Some specific gene markers have been identified as possible causative genes in MS, although their consistency across the MS population has yet to be established. Patients may ask for genetic counselling if they are planning a family, but because of the complexity of genetics and the interplay of genetic and environmental factors, genetic screening or counselling is difficult. There is currently no genetic testing for MS available. There is an association with certain human leukocyte antigen (HLA) alleles, such as HLA-DR2, and the development of MS²⁸. Other non-HLA genes may also play a role in MS susceptibility.

MS is not an exclusively inherited disease as shown by [twin data](#). The higher concordance rate for monozygotic twins (25–34%) than for dizygotic twins (2–5%) indicates a high heritability. Various genetic studies have examined the risk of the disease to family members of an affected individual. Thus, those genetically identical (monozygotic twins) have the highest risk (~25–34%), and those genetically unrelated (general population) have the lowest risk (~0.1–0.2% in high risk areas). Adoptees have a comparable risk to the general population indicating that living with an affected individual has little or no effect on one's susceptibility in the absence of biological relatedness^{7,26}. Researchers have concluded that both genetic susceptibility and environmental influences affect the development and clinical manifestations of MS²⁹.



Genetic susceptibility and environmental influences affect the development and clinical manifestations of MS.

Because there are no tests to evaluate the genetic susceptibility of people to MS, it is difficult to counsel patients who want to know their chances of passing the disease on to their children. The best we can do is to evaluate the family history and be empathetic.

[Twin data](#)

In theory, if genes were solely responsible for determining the risk of the development of MS, then it would follow that if one monozygotic twin were diagnosed with MS, then there would be a 100% chance of the other twin also developing the disease. In fact, this is not the case. In a Canadian study of twin pairs, Sadovnick and colleagues followed up their study group for 7.5 years³⁰. They discovered the concordance rate is approximately 30% in monozygotic twins, which contrasts with the rate in dizygotic twins of approximately 4.7%. The rate in the latter group is roughly the same risk as in non-twin siblings.

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This has led to the conclusion that up to 75% of MS cases must be due to non-genetic factors^{33,34}.

2.5.5 Vitamin D

Another factor believed to contribute to MS is dietary and sunlight-activated [vitamin D](#) in the body³⁵. Geographical gradients have been observed repeatedly in MS, with disease prevalence rates increasing at higher latitudes – i.e. with increasing distance from the equator.

The hygiene hypothesis – the idea that our modern, ultra-clean living conditions induce hyper-reactivity of the immune system – may also play a role, since the geographical distribution also coincides with the location of the ‘first-world’ countries³⁷.

2.5.6 The Role of Stress in MS

The concept that stress might trigger MS relapses dates back a long time and has been borne out in more recent studies. For instance, in patients living in a war zone there was a significant increase in MS relapses³⁸.

2.5.7 Smoking and MS

Smoking has been observed to play a contributory role in MS. Epidemiology studies have shown smoking increases the risk of MS by 40–80%³⁹. Children exposed to cigarette smoke (i.e. passive smoking) are also at an increased risk of developing MS – and the longer the exposure, the higher the risk³⁹. There are conflicting data as to whether cigarette smoking is a risk factor for transforming RRMS to SPMS.

Among people with MS, smoking is associated with higher levels of disability, greater number of enhancing T2 and T1 lesions, greater lesion volume and more brain atrophy⁴⁰.

2.5.8 Viral Factors

Several studies suggest that MS and its accompanying exacerbations are associated with viral or microbial infections⁴¹. For instance, a relapse may be triggered following a viral infection such as an upper respiratory infection⁴². Many viral triggers have been cited, for example paramyxo virus, coronavirus, Epstein-Barr virus, herpes zoster, herpes simplex virus, human herpes virus, measles and rubella⁴³.

[Vitamin D](#)

The effects of vitamin D on the immune system and in the CNS are increasingly understood, as are the underlying effects of vitamin D in MS. Experimental studies have shown that the biologically active metabolite of vitamin D is able to skew the composition of T cells into a more anti-inflammatory and regulated state³⁶. The geographical distribution of MS may thus be explained by the vitamin D hypothesis.



Nursing tip

How might you describe some of the current theories about causes of MS to someone who is just diagnosed?

How would you check the person has understood the information you have given them?

There are several theories about what causes MS and newly diagnosed patients often want to know “How did I get this disease?” This is important to explain because without a clear understanding they often deny they have the disease and may choose not to treat with disease modifying therapies. Both environmental and genetic factors contribute to the aetiology of MS, and genetic factors also contribute to MS susceptibility. MS is particularly prevalent in populations from Northern Europe and their descendants. There is no one cause and the disease is multifactorial – including genetic susceptibility, environmental factors, viral exposure and possibly hormonal interplay.

MS affects Caucasians more than other races. The potential for developing MS may be established in early life. Persons born in a high risk area (e.g. Northern Europe, Northern USA,) but moves to a low risk area (e.g. Asia, Latin America, Middle East) before the age of 15 years, he or she will assume the low risk potential. Although MS can occur at any age, the average age at diagnosis is approximately 30 years worldwide. It can be seen in children and the elderly also. Like the majority of other autoimmune diseases, MS predominately affects women.

Some of the geographic variation of this disease may result from genetic predisposition. The prevalence of this disease among first-degree relatives of affected individuals is 20 to 40 times higher than the overall population. However, this cannot be entirely attributed to genetics, as most family members share a similar environment and lifestyle. Some specific gene markers have been identified as possible causative genes in MS, although their consistency across the MS population has yet to be established.

Another factor believed to contribute to MS is dietary and sunlight-activated vitamin D in the body. Geographical gradients have been observed repeatedly in MS, with disease prevalence rates increasing at higher latitudes – i.e. with increasing distance from the equator. Smoking has been observed to play a contributory role in MS. Epidemiology studies have shown smoking increases the risk of MS by 40–80%. Several studies suggest that MS and its accompanying exacerbations are associated with viral or microbial infections.

Nurses should review the information with the patient and their families. Particular attention should be paid to any specific questions they may have such as a history of MS in the family. All of this information can be reviewed when a discussion about disease modifying therapies is held. Patients can also be asked to repeat in their own words their understanding of the causes.

2.6 Summary



- MS is the most common chronic neurological disorder in young adults.
 - It tends to be most common in countries furthest from the equator.
 - Race, gender, genetics and environmental factors can influence the incidence of the disease.
 - While MS is typically classified into four main types (RRMS, SPMS, PPMS and PRMS), the prognosis can vary considerably between patients.



Reflective learning point

How does knowing about the factors contributing to MS link to my competencies as an MS Nurse?

3 Understanding the causes of MS

3.1 Recommended Reading for this Section



Marieb EN. *Essentials of Human Anatomy and Physiology*. 8th Edition. San Francisco, CA: Pearson Benjamin Cummings; 2006.

Herlihy B. Nervous system: nervous tissue and brain. In: Herlihy B. (ed.), *The Human Body in Health and Illness*. 3rd ed. Philadelphia, PA: W B Saunders; 2007.

Hauser SL (ed.). *Harrison's Neurology in Clinical Medicine*. New York, NY: McGraw Hill; 2006.

3.2 Introduction



A sound knowledge of the pathophysiology of MS is important to the MS Nurse as one of the most common questions asked by people with MS is ‘What causes this disease?’ It is therefore important to be able to provide a clear answer that helps patients gain greater insight into their condition and provides a foundation for their understanding the rationale of their treatment, both in terms of their prescribed medication and the all-important self-management that they will be recommended to undertake.



A sound knowledge of the pathophysiology of MS is important to the MS Nurse as one of the most common questions asked by people with MS is “What causes this disease?”

The pathophysiology of MS also includes the mechanisms underlying the inflammation and degeneration of the nervous system that typically occurs in MS. This has practical implications for the use of the currently available disease-modifying therapies, and ongoing and future research efforts. This knowledge provides a framework for rational treatment selection, helps to anticipate response and aids the understanding of adverse events, should they occur.

3.3 Learning Objectives

After review of this section, you should be better able to:



- Describe the structure of the nervous system and how its function is altered by MS.
- Explain the function of the immune system and how its role is disrupted by MS.

3.4 Overall Structure of the Healthy Nervous System

The nervous system is divided into essentially two components:

- the central nervous system (CNS).
- the peripheral nervous system (PNS): which consists of nerves outside the brain and spinal cord.

The **CNS** consists of the brain and the spinal cord, plus the optic nerve. It is the body’s primary command and coordination system, receiving and processing incoming data and instructing responses. The brain comprises of four main regions:

The **cerebral hemispheres** which are responsible for higher functions of the brain i.e., speech, memory, logic, emotions, consciousness, interpretation and processing of sensation and voluntary movement. The cell bodies of neurons which are involved in these higher functions are located in the outermost non-myelinated, grey matter of the brain, called the **cerebral cortex**. This consists of several hundreds of billions of neurons and is where information processing takes place. The myelinated white matter comprises of densely packed bundles of nerve fibres carrying electrical impulses to the cortex. The white matter provides the communication between different areas of grey matter and between the grey matter and the rest of the body (see Figures 5 and 6).

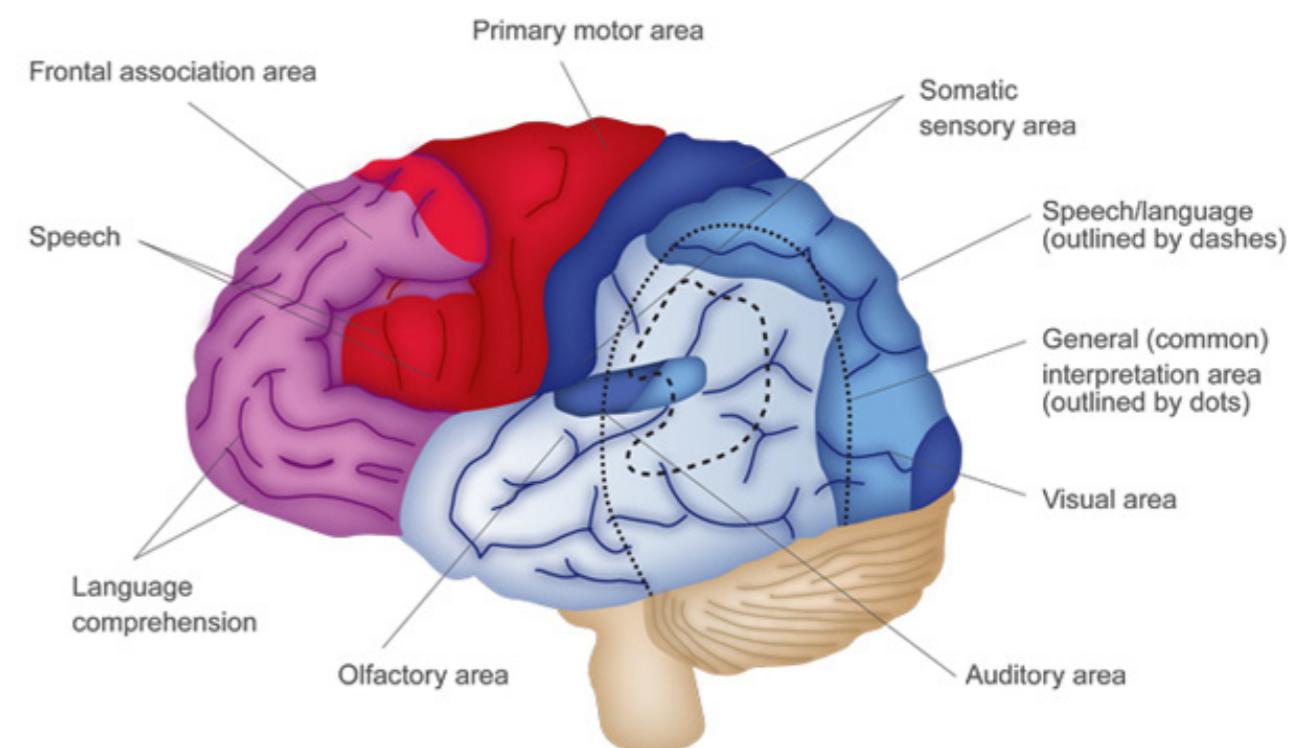


Figure 5 – The functional areas of the left hemisphere

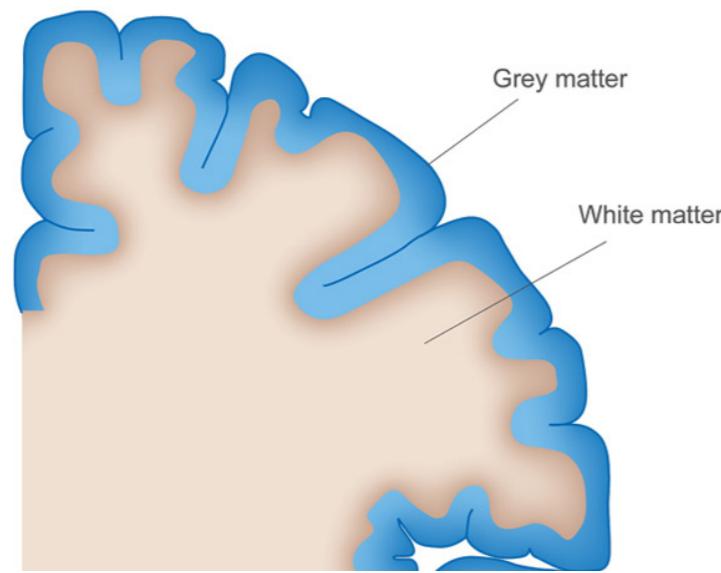


Figure 6 – The cerebral cortex

The diencephalon which is located at the top of the brain stem is enclosed by the cerebral hemispheres. It contains the:

- **thalamus**, a relay station for sensory impulses passing into the sensory cortex;
- **hypothalamus**, which regulates body temperature, water balance and metabolism.

The epithalamus, which contains the pineal body and the choroid plexus- a knot of capillaries from which the cerebrospinal fluid is derived

The brain stem, which controls, among others, essential bodily functions such as breathing, blood pressure, swallowing and vomiting

The cerebellum, which co-ordinates skeletal muscle activity and controls balance and equilibrium (See Figure 7).

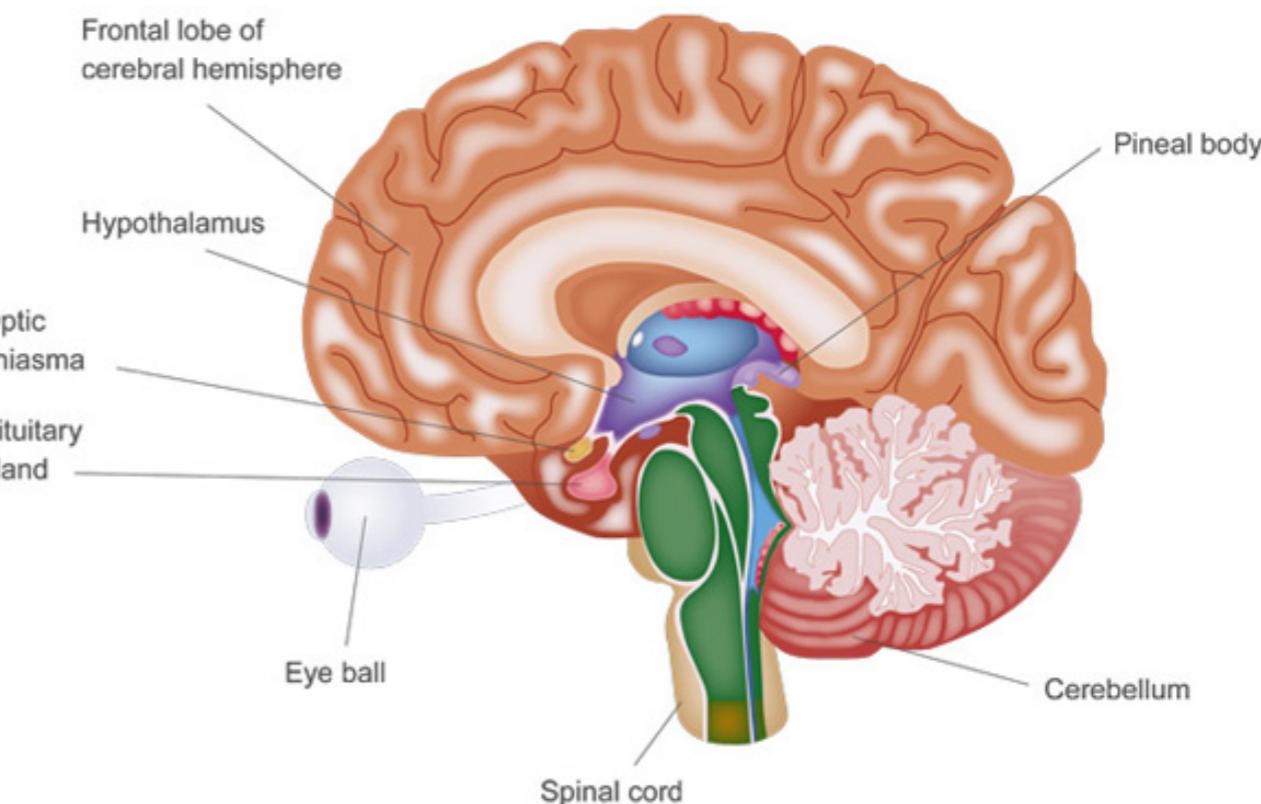


Figure 7 – The brain stem, cerebrum and cerebellum

A **neuron** is comprised of the soma, or the main body of the cell, which contains the nucleus and other cell structures and is the metabolic centre of the cell (see *Figure 8*). From the cell there are arm-like processes or fibres that can be as long as one metre in length. These fibres are of two types:

- **Dendrites** which receive electrical signals from neighbouring cells.
- **Axons** which generate, transmit and propagate the signals onto the next neuron.

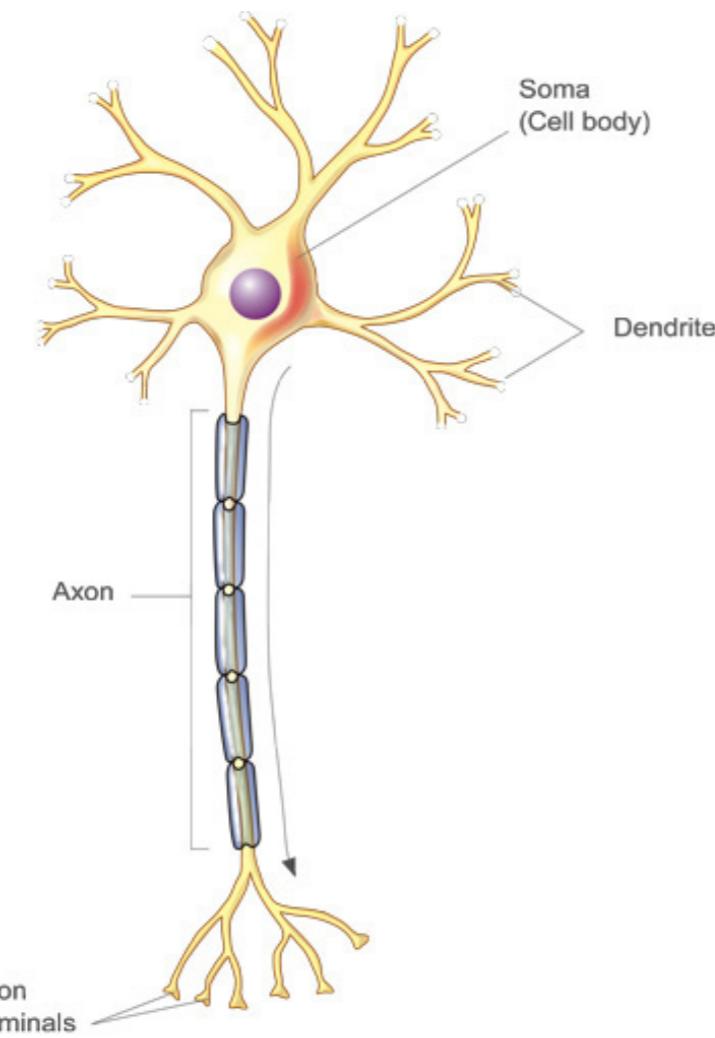


Figure 8 – Diagram of a neuron

Information is conveyed along a neuron by electrical signals (see *Figure 9*). These signals involve a series of events (primarily the movement of ions, particularly sodium (Na^+) and potassium (K^+)) which cause the electrical charge inside the cell to move from its positive depolarised state back to its negative resting state again. The resultant waves of electrical activity are known as action potentials.

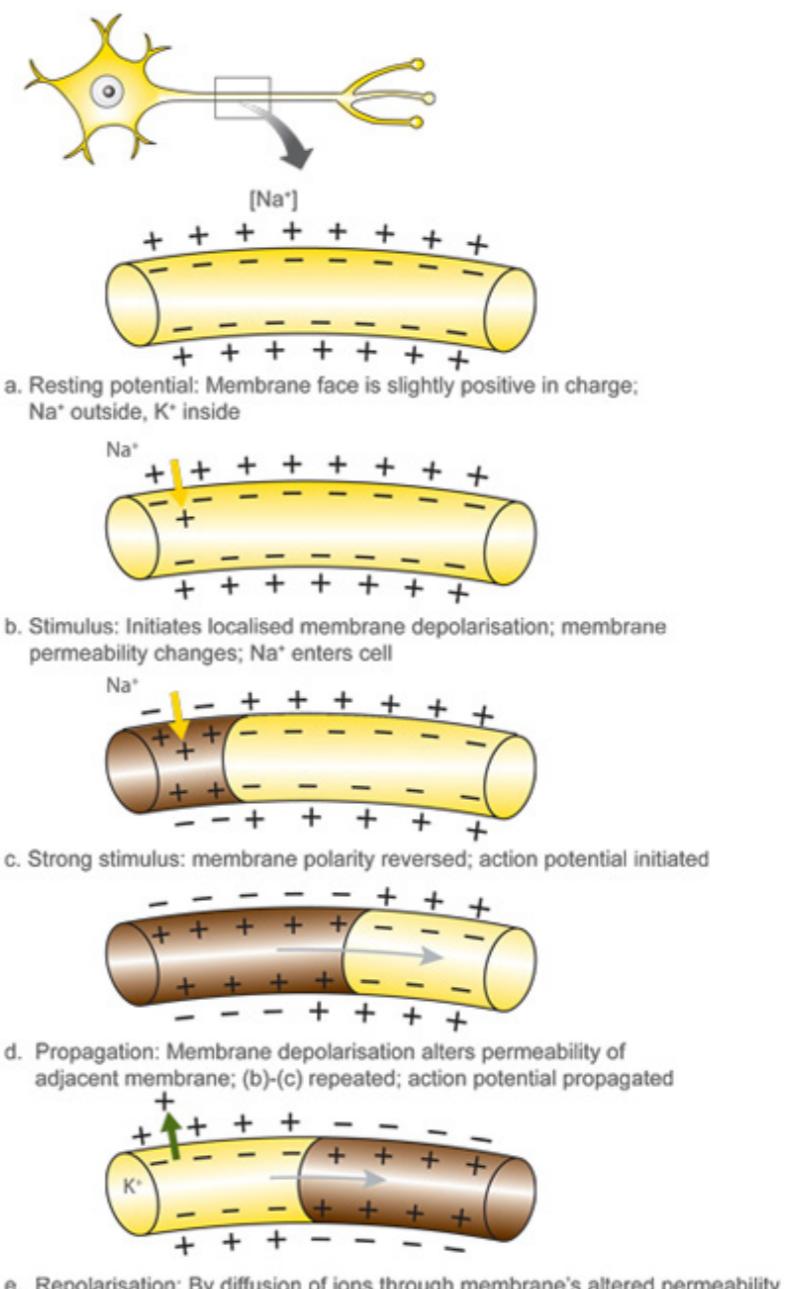


Figure 9 – The nerve impulse

Arrival of the nerve impulse at the termination of an axon stimulates the release of neurotransmitters into the synaptic cleft between the two neurons. The neurotransmitters then diffuse across the synaptic cleft, bind to the receptors, and stimulate the dendrites of the second neuron. Hence a nerve signal is propagated by both electrical and chemical means, within and between cells.



A nerve signal is propagated by both electrical and chemical means, within and between cells.

Axons are insulated by **myelin sheaths** like the plastic coating that surrounds a metal core in an electrical cable. It prevents dissipation of the electrical signal along the length of the axon. These sheaths are formed by cells exclusive to the CNS called the *oligodendrocytes* which coil round multiple axons – up to 60 different axons at a time. The myelin sheaths are interrupted by a series of gaps along each axon called the Nodes of Ranvier, where myelin is absent. The Nodes of Ranvier are the means by which electrical nerve impulses are rapidly conducted through an axon – they allow action potentials to jump from node to node at an accelerated rate.

Myelin is a glycoprotein (a protein that has carbohydrate molecules attached), and as such is recognised by components of the immune system. In MS, myelin is attacked by the patient's own immune system and compromised, resulting in hardened plaques called **scleroses**. The myelin sheath is thus damaged and electrical signalling is short-circuited. Initially, the myelin sheath is repaired (accounting for remission in early stages of some types of MS), but eventually the myelin sheath breaks down and axons themselves come under attack and are severed. This is associated with increasing disability.



In MS, myelin is attacked by the patient's own immune system and compromised, resulting in hardened plaques called **scleroses**.

The different types of cells surrounding the neurons are known as **glial cells**.

The brain and the nervous system are protected from potentially toxic chemicals (including some drugs) and organisms by the **blood-brain barrier**. This is composed of the least permeable capillaries found in the body, lined with endothelial cells that are more tightly packed together than in the rest of the body, forming tight junctions. In addition, on the CNS side of the barrier, the endothelial cells are covered by a thin basement membrane of cells called pericytes and the 'feet' of the astrocytes (see Figure 10).



The brain and the nervous system are protected from potentially toxic chemicals and organisms by the **blood-brain barrier**.

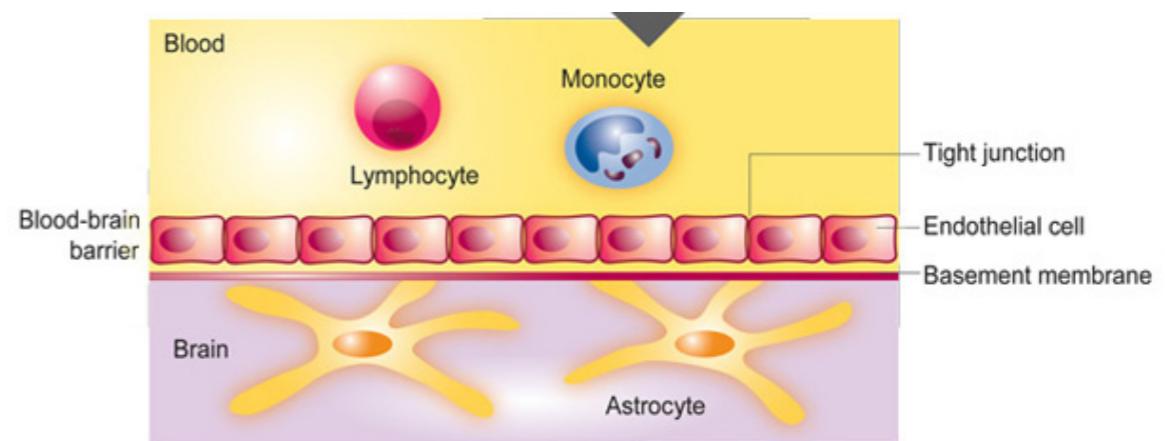


Figure 10 – Diagram of a blood vessel in the CNS forming the blood–brain barrier

Only water, glucose, essential amino acids, lipids and lipid-soluble molecules can pass through the membranes of these capillaries; thus, hormones do not normally cross this barrier but lipid soluble compounds such as alcohol, anaesthetics and certain drugs can cross the blood–brain barrier.

The glial cells comprise:

Astrocytes

The cells provide bracing and anchorage between neurons and blood capillaries. They also play a role in making exchanges between the neurons and capillaries and are a buffer that protects the delicate neuron from toxic substances in the blood

Microglia

These cells play a phagocytic (cell-engulfing) role and are immunocompetent. They are implicated in the progression of several demyelinating diseases including MS.

Ependymal cells

Glial cells that line the cavities of the brain and spinal cord, and help to circulate fluid which forms a protective cushion around the CNS

3.4.1 Structure of the Spinal Cord

The spinal cord is the long extension of the brain stem that provides two-way communication between the body and the brain. In humans, there are 31 pairs of spinal nerves which enter the spinal cord by penetrating the vertebral column from the surrounding body.

The spinal cord comprises grey and white matter. Grey matter surrounds the central canal of the cord, which is filled with cerebrospinal fluid, and is shaped into horns - dorsal and ventral. Nerves enter the spinal cords by dorsal and ventral root ganglia, while motor neurons enter via the ventral root ganglion. White matter is located in posterior, lateral and anterior columns, surrounding the horns of grey matter (see *Figure 11*).

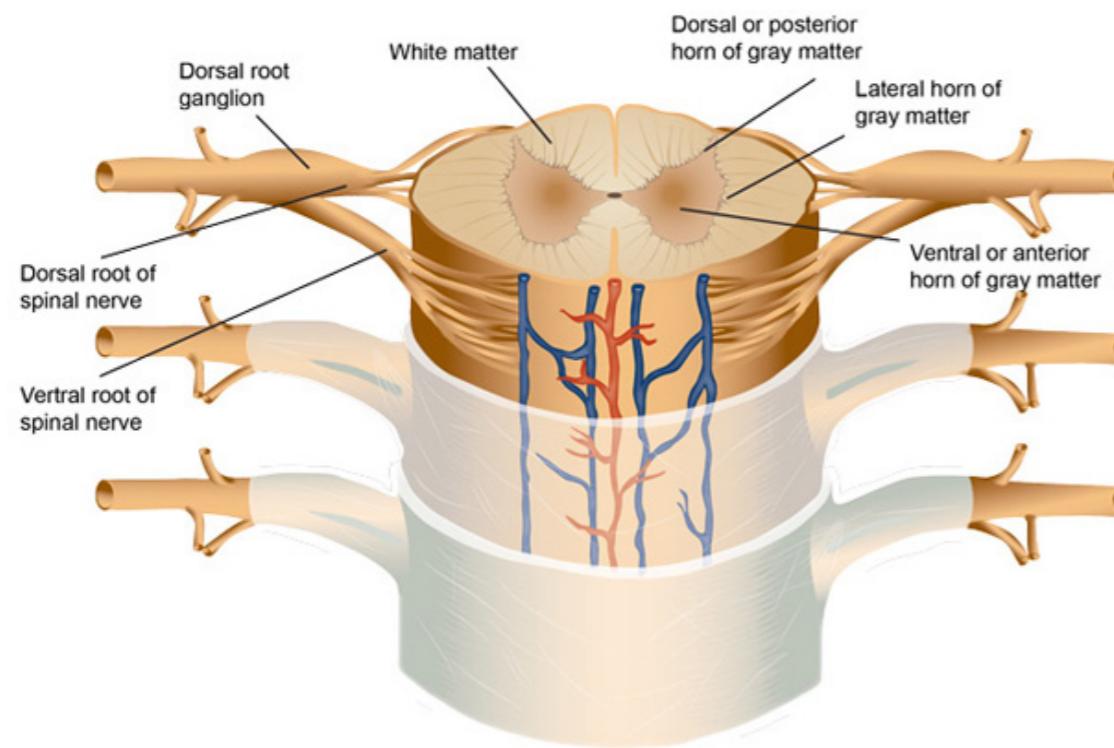


Figure 11 – Diagram of the structure of the spinal cord

3.4.2 Summary



The nervous system is divided onto components – the central nervous system (CNS) and the peripheral nervous system (PNS). Together they relay both physical and cognitive information about macro and microenvironments in and around the body, using electrical impulses as the signal device.

The sheath that surrounds an axon fibre is made of myelin and this is vital for the generation and propagation of electrical signals along the axon fibre. In MS, this myelin sheath is attacked by a person's own immune system and destroyed.

3.5 The Overall Function of the Healthy Immune System

The immune system is highly specialised and comprises many different cell types, and many complex mechanisms. It evolved as a means to protect the body against specific threats, including microorganisms, certain molecules, such as toxins, and internal threats such as malignancies. The immune system:

- Is antigen specific – it recognises proteins or glycoproteins on an invading cell's membrane.
- Is systemic – the components are found in the systemic circulation.
- Has memory – once the body recognises an antigen, it retains the capacity to raise an immune response against that antigen should it appear in the body again.



The immune system protects the body against specific threats, including microorganisms, certain molecules, such as toxins, and internal threats such as malignancies.

3.5.1 Innate and Adaptive Immunity

The immune system has two distinct functions which interact to protect the body against dangerous organisms and compounds that enter the body:

- the more primitive **innate immune system** (the first line of non-specific defense against infection by other organisms)
- the **adaptive immune system** composed of highly specialised, systemic cells and processes that eliminate or prevent pathogenic growth. It provides the ability to recognise and remember specific pathogens (to generate immunity), and to mount stronger attacks each time the pathogen is encountered.

All immune system cells derive from stem cells in the bone marrow. After proliferating as non-specialised stem cells, they begin to specialise into lymphoid and myeloid cell types.

Lymphoid cells (T and B lymphocytes) are very specific in their actions and are part of the adaptive immune response.

Lymphoid cells differentiate into either **B cells** or **T cells**, depending on whether they are produced in the marrow (B cells) or are produced in the marrow and migrate to the thymus, where they mature (T cells). They each display a unique type of receptor on their surfaces and so only recognise one specific type of antigen (see *Figure 12*).

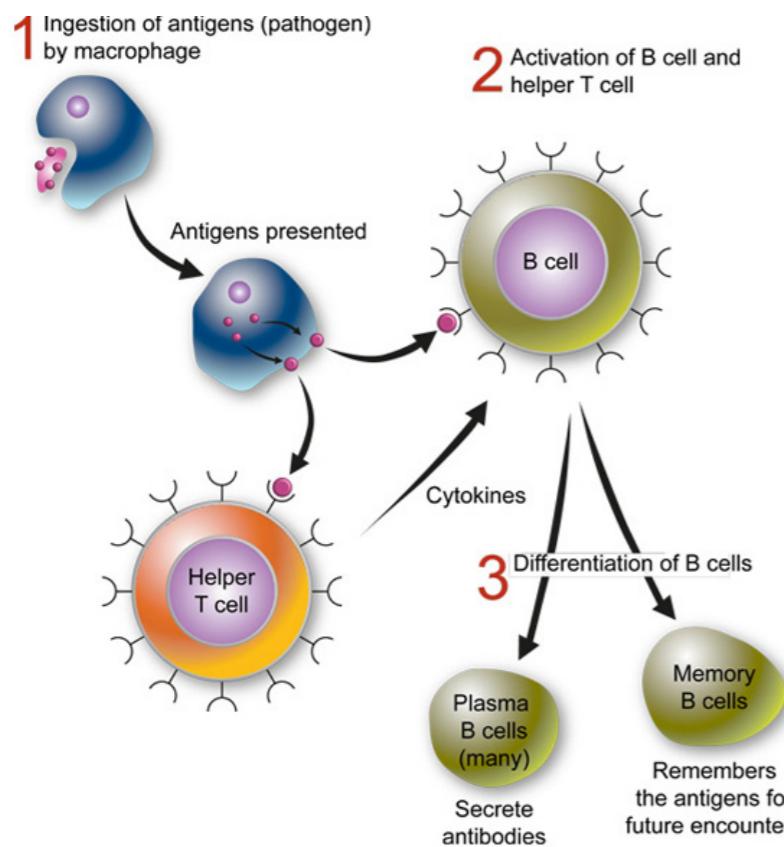


Figure 12 – The humoral immune response

B cells

B-cells migrate to the spleen, lymph nodes and mucosal-associated lymphoid tissue (MALT). They are responsible for producing and secreting antibodies. They can differentiate into plasma B cells, which produce antibodies in response to antigen challenges and memory B cells (which carry antibody or receptor for a specific antigen, formed after its first exposure to that antigen). When stimulated by a second exposure to the antigen, memory B cells mount a more rapid and effective immune response than a B-cell that has not been previously exposed.

T cells

T cells mature in the thymus and then concentrate in secondary lymphoid organs where they differentiate into cytotoxic T cells (also known as CD8⁺ T cells) or Helper T cells (also known as CD4⁺ T cells). T cells are stimulated by macrophages that have engulfed invading cells or viruses, partially digested them and then presented various parts of the invader on their cell surface together with a cell marker of their own from the major histocompatibility complex (MHC). This stimulates cytotoxic T cells to react by releasing toxic chemicals to kill the infected cells. Cytotoxic T cells also stimulate T cells to differentiate into:

Lymphocytes that recognise ‘self’ are normally rapidly and effectively destroyed as soon as they emerge. This process fails in the case of autoimmune disease.

T cells (cont'd)

- Killer T cells (kill cells expressing antigens for which they are specific)
- Helper T cells (stimulate T and B cells)
- Regulatory T cells (inhibit T and B cells and wind down the immune response once the attack is completed)
- Memory T cells (remember antigens for future encounters)

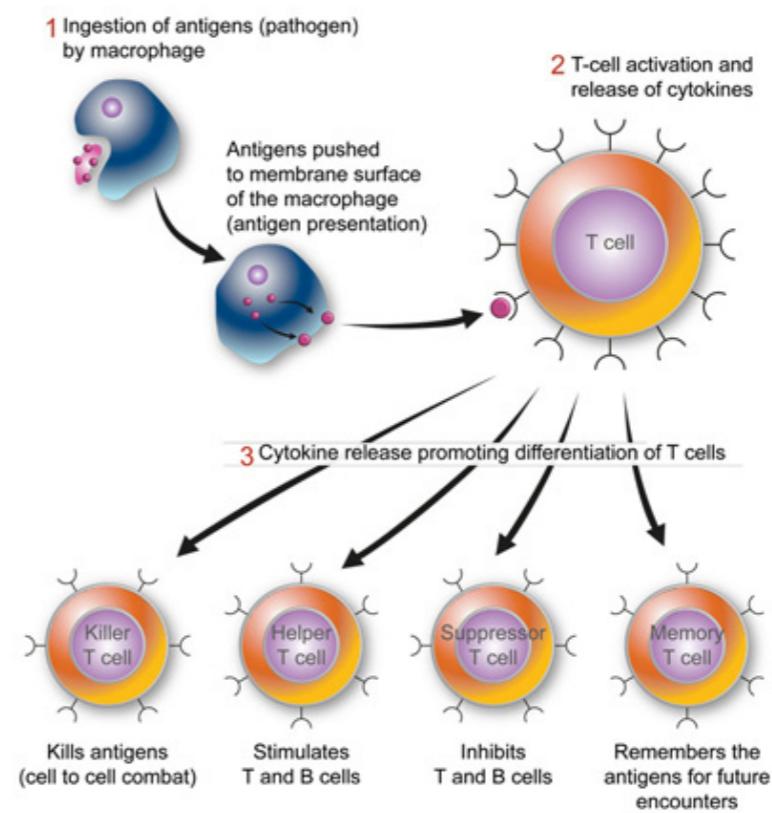


Figure 13 – The cellular immune response

3.5.2 Innate Immunity

Myeloid cells respond early and non-specifically to infection and form the innate immune response.

The innate immune system is a genetically determined, non-specific defence mechanism that provides an immediate barrier to infection. It lacks specificity and memory, and does not confer long-lasting or protective immunity. However, it does play a vital role in activating the adaptive immune system through the process of antigen presentation.

The cellular mediators of the innate immune system are phagocytes (monocytes, macrophages, dendritic cells and granulocytes) and natural killer (NK) cells; the soluble components are complement proteins and cytokines, among others.

3.5.3 Adaptive Immunity

There are two types of specific adaptive immune response: the humoral immune responses and the cellular response. T cells are the effective mediators of the cellular response, while antibodies secreted by B cells are the effectors of the humoral response.

Cellular or cell-mediated immunity

This is where the white cells are engaged in immune activity. Principally lymphocytes are involved, some of which act directly by destroying foreign cells, or indirectly by releasing chemical mediators that enhance the inflammatory response or activate cells to destroy the invaders.

Humoral immunity

The immune system mainly works by producing antibodies against antigens. Antibodies are molecules produced by B lymphocytes and they circulate in the blood and the lymph. They attach to antigens displayed by invading bacteria, viruses or other organisms, and either inactivate them or facilitate their destruction by cells of the immune system.



Nursing tip

In what way would you describe the function of the immune system to a person with MS?

A sound knowledge of the pathophysiology of MS is important as one of the most common questions asked by people with MS is ‘What causes this disease?’

I normally begin by explaining about the nervous system and how it is divided into essentially two components:

- the central nervous system (CNS)
- the peripheral nervous system (PNS): which consists of nerves outside the brain and spinal cord.

The CNS consists of the brain and the spinal cord, plus the optic nerve. It is the body's primary command and coordination system, receiving and processing incoming data and instructing responses. The CNS is made up of many types of cells including the neurons. Neurons are the cells that send messages from the brain to the body and back. Neurons are made up of the cell body and the axon which is like a long tail. The axon is often covered in a protective coating called myelin. In MS, myelin is attacked by the patient's own immune system and compromised, resulting in hardened plaques called scleroses. When the myelin is damaged axons may also be destroyed. These areas of damage are often seen on MRI scans and many produce symptoms of MS.

The immune system protects us from pathogens and responds to injury. The normal immune system can recognise a wide variety of pathogens, leave its own tissue alone and remember a previous exposure to a foreign pathogen. However, if the immune system is abnormal, immune cells such as T and B cells will mistakenly damage a person's own tissues. This is the case in an autoimmune disease such as MS. Research suggests that MS is a consequence of an abnormal autoimmune response to myelin that develops after exposure to some environmental agent in genetically predisposed individuals.

The combined effects of this autoimmune response cause demyelination, axonal damage and scarring, and account for the new brain and spinal lesions seen on the MRI of people with MS.

3.5.4 Summary



- The immune system protects us from pathogens and responds to injury. It has several important characteristics: diversity, specificity, the ability to distinguish self from non-self, and memory.
- The normal immune system can recognise a wide variety of pathogens, leave its own tissue alone and remember a previous exposure to a foreign pathogen and responses.
- Some T and B cells also have the ability to react to self-antigens. A normally operating immune system keeps these autoreactive immune cells in check so that they do not provoke unwanted responses.
- However, if the immune system is dysregulated, tolerance to some self-antigens may be disrupted and autoreactive T and B cells will mistakenly damage a person's own tissues. This is the case in an autoimmune disease such as MS.

3.6 Pathophysiology of MS

The cause of MS is not known, but it appears that it occurs when the immune system is unable to distinguish self-antigens from foreign antigens. Research suggests that MS is a consequence of an abnormal autoimmune response to myelin that develops after exposure to some environmental agent in genetically predisposed individuals⁴⁴.



Research suggests that MS is a consequence of an abnormal autoimmune response to myelin that develops after exposure to some environmental agent in genetically predisposed individuals⁴⁴.

When the immune response is triggered, there is peripheral activation of T cells and these activated lymphocytes egress from the lymph nodes and migrate across the blood-brain barrier (BBB) into the CNS. Once inside the CNS, these cells are reactivated and stimulate production of inflammatory cytokines that damage the BBB and the components of the CNS.

The combined effects of this autoimmune response cause demyelination, axonal damage and scarring, and account for the newly evolving cranial and spinal lesions seen on the MRI of people with MS⁴⁴. Axonal degeneration and axonal transection may lead to permanent neurological dysfunction and this may begin early in the disease course. This disruption of conduction in nerves and nerve function causes the hallmark sensory, motor and cognitive signs and symptoms of MS. In addition, brain atrophy may occur and is thought to reflect irreversible tissue damage.

- A genetic component is certain.
- Potential environmental risks have been proposed.



This disruption of conduction in nerves and nerve function causes the hallmark sensory, motor and cognitive signs and symptoms of MS.

3.6.1 The Multiple Sclerosis Lesion

The pathological hallmark of MS is the plaque^{45,46}. Lesions are characterised histologically by hypercellularity, lymphocyte infiltration around blood vessels, loss of oligodendrocytes and myelin, axonal damage and parenchymal oedema. Remyelination is seen occasionally. Lesions can occur anywhere in the white and grey matter of the CNS; however, most are seen in deep white matter and in the spinal cord.



The pathological hallmark of MS is the plaque. Lesions can occur anywhere in the white and grey matter of the CNS; however, most are seen in deep white matter and in the spinal cord.

There is a preference for perivascular and perivenular lesion formation. Accordingly, lesions are commonly found in areas with high vascularity, including the optic nerve, spinal cord, the juxtacortical area and periventricular zone.

Thus, initial clinical symptoms are often associated with the brainstem, optic nerve, spinal cord, or cerebellum lesions, causing optic neuritis, transverse myelitis or a brain-stem syndrome.

3.6.2 The Main Pathological Processes: Inflammation and Neurodegeneration

The principle clinical expression of MS is relapses and disease progression leading to progressive permanent disability.

- Relapses are caused by **acute inflammatory demyelination**
- Progression reflects **neurodegeneration**, including axonal loss and gliosis (sclerosis) with increasing brain atrophy⁴⁷⁻⁵⁰.

At one time it was thought that the pathological sequence was initial inflammation causing demyelination leading to axonal loss later in the disease, secondary to repeated inflammatory events. However, recent data suggest that the inflammation and neurodegeneration occur at, or near, the same time. This is supported by autopsy and MRI studies which have revealed that axonal damage occurs in the earliest phases of MS^{14, 47,50-52}. Indeed, there are data that show that axonal/neuronal damage in MS can occur largely independent of the inflammatory processes⁵².

These data argue in favour of initiation of treatment in MS as early as possible, certainly before permanent disability is apparent.



Relapses are caused by acute inflammatory demyelination. Progression reflects neurodegeneration, including axonal loss. Data suggest that the inflammation and neurodegeneration occur at, or near, the same time.

3.6.3 Cells Involved in the Pathogenesis of MS

The main cell types involved in MS are T cells and B cells. MS appears to be caused by activated myelin-specific T cells, which react with one or more antigens in myelin, leading to formation of the typical inflammatory demyelinating lesions^{46,47,53}.

This is supported by animal data which have shown that auto reactive CD4+ or CD8+ T cells cause CNS demyelination. Entry of these activated cells from the periphery into the CNS results in disruption of the blood-brain barrier (BBB). In persons genetically disposed to MS, this is presumably initiated by an environmental trigger, as alluded to above (e.g. an infectious agent)^{46,53}. This initial event may up-regulate the adhesion molecule on brain and spinal cord endothelium (e.g. VCAM-1), allowing transmigration of circulating lymphocytes^{46,53}.

T cells must be activated to enter the CNS and this process and events involved in the BBB penetration and subsequent tissue damage are **complex**, requiring adhesion and subsequent reactivation after entry:

Although the focus of CNS injury in MS focuses on T cell-mediated pathogenesis, mounting evidence suggests that humoral immunity also plays a role⁵⁴⁻⁵⁶. Elevated levels of immunoglobulins in CSF have long been observed in people with MS⁵⁴.

In recent years the potential for demyelination induced by the presence of immunoglobulins has been suggested^{54,55}. **B cells have been reported in the meninges of many MS patients**, especially those with SPMS, which indicates that B cell maturation can be sustained in the CNS⁵⁶.

Complex

The first step is peripheral activation of T cells that recognise antigens in the CNS. For this to happen, the antigen fragment must be presented to the T cell enfolded in the MHC which is presented on antigen-presenting cells (dendritic cells, monocytes, macrophages, CNS microglial cells and B cells)⁴⁴. The activated T cells adhere to the endothelial cells of the BBB (step 2). Soluble proteins degrade the BBB which help the T cells invade the CNS, where they become reactivated and injure the myelin.

Activated T cells differentiate into subsets known as helper cells, which include:

- Type 1 helper cells (Th-1): The cytokines produced include the damaging, proinflammatory IL 12, IL 23, INF γ , TNF α
 - Type 2 helper cells (Th-2): The cytokines released include the anti-inflammatory / protective IL 4, IL 5 and IL 13, and possibly IL 10

In MS the balance is tipped towards a Th-1 response and modulating Th-1 and Th-2 responses is one target of MS therapy⁴⁴.

B cells have been reported in the meninges of many MS patients

Potential mechanisms by which the accumulation of B cells in the CNS may contribute to the pathogenesis of MS include antigen presentation, production of proinflammatory cytokines, complement fixation and anti-idiotypic networks. One theory is that memory B cells in the CSF from MS patients may amplify T cell responses in the CNS via presentation of antigenic peptides.

3.6.4 Summary



- The pathophysiology of MS comprises of two components: inflammation and neurodegeneration.
 - Relapses are the clinical expression of acute inflammatory demyelination, whereas progression reflects neurodegenerative processes, including axonal loss, with increasing brain atrophy.
 - Recent research suggests that inflammation and neurodegeneration happen at, or near, the same time.
 - These data argue in favour of the early initiation of treatment for MS.



Reflective learning point

What is the significance of understanding the inflammatory and neurodegenerative processes in MS to my role as an MS Nurse?

4 Relating pathophysiology to MS symptoms

4.1 Learning Objectives

After review of this section, you should be better able to:



- Describe the underlying pathophysiological causes of the most common symptoms associated with MS.
- Recognise that central to this is the inflammation and demyelination of axons which disrupts neural conduction.
- Appreciate that cortical pathology, that is, inflammatory focal lesions (cortical lesions) and atrophy (cortical thickness), may determine cognitive disability in MS.

4.2 Introduction



People with MS can exhibit an exceptionally wide variety of symptoms. This is largely due to the semi-random distribution of the lesions in the central nervous system (CNS). Most lesions occur in apparently “silent” areas in the brain, and so cause no detectable symptoms. The disease is therefore much more active than clinical monitoring would suggest. Most symptoms are related to a loss of function. During relapses, this is due to a failure of axonal conduction at the site of the lesion(s). The conduction block is caused by the local demyelination which prevents the saltatory conduction. It is also affected by inflammation which contributes to neurological deficit by modifying the properties of glial cells, particularly astrocytes and microglia. This can affect neurological function.

Remissions are related to a recovery of function of the affected axons and remyelination which restores conduction to demyelinated axons. There is also resolution of inflammation. However, nerve conduction remains slower and less secure than normal, easily altered by changes such as increase in body temperature (Uhthoff’s phenomenon), and a recent history of conducting a large number of impulses. Remission is incomplete when the lesion has led to axonal transection and therefore axonal loss. Progression in MS is mainly related to “slow-burning” diffuse and chronic axonal loss in a setting of inflammation.



Recommended reading: Smith KJ. Pathophysiology of multiple sclerosis. *Rev Prat* 2006; 56(12): 1299–303.



Remissions are related to a recovery of function of the affected axons and remyelination which restores conduction to demyelinated axons. Progression in MS is mainly related to “slow-burning” diffuse and chronic axonal loss in a setting of inflammation.

Some symptoms in MS are so-called “positive” ones, arising from an acquired hyperexcitability of demyelinated axons. These can occur either spontaneously (e.g. paraesthesia) or mechanically.

4.3 Sensitivity of People with MS to Heat



Recommended reading⁵⁷: Flensner G, Ek A-C, Söderhamn O, et al. Sensitivity to heat in MS patients: a factor strongly influencing symptomology – an explorative survey. *BMC Neurol* 2011; 11: 27.

Between 60% and 80% of individuals diagnosed with MS have been reported as being sensitive to environmental heat⁵⁸. Indeed, blurred vision, known as Uhthoff’s phenomenon and first described in 1890, is caused by increased body temperature due to physical exercise or physical restraint⁵⁹. In a multinational Internet-based survey of people with MS (n=2,529), 70% reported that high temperatures worsened their MS (e.g. taking a hot shower or using the hair drier); while drinking a glass of cold water could relieve symptoms⁶⁰.



Between 60% and 80% of individuals diagnosed with MS have been reported as being sensitive to environmental heat.

The heat reaction blocks the action potential/conduction block of the demyelinated neuron^{59,61}. The demyelination results in a slower nerve conduction velocity. Interestingly, very small increases in temperature (due to both external conditions and exercise) can also block action potentials^{61,62}. Patients’ reports of temperature aberrations can vary greatly, indicating that the mechanisms may be multiple.

After normalisation of the temperature, signs and symptoms usually improve or disappear^{58,59}. Heat sensitivity has been described as a significant correlate of the symptom of fatigue in MS⁶³⁻⁶⁵.



Very small increases in temperature can block action potentials. After normalisation of the temperature, signs and symptoms usually improve or disappear.

4.4 Relationship of Fatigue to MS Pathophysiology



Recommended reading⁶⁶: Pellicano C, Gallo A, Li X, et al. Relationship of fatigue to MS pathophysiology. *Arch Neurol.* 2010; 67(4): 447–53.

Fatigue is a frequent symptom of patients with multiple sclerosis⁶³. It has a severe effect on their quality of life⁶⁷, but its pathophysiologic mechanisms remain incompletely understood. One explanation is that fatigue in MS could be due to impaired selecting and planning of actions, as well as integrating different information, rather than the extent of physical disability and motor impairment^{68–71}. This is in line with a model proposed by Chaudhuri and Behan, stating that there is, “failure to initiate and/or sustain attention task (mental fatigue) and physical activities (physical fatigue) requiring self-motivation”⁷².



Fatigue in MS could be due to impaired selecting and planning of actions.

4.5 Optic Neuritis



Recommended reading⁷³: Chu ER. Optic neuritis-more than a loss of vision. *Australian Family Physician* 2009; 38(10): 789–93.

Optic neuritis (ON) is caused by acute inflammation of the optic nerve that results in painful loss of vision. It is the most commonly encountered optic neuropathy in clinical practice^{74,75} and is often associated with MS⁷⁶. However, between attacks optic nerves can undergo recovery of vision.



Optic neuritis is caused by acute inflammation of the optic nerve that results in painful loss of vision.

ON may be due to demyelination and inflammation of the optic nerve and its lining, resulting in inflammation of the extraocular recti muscles that surround the optic nerve. Recti muscle involvement results in ocular pain, especially with eye movements. Regardless of etiology, inflammatory cells surround the optic nerve resulting in swelling and fragmentation of the nerve tissue which are subsequently phagocytised by macrophages, resulting in further degeneration of the nerve and the signs of optic nerve dysfunction⁷⁷.

4.6 Positive Symptoms and MS

People with MS can experience a wide range of positive phenomena and recordings in experimentally demyelinated axons suggest that this is due to ectopic activity in hyperexcitable demyelinated axons. This is manifested clinically as tingling in the trunk and limbs. Some patients also report the presence of sensations provoked by body movements which distort areas of the nervous system containing demyelinated axons. For instance, patients with cervical posterior column lesions can experience an ‘electric shock’ sensation when they turn their head and, similarly, patients with demyelinating lesions in the optic nerve can experience flashes of light on eye movement.

Pain is a common complaint in MS patients and it appears to have several origins. It seems that painful sensations will result from ectopic impulses generated in pain fibres. There is evidence to suggest that some positive phenomena can be triggered by propagation of the normal impulse traffic through the site of demyelination.

4.7 Psychiatric Disorders in People with MS



Recommended reading⁷⁸: Fazzito MM, Jordy SS, Tilbery CP. Psychiatric disorders in multiple sclerosis patients. *Arq Neuropsiquiatr* 2009; 67(3a): 664–7

MS may be related to several psychiatric disorders which disturb mood, behaviour and personality. Among those disorders, depression is the most frequently reported⁷⁹. Psychiatric symptoms are commonly observed during disease evolution, but they are unusual as first symptoms and their occurrence is estimated at 1% of MS cases.

People with MS show psychiatric disorders secondary to demyelinating lesions at the temporal lobe. The physiopathology of this observation is not fully understood^{80,81}. The temporal lobe functions are language, memory and emotion. Lesions at this brain location may cause hallucinations, mood and thought disorder, euphoria, irritability and cognitive deficit. This brain location is especially associated with psychiatric alteration⁸⁰.

4.8 Cognitive Impairment in MS

Depending on the disease phase and type, 40–65% of people with MS develop various degrees of cognitive dysfunction. Pathological and MRI studies have failed to demonstrate the existence of a strict relationship between cognitive impairment and subcortical white matter pathology. The correlation is also poor when MRI metrics of whole brain (white plus gray matter) atrophy are considered. Over the past decade, increasing observations have provided evidence of a primary role of cortical pathology – that is, inflammatory focal lesions (cortical lesions) and atrophy (cortical thickness) – in determining global and/or selective cognitive disability in patients with MS. By applying a new technique, it has been observed that specific cognitive deficits, such as memory impairment, attention deficits and reduced mental processing speed, could be better explained by cortical structural abnormalities than by subcortical white matter lesions. Therefore, MRI evaluation of cortical pathology should be included in the routine examination of people with MS, especially those with initial signs/symptoms of cognitive dysfunction.



Pathological and MRI studies have failed to demonstrate the existence of a strict relationship between cognitive impairment and subcortical white matter pathology. MRI evaluation of cortical pathology should be included in the routine examination of people with MS.

These observations were borne out by a study by Calabrese and colleagues in which 24 patients with relapsing-remitting MS (34.3%) were classified as cognitively impaired⁸². The study provided evidence that the burden of cortical lesions and tissue loss are among the major structural changes associated with cognitive impairment in relapsing-remitting MS.

4.9 Pathophysiological Bowel Dysfunction in MS



Recommended reading⁸³: Wiesel PH, Norton C, Glickman S, et al. Pathophysiology and management of bowel dysfunction in multiple sclerosis. *Eur J Gastroenterol Hepatol* 2001; 13(4): 441–8.



MS can affect the extrinsic neurological control of gut and sphincter function.

Bowel function and continence depend on the integrity of bowel transit, pelvic floor muscle function, anorectal sensation, the motivation to maintain bowel control, and the ability to access the toilet. MS can affect the extrinsic neurological control of gut and sphincter function. This can occur at any level of the neural hierarchy. For example, emotional disturbance due to frontal lobe involvement can lead to behavioural disturbances which can cause failure of pelvic floor relaxation or ignoring of the call to stool. Involvement of cerebral centres of autonomic control may diminish colonic motor function.

There is also evidence for involvement of motor spinal pathways in people with MS with bowel dysfunction. Other factors which could affect bowel function include muscle weakness, spasticity, fatigue and poor mobility. Some medications affect visceral function, for example, anticholinergics prescribed for bladder dysfunction, antidepressants or antispasmodics.

4.10 Bladder Symptoms and MS



Recommended reading⁸⁴: Nicholas R, Young C, and Friede T. Bladder symptoms in multiple sclerosis: a review of pathophysiology and management. *Expert Opin Drug Saf* 2010; 9(6): 905–15.

It is estimated that 64–68% of patients with MS have increased daytime urinary urgency. The final pathway mediating bladder motor function is via the cholinergic pathways. MS can cause a complex multi-level urinary tract dysfunction, which can progress. The urinary symptoms increased with prolonged disease duration and involvement of the motor system. The anatomical lesions are usually on the spinal cord – but there may also be involvement of the cortical centres.

4.11 Summary



- The major cause of symptoms such as paralysis, blindness and numbness is conduction block in the nerves. This is largely caused by demyelination and inflammation.
- The sensitivity of these symptoms to changes in body temperature is well recognised.
- Symptoms such as tingling are due to ectopic bursts of impulses and the triggering of other spurious impulses by the transmission of normal impulses in the areas of demyelination.
- Cognitive impairment is probably due to lesions associated with the cerebral cortex.



Reflective learning point

How does understanding the pathophysiology of MS symptoms link to the successful management of your patients?

Summary of Module



- MS is the most common chronic neurological disorder in young adults.
- It tends to be most common in countries furthest from the equator.
- Race, gender, genetics and environmental factors can influence the incidence of the disease.
- While MS is typically classified into four main types, the prognosis can vary considerably between patients.
- The nervous system is divided onto components – the central nervous system (CNS) and the peripheral nervous system (PNS).
- Together they relay both physical and cognitive information about macro and microenvironments in and around the body, using electrical impulses as the signal device.
- The sheath that surrounds an axon fibre is made of myelin and this is vital for the generation and propagation of electrical signals along the axon fibre.
- In MS, this myelin sheath is attacked by a person's own immune system and destroyed.
- The immune system protects us from pathogens and responds to injury. It has several important characteristics: diversity, specificity, the ability to distinguish self from non-self, and memory.
- The normal immune system can recognise a wide variety of pathogens, leave its own tissue alone and remember a previous exposure to a foreign pathogen and response.
- Some T and B cells also have the ability to react to self-antigens. A normally operating immune system keeps these autoreactive immune cells in check so that they do not provoke unwanted responses.
- If the immune system is dysregulated, tolerance to some self-antigens may be disrupted and autoreactive T and B cells will mistakenly damage a person's own tissues. This is the case in an autoimmune disease such as MS.
- The pathophysiology of MS comprises of two components: inflammation and neurodegeneration.
- Relapses are the clinical expression of acute inflammatory demyelination, whereas progression reflects neurodegenerative processes, including axonal loss, with increasing brain atrophy.
- Recent research suggests that inflammation and neurodegeneration happen at, or near, the same time.

- The major cause of symptoms such as paralysis, blindness and numbness is conduction block in the nerves. This is largely caused by demyelination and inflammation.
- The sensitivity of these symptoms to changes in body temperature is well recognised.
- Symptoms such as tingling are due to ectopic bursts of impulses and the triggering of other spurious impulses by the transmission of normal impulses in the areas of demyelination.
- Cognitive impairment is probably due to lesions associated with the cerebral cortex.

Recommended Reading



<Selected references will follow>

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