PBL TITLE	**A CASE STUDY OF MULTIPLE SCLEROSIS (MS)**
YEAR/BLOCK	**YEAR 1 BLOCK 3 2017/2018**
DURATION	Total contact hours: 4 hours (2 hours x 2 weeks)
PBL MODULE DESIGNED BY	**DR WAEL MOHAMED** Department of Basic Medical Sciences, Kulliyyah of Medicine, International Islamic University Malaysia (IIUM), Kuantan, Malaysia wmy107@gmail.com
AIM	To expose students to the concepts of and approach to neuroinflammation/neurodegeneration, with specific focus on MS
LEARNING OUTCOMES	At the end of this PBL module students should be able to discuss: 1. Basic gross anatomy of the CNS/PNS. 2. The causes of fatigue and difficulty walking 3. Discuss the control of posture and voluntary movement as well as normal gait and balance mechanism. 4. Describe the common causes of muscle wasting and imbalance 5. Describe neuroinflammation pathophysiology e.g. viral infection 6. Discuss epidemiology, complications and prognosis of MS 7. Discuss the investigation for MS 8. Discuss the basic principles of MS managment 9. Islamic input: MS is a lifelong condition. People with MS should find ways to manage their symptoms and function well. Psychological, religious as well as spiritual support is very essential for coping against disease. Believing in destiny gives inner peace and supports the immune system, which is essential in treatment.

TRIGGER 1: CHIEF COMPLAINT

Ms. Z, a 45-year old Malay woman presented to Neurology Clinic of HTAA (Tengku Ampuan Afzan Hospital) because of stumbling gait and a tendency to fall since 6 months.

STUDENTS' TASKS

1. Are there any term that you do not understand?
2. Identify the chief complaint - FACTS
3. Discuss your IDEAS (hypotheses) by integrating relevant basic medical sciences and clinical sciences knowledge into the case.
   (please note that ideas/hypotheses are not necessarily confined to 'the diagnoses')
4. Decide on further information needed in the history and give reasons (what you NEED to know)
5. During the discussion identify 1-3 KEY (PRIMARY) LEARNING ISSUES (IMPORTANT **basic medical sciences** and or **clinical sciences** knowledge that the group need to find out more in order to work through the case).
   Other issues that require further research can be categorised as SECONDARY LEARNING ISSUES

FACILITATOR NOTES	
FACTS (What you know)	• 45-years-old woman • Malay • Unstable gait and tendency to fall since 6 months
IDEAS (Hypotheses)	• The patient is most probably suffering from neurological disorders • The problem is most probably chronic • **Possible causes of unstable gait and fall are as follows (the possible DD at this point include):** -CNS: neurodegenerative disorders, stroke -CNS infection: brain abscess, meningitis or encephalitis -PNS: demyelinating disorders, polyneuropathy -Sleep deprivation -Middle ear problem, Migraine -Ms spasm, Rheumatoid arthritis, LL bone fracture, Spinal cord trauma -Medications/Drugs: Seizure drugs, Alcohol, Drugs that affect sleeping pattern, Hypoglycemia due to anti-DM -Systemic disorders: DM, Tumour -STD: Neurosyphilis -Eye: Cataract
What you NEED to know:	**Questions to refine the differential diagnosis from history of presenting illness:** • The onset of the unstable gait whether it is sudden or gradual and whether it is getting worse *Reason: will suggest the possible underlying cause of unstable gait. If it is acute (due to trauma or stroke)* • The patient's activity before: *Reason: acute onset usually related to trauma. Chronic onset is usually related to infection or neurodegeneration* • Which part of the body involved: *Reason: to locate the site of injury-hemiparesis (stroke), local involvement (back, hip, knee or foot), or generalized (demyelinating disease, neurodegeneration)* • Presence of associated signs and symptoms: • Resting tremors, sluggish movement, and muscle rigidity-PD • Localizing signs (hemiparesis/facial asymmetry)-CVS (ischemic or old hemorrhagic) • Headache with limb weakness – TIA • Peripheral numbness (unable to feel her feet on walking or standing) – polyneuropathy • History of fall, pain at limbs and reduce mobility – bone fracture by falls due to rheumatoid arthritis

	• History of fall with head injury, drowsiness, and headache – subdural hematoma (SDH) • History of fall from high landed on back first or hit at the back – spinal cord trauma • Back pain with lower limbs weakness post lifting heavy objects – herniated lumbar disc • Restriction of movement – muscle spasm or rheumatoid arthritis • Headache, memory problems and sign of space-occupying lesions – brain tumor • Fever with increase ICP symptoms – brain tumor/abscess • Fever with neck stiffness – meningitis/encephalitis • History of promiscuity – STDF (neurosyphilis) • Other associated symptoms such as: • History to suggest the presence of recurrent gait problems • Constitutional symptoms such as loss of appetite and weight - chronic problem or an underlying malignancy • Headache (to rule out space occupying lesion or hypertensive encephalopathy) • Past medical history (to rule out risk factors such as IHD, valvular heart disease, hypertension or DM) • Family history – risk factors (might having hypertension, stroke, heart disease or cancer) • Drug history – medications for DM, hypertension or seizures. The patient compliance to medications • Predisposition to TB infection – contact history • Social and personal history – smoking and alcohol history (predispose to stroke). • History of promiscuity – neurosyphilis or AIDS

KEY LEARNING ISSUES
1. Discuss regarding control of posture and voluntary movement or normal gait
2. Discuss the definition and classification of unstable gait
3. Causes of unstable gait in this age group with its DD

TRIGGER 2: HISTORY

HISTORY OF PRESENT ILLNESS:

Ms. Z noticed inability to walk and stand for long time prior to admission. She complained before attacks of disturbances in her vision, weakness in her limb muscles, sensory defects and movement incoordination along with difficulty in urination control. She had these signs and symptoms several years ago in the form of attacks with remission and relapses every now and then.

A few months prior to this episode she was under a lot of stress in home. She got sick with common cold with appearance of cold sores and fever blisters around her mouth and on the face. At that time, her neurologic condition exacerbated, hence she could not hold objects in her hands, had significant tremors and severe exhaustion. She also had several bad falls. Further, she had noticed arthralgia on the right and subsequently on the left side of her body. Then, few days ago she abruptly developed a right hemisensory deficit.

There was no history of head injury or trauma. She denied having inflammation of the conjunctiva, edema of the eyelids or photophobia. She has no joints pain or swelling, no pustular skin lesions. There was no history of other systemic infections or fever. Also, she denied that she had any history of seizures, TB contact, loss of appetite or loss of weight.

PAST MEDICAL/SURGICAL HISTORY

A positive history of viral infection with Herpes virus some years ago. There is no history of any other CNS infection (e.g. meningitis), DM, TIA, or valvular heart disease.

DRUG HISTORY

She is not on any antihypertensive, antiepileptics or anti-diabetic drugs.

FAMILY HISTORY

Her parents passed away in a car accident when she was 5-year-old. She has only one elder sister who is married without any similar illness in the family

SOCIAL AND PERSONAL HISTORY

She is married with two children aged 5 and 3 years. She quitted school because of repeated poor performance in secondary school examinations. She began smoking at the age of 15 years but denied any involvement in substance abuse. Although she is married, she confessed that she had two intimate relationships with men other than her husband over the past few years.

STUDENTS' TASKS

1. Are there any term that you do not understand?
2. Summarize the additional information obtained from the trigger- FACTS
3. Discuss further your IDEAS (hypothesis) based on the additional information provided by integrating relevant basic medical sciences and clinical sciences knowledge into the case.
4. List the physical examination findings you would look for and give reasons (what you NEED to know)
5. During the discussion identify 1-3 KEY (PRIMARY) LEARNING ISSUES (IMPORTANT **basic medical sciences** and or **clinical sciences** knowledge that the group need to find out more in order to work through the case).
   Other issues that require further research can be categorised as SECONDARY LEARNING ISSUES

FACILITATOR NOTES	
FACTS (What you know)	• Unstable gait and tendency to fall for years • Attacks of visual disturbances, weakness in her limb muscles, sensory defects and movement incoordination • Remission and relapses • History of cold sores and fever blisters • Social history - stress • No history of loin pain, or fever • No history of brain trauma • No loss of appetite or loss of weight
IDEAS (Hypotheses)	• The case seems to be acute attack on top of chronic one • The neurological manifestations deteriorate • The problem is most probably confined to systemic cause in nervous system and less likely (not totally excluded) to involve local cause • The possible diagnoses at this point include: **Neuroinflammation (e.g. MS)** **Cerbrovascular accident (Stroke)** **Neurodegenerative disorders (e.g. PD)** **Brain tumour - still possible** **Neurosyphilis (STD)**
What you NEED to know:	**To look for the following signs on physical examination:** **General examination** • Posture and gait *Reason: type of gait can determine the source of problem e.g. propulsive gait, scissor gait, spastic gait, steppage gait, waddling gait* • Facial asymmetry, slurred speech with saliva drooling

	Reason: suggestive of CVA • Lymphadenopathy *Reason: it is present in acute leukaemias or lymphomas* • Genital ulcers *Reason: develop syphilitic infection* • Hepatosplenomegaly *Reason: will be present in hepatitis, acute leukaemias, and lymphomas* • Pallor *Reason: evidence of anemia if sever bleeding in the brain* • Carotis bruit *Reason: risk factors for ischemic stroke* • Neck stiffness *Reason: meningeal irritation - meninigitis* • Height and weight *Reason: to exclude malignancies* **Fundoscopy:** *reason: papilloedema or optic neuritis* **Systemic Examination of CNS** *Reason: to assess objectively the patient conscious level* **Based on the history, there is high possibility of neurological disease, thus we would seek for the following signs:** • Hemiparesis with facial asymmetry *Reason: CVA* • Muscle bulk, tone, power and reflexes *Reason: to assess the severity of the stroke and differentiate between UMNL and LMNL* • Babinski's reflex *Reason: UMNL* • Signs of cranial nerve palsy or hydrocephalies *Reason: increase ICP secondary to bleeding, cerebral edema or brain tumor* • Visual field examination *Reason: to assess visual pathway and optic nerve involvement* • ENT examination *Reason: to assess stability, balance and equilibrium* **Other physical examination are done to rule out other possible causes though less likely:** • Lung examination *Reason: Aspiration pneumonia* • Heart examination *Reason: risk of CVA* • GIT *Reason: liver disease may lead to coagulopathy…increase risk of brain*

	bleeding

KEY LEARNING ISSUES

Elaboration and discussion on each of the possible causes:

- **Sexually transmitted disease**
- **Risk factors for cerebrovasular accident**
- **Clinical presentation of neurodegenerative disorders**
- **Genital herpes**
- **Hypertensive encephalopathy**

TRIGGER 3: PHYSICAL EXAMINATION

GENERAL EXAMINATION:

The patient was alert, conscious and oriented to time, place and person. Her GCS (Glasgow Coma Scale) was 15/15. She was of medium size built. She was not pale. Her nutrition and hydration status were good. There was no pallor, jaundice, cyanosis or clubbing. Her pupils were equal and reactive to light. There was no neck stiffness and no carotid bruit

VITAL SIGNS:

Temperature: 37 ^{0}C
Pulse: 90 beat per minute, regular with good volume
Blood pressure: 110/70 mmHg
Respiratory rate: 18 breaths per minute

FUNDOSCOPY: showed grade II retinopathy.

SYSTEMIC EXAMINATION:

CARDIOVASCULAR SYSTEM:

Apex beat was palpable at the 5th intercostal space within the mid-clavicular line with normal character. There was no thrill or parasternal heave. Both first and second heart sound were heard. There was no murmur.

RESPIRATORY SYSTEM:

The shape of the chest was normal without any deformity. The chest moved symmetrically with respiration. On palpation, the trachea was centrally located. Tactile fremitus and vocal resonance were normal. Percussion note was resonant all over the lung fields. Vesicular breath sound with no crepitation heard.

ABDOMEN:

The abdomen was soft, not distended and non-tender. There was no hepato-splenomegaly. Both kidneys were not ballotable. Bowel sounds were present.

NEUROLOGICAL EXAMINATION:
There was right-sided facial weakness but the muscles of the forehead were not affected.
There was homonymous hemianopia
The right limbs muscle power was reduced. The power was much more reduced in the right upper limb (grade 2/5) than the right lower limb (grade 3/5). Reflexes were increased (brisk) on the right with positive Babinski's plantar response. Sensation was also reduced on the right side

Sensory exam reveals paresthesia on the right to touch and decreased pin sensation on the right diffusely. The patient has mild vibratory sense loss in the distal lower extremities.

Romberg's is negative. Tandem gait is mildly unstable. Ambulation index is 7.0 seconds for 25 feet (normal) i.e. the patient takes 7.0 seconds to walk 25 feet

Cranial nerve examination is normal except for decreased hearing on the left, and numbness in the right face. The weber test reveals greater conductance to the right. Rinne's test revels air greater than bone bilaterally. The palate elevate well. Swallow appears to be intact. Tongue movements are slowed, but tongue power appears to be intact.

EXTERNAL GENITALIA: There was submucous inflammatory "soft" infiltration of the genitalia.

STUDENTS' TASKS

1. Are there any term that you do not understand?
2. Summarize the additional information obtained from the trigger - FACTS
3. Discuss further your IDEAS (hypothesis) based on the additional information provided by integrating relevant basic medical sciences and clinical sciences knowledge into the case.
4. List the investigations you would perform and give reasons (what you NEED to know)
5. During the discussion identify 1-3 KEY (PRIMARY) LEARNING ISSUES (IMPORTANT **basic medical sciences** and or **clinical sciences** knowledge that the group need to find out more in order to work through the case).
   Other issues that require further research can be categorised as SECONDARY LEARNING ISSUES

FACILITATOR NOTES

FACTS (What you know)	Patient is alert, conscious and oriented to time, place and person with a medium sized built. No pallor with a good nutritional and hydration status Normal BP and normal heart Neurological examination revealed UMNL with positive Babinski's sign

	and unstable gait Cranial nerve affection e.g. optic nerve, facial nerve
IDEAS (Hypotheses)	• The presence of grade II retinopathy with right homonoymous hemianopia on fundoscopy • The presence of right facial weakness with reduced the power of right limb muscles • The presence of brisk reflexes on the right with positive Babinski's sign • The presence of paraesthesia on the right side to touch and decreased pin sensation on the right diffusely • There is decreased hearing on the left and numbness on the right side of the face • The patient was not in heart failure – no cyanosis, no cardiomegaly, no gallop rhythm and no signs of pulmonary oedema (basal crackles). • The absence of bleeding tendencies and lymphadenopathy makes acute leukaemia and lymphoma less likely • No distension in abdomen with absence of hepatomegaly • Both kidneys are not ballotable with normal bowel sounds • The possible diagnoses at this point include: 1. **Left cerbrovascular accident with right hemiparesis** is a provisional at this point 2. **Neuroinflammation of the CNS with right hemiparesis**
What you NEED to know:	Results of the following investigations: • Blood culture and sensitivity test *Reason: to look for the presence of infection or not* • Full blood picture *Reason: Hb (anemia), TWC (infection), HCT (dehydration), Platelet (Bleeding), to exclude any malignancy* • BUSE *Reason: to look for electrolyte status (dehydration or electrolyte imbalance causing paralysis specially hyperkalemia)* • Screening for sexually transmitted diseases (HSV and HIV) *Reason: since the patient is most likely to have STD* • **CSF culture** *Reason: necessary for detection of inflammatory biomarkers*

KEY LEARNING ISSUES

1. **Neuroinflammation e.g. MS**
2. **Approach to investigations for MS.**

TRIGGER 4: INVESTIGATION RESULTS

INVESTIGATIONS

1. **Full Blood Count (FBC):**

Haemoglobin	13.5 g/l	(13-18)
Haematocrit:	40 %	(40-52)
MCV	82 fl	(80-87)
MCH	28 pg	(27-30)
MCHC	30 g/dl	(25-33)
Total White Cells	13x 10^9/L	(4.0-11)
Neutrophils	68 %	(37-80)
Lymphocytes	20 %	(10-50)
Monocytes	5 %	(0-12)
Eosinophils	5 %	(0-7)
Basophils	2 %	(0-2.5)
Platelet count	280 x 10^9/L	(150-450)

2. **Erythrocyte Sedimentation Rate:** 25 mm/hr (<20)

3. **Fasting blood glucose:** 4.5 mmol/l (3.5-6.1)

4. **Renal Profiles**

Urea	2.1 mmol/l	(1.7-8.3)
Sodium	137 mmol/l	(135-154)
Potassium	4.2 mmol/l	(3.5-5.4)
Chloride	99 mmol/l	(98-108)
Phosphate	1.1 mmol/l	(0.87-1.45)
Calcium	2.2 mmol/l	(2.1-2.6)
Creatinine	80 µmol/l	(70-120)
Uric acid	200 µmol/l	(180-420)

5. **Lipid Profiles**

Total cholesterol	5.1 mmol/l	(<5.2 mmol/l)
Triglycerides	1.5 mmol/l	(<1.71 mmol/l)
HDL-cholesterol	1.2 mmol/l	(>1.04 mmol/L)
LDL-cholesterol	2.5 mmol/l	(<2.6 mmol/l)

6. **Liver Function Test:**

Total protein	65 g/l	(60-80)
Albumin	42 g/l	(35-55)
Total bilirubin	12 µmol/l	(up to17.1)
Direct bilirubin	1.2 µmol/l	(0.8-5.1)
Alkaline Phosphatase	55 U/l	(53-128)
Alanine Transaminase	35 U/l	(up to 42)
Aspartate Transaminase	36 U/l	(up to 40)

7. **Urine analysis:**

Colour	:	yellowish
pH	:	6.1 (N: 5.0 – 9.0)
S.G.	:	1.005 (N: 1.003 – 1.030)
Albumin	:	nil
Glucose	:	nil
Microscopy:		
WBC	:	10-15 / HPF
RBCs	:	Few
Crystals	:	Few calcium oxalate

8. **Blood Culture & Sensitivity:** No bacterial growth, presence of proinflammatory markers and cytokines

9. **CSF culture:** positive for *IgM, TH17 cell, and presence of proinflammatory markers and cytokines.*

10. **Venereal Disease Research Laboratory (VDRL)** – positive for Syphilis.

11. **HIV-** ELISA (enzyme-linked immunosorbent assay) – Negative

12. **DTI** (Diffusion Tensor Imaging): reveals several patches of axonal loss

13. **MRI (**Magnetic Resonance Imaging): presence of multiple local inflammatory lesions in the white matter)

A final diagnosis was made and discussion on the management was to be held with the patient and the family members

STUDENTS' TASKS

1. Are there any term that you do not understand?
2. Discuss the investigation results- FACTS
3. Discuss further your IDEAS (hypothesis) and finalise your diagnosis.
4. During the discussion identify 1-3 KEY (PRIMARY) LEARNING ISSUES (IMPORTANT **basic medical sciences** and or **clinical sciences** knowledge that the group need to find out more in order to work through the case).
   Other issues that require further research can be categorised as SECONDARY LEARNING ISSUES
5. Discuss the **Islamic Perspective of Alternative/Complementary Medicine**.

FACILITATOR NOTES	
FACTS (What you know)	• Presence of pro-inflammatory markers ad cytokines in blood and CSF • Positive VDRL for syphilis • MRI and DTI reveal multiple focal inflammatory lesions
IDEAS (Hypotheses)	**This is a case of Neuroinflammation especially MS.** **Point to support the diagnosis:** • Presented with signs and symptoms related to neuroinflammation • On examination there were evidence of motor and sensory affection • Raised total white cells count and ESR • Signs of UMNL • Vision affection in the form of homonymus hemianopia
What you NEED to know:	• Any other family members who are affected? *Reason: it is an inflammation* • Further investigations to be done include family screening and molecular study *Reason: Family screening to identify any other STD* • Principles of management of MS

KEY LEARNING ISSUES

1. Neuroimaging diagnosis of MS
2. Principles of management of MS

NOTES ON KEY LEARNING ISSUES

Epidemiology

One of the most striking features has been the unique geographical distribution of the disease. The highest incidence of the disease is found in areas corresponding to the so-called temperate zone, with the lowest incidence in regions around the equator. Indeed, this observation has been refined in recent years, with multiple studies in individual countries, such as Australia, (Tasmania to Darwin) and Canada (Northern and Southern Newfoundland), which show an increasing incidence the further the distance from the equator. The prevailing view on this differential for many years has implicated exposure to some infectious agent found in temperate climates. This strong latitude-dependent susceptibility appears to be slightly decreasing, perhaps related to the increasing mobility of populations, or else local factors. For example, in Norway, the incidence appears greatest closest to the sea. However, two features have recently emerged as leading causes. The first is the high prevalence in temperate areas, especially in Europe and North America, of people with a genetic makeup consistent with a Northern European ancestry. The second is the demonstration that high-prevalence areas are subjected to fewer hours of sunlight and consequently lower levels of vitamin D than those closer to the equator. These factors will be discussed in greater detail below. The influence of race is striking. Prevalence studies show the highest incidence in countries with a higher Caucasian population. However, among Caucasians, the incidence varies with many factors, including latitude. It is less common in blacks and aboriginal peoples. US military records show a significantly higher incidence in Caucasians than in Afro-Americans, Mexicans, Japanese, and Puerto Ricans. While it is rare in Asia and Africa, there are some areas where the incidence is higher, such as Northern China and parts of Japan. In Hawaii, Asians have half the incidence rate of Caucasians. In addition, race appears to play a role in the phenotype of the disease, with African Americans often a more aggressive course and Japanese having a higher incidence of opticospinal disease. Migration studies have helped to dissect out the relationship between race and environmental studies. These have been carried out in countries where there have been significant shifts in population because of immigration, namely, in South Africa, Hawaii, Israel, and the United Kingdom. Although the details vary, in general, these studies have shown that immigrants retain the incidence of the region of childhood if their immigration occurs after the age of 15–20, whereas if this event occurs prior to that cutoff, they acquire the incidence of their new country. This obvious environmental influence has been ascribed for many years to childhood infections, which may still be valid, but other factors, such as sun exposure, may also play a role. The influence of gender is also striking. As with many putative autoimmune diseases, there is a high female to male ratio, ranging from two to three. This ratio appears to be increasing, as in Canada, where it is now estimated as over 3.2:1. Hormones, specifically estrogens and progesterone, may play a role in modulating the effects not only on the immune process but also on the potential for remyelination and the age of onset of the disease. It is known that relapses are ameliorated during pregnancy, although in postpartum there is often an upsurge of attacks. There have been some instances where there have been epidemics of an increase in incidence occurring within a defined period. While some of these have undoubtedly been due to greater awareness of the diagnosis, some may have been genuine. The classic examples of potential epidemics occurred in the Faroe and

Channel Islands off the coast of Britain and in Iceland. The spikes in incidence were attributed to the sudden influx of British soldiers during the Second World War and supported the suggestion of a viral etiology. More recent examples have occurred following clusters of MS cases in people who had infectious mononucleosis, or Epstein-Barr virus (EBV) infection, which will be dealt with below. In recent years, a theory has been posited that MS is caused by venous obstruction to the vessels draining the brain and spinal cord (called chronic cerebrospinal venous insufficiency (CCSVI)), with subsequent leakage of iron causing tissue damage. The venous obstruction has been demonstrated by specialized Doppler studies. This theory has attracted much attention in the popular press. Other studies have failed to show these changes in MS patient more than in controls, especially at early stages in the disease. These observations cast doubt as to whether they bear any relationship to MS or even whether they actually exist. Further well-conducted studies will be necessary to resolve this issue.

Environmental Factors

Since the description of the disease, numerous environmental causes have been postulated. The evidence of the importance of MS patients' genetic makeup has necessitated understanding how these factors may interact with a genetic susceptibility to produce disease. In this context, environmental factors may be operating to cause the disease, or to act as a trigger to the immune system to produce attacks. Many of the postulated etiologies have shown only weak effects, or have not stood the test of time. Various studies over the years suggesting a role for toxins, such as organic solvents, in etiology have been published, but the evidence for this has not been strong or consistent. Similarly, the role of stress in causing MS is still being questioned. In this regard, it is at times difficult to determine whether reported stress is a cause or a consequence of the disease. Much has been written on the influence of diet in MS development. This factor has potentially some relationship to ethnic group, race, and geography. Dietary factors such as meat and dairy consumption, malnutrition, and levels of linoleic acid have been studied, with variable and inconclusive results as having a wide variety of other, sometimes common, foodstuffs. Populations with higher fish consumption have been noted to have a lower risk of MS. Pooled data from many studies suggest an association with smoking and MS. Infectious agents, sunlight, and vitamin D status are the three environmental factors which appear to be more robust as etiological influences capable of interacting with immune and genetic processes. The latter two are probably related and will be considered together.

Infection

Since the identification of MS as an inflammatory disease, infectious agents have always been strong and tempting suspects. The migration and geographic studies have supported this view, suggesting the presence of a past infection in endemic areas. In addition, strong data suggested that viral infection could trigger attacks, and subsequently, a wide variety of agents have been proposed, including measles, parainfluenza, canine distemper, retroviruses, Epstein-Barr virus (EBV), and human herpes virus 6 (HHP6). With the advent of new and sensitive molecular techniques, the search for old and novel pathogens continues. Studies have shown that these agents may cause immune disease, through the mechanisms of molecular mimicry, epitope spreading, and bystander damage. The concentration on viruses should not preclude the possibility that other infectious agents could not play roles, either in the causation or in triggering attacks. The relationship between infection and immunity is also strengthened by the so-called hygiene theory of susceptibility, which suggests that a vigorous early immune response to infections is necessary to protect against the development of autoimmune disease. In developed countries, improved sanitation and widespread use of antibiotics have interfered with the body's ability to mount a normal response to infection, leading to an increase in autoimmune disease incidence. This credence has gained credibility

by the observation that prior infection with parasitic helminthes protects individuals from contracting MS. Currently, most attention is given to the role of EBV in causing MS. Almost 100% of patients are seropositive for EBV, although it should be noted that the rate in the general population is 90%. This difference is even higher in the pediatric population. EBV DNA is higher in patients than in controls, and during relapses, in patients prior to the onset of disease, EBV titers are higher than those in controls. Lymphocytes from MS patients are more likely than those from controls to transform spontaneously under EBV induction, and patients are more likely than controls to have EBV-specific cytotoxic T cells. MS patients are more likely than controls to have had infectious mononucleosis, and clusters of MS cases in Denmark have followed community outbreaks of infectious mononucleosis.

Finally, there is some evidence, not accepted by all, that the meningeal B-cell follicles found in MS cases contain EBV-infected lymphocytes. There is a higher level of intrathecal and CSF EBV than other viruses. As with other viruses, there is no specificity for EBV, in the CSF oligoclonal bands, a hallmark of MS. However, protein arrays from human dDNA libraries have shown a high reactivity to EBV antigens BRRF2 and EBNA-1. Although several studies have shown evidence of HHV6 in plaques and in blood and CSF of MS patients, the epidemiological evidence for this virus is not as strong as for EBV. Evidence for the involvement of human endogenous retroviruses (HERVs) is suggested by the finding of HERV proteins in the sera and CSF of MS patients and by the relationship between this virus and both EBV and HHV6, suggesting that infection may depend on the interaction of more than one virus. In this context, it should be pointed out that HHV6 and paramyxoviruses use a common cell receptor, CD46, to enter cells and that numerous other agents, including common bacteria, make use of the same molecule and thus may share common pathways to cellular entry.

Clinical Aspects of MS

MS has been well recognized as a clinical-pathologic entity since the 1870s. The classical descriptions detail a disease course that evolves over many years. The early phases of the disease feature recurrent episodes of neurologic dysfunction (relapses), each followed after days to weeks by variable degrees of recovery and periods of stability (remission). This classical form of the disease is known as relapsing-remitting MS (RRMS). Although the actual frequency of relapses may decline over time, the affected individual can develop a gradual increase in neurologic disability, now referred to as secondary progressive disease (SPMS). The recognition of these features permitted accurate clinical diagnoses of large patient cohorts that could be followed over many years. Standardized clinical criteria were established (Table 90.1) to make the diagnosis of definite MS, permitting standardized selection of patients for entry into clinical trials and for large population-based studies aimed at delineating the complete clinical spectrum of the disease, variations in its natural history, and epidemiologic features of the disease (age of onset, geographic distribution, familial incidence). Such studies were also supported by the relatively wide acceptance of a standardized neurology assessment scale initially termed “the disability status scale” (DSS) later adapted to the expanded disability status scale (EDSS). Other forms of the disease include the clinically isolated syndromes (CISs), benign MS, and primary progressive MS (PPMS, see below). Progressive forms of MS refer to continued accumulation of neurologic deficits, which cannot be ascribed to recurrent inflammatory events that are associated with disease relapses and new MRI-defined lesions. The latter can continue to occur concurrently in patients with progressive disease. Most commonly, progressive disease evolves in those with an initial relapsing disease course, usually apparent after several decades after disease onset and then evolving over subsequent years. An estimated 10% of patients have a progressive course from the start. Additional clinical-pathologic studies helped establish the

extremes of the disorder (fulminant or Marburg variant) versus benign MS (asymptomatic lesions discovered at autopsy or no disability after 20 years) and existence of disease variants whose relation to the classic disease form remains under study. These include primary progressive MS, neuromyelitis optica, and recurrent myelitides. The observation from the late 1940s of increased intrathecal synthesis of immunoglobulin (Ig) in the CNS in cases of MS that could be measured by analysis of the cerebrospinal fluid (CSF) increased amount of Ig that had restricted heterogeneity (oligoclonal bands) provided the first laboratory adjunct to support the diagnosis of MS. The development of electrophysiologic measures to document presence of demyelinated CNS pathways (visual, auditory, and somatosensory evoked responses) provided further laboratory support for the diagnosis leading to their inclusion in revisions made to the original diagnostic criteria that were limited to clinical measures.

The 1980s marked the inclusion of magnetic resonance imaging (MRI) in the evaluation of MS patients leading to further revision of diagnostic criteria (MacDonald). New lesion formation on MRI examination became accepted as a means to diagnose an individual case as having recurrent disease and qualifying for therapeutic intervention rather than requiring a second clinical event. MRI confirmation of lesions consistent with CNS demyelinating disease has become a sine qua non for acceptance of the diagnosis of MS including for inclusion into therapeutic trials. To date, clinical criteria remain the primary endpoints for clinical trials seeking drug registration, but MRI confirmation is an important adjunct. In the MRI era, the time from first reported symptom to the individual being given the diagnosis of MS has been reduced from a mean of _ 8 years to a mean of a few weeks to months with the introduction of the term “clinically isolated syndrome” to bypass the debate as to whether individuals with their first clinical event and an MRI with demyelinating lesions should be called MS or be considered for therapy (see later section regarding early initiation of therapy). Laboratory criteria to support the diagnosis of the progressive component of MS remain under development. New criteria include MRI measures of brain atrophy and optical coherence tomography that measures retinal nerve fibers, as a surrogate of axonal loss throughout the CNS.

Table 90.1 McDonald diagnostic criteria (2001) with Polman MRI revisions (2005)

Clinical presentation	Additional data needed
• 2 or more attacks (relapses) • 2 or more objective clinical lesions	None; clinical evidence will suffice (additional evidence desirable but must be consistent with MS)
• 2 or more attacks	Dissemination in space, demonstrated by: • MRI
• 1 objective clinical lesion	• or a positive CSF and 2 or more MRI lesions consistent with MS
	• or further clinical attack involving different site
• 1 attack	Dissemination in time, demonstrated by: • MRI
• 2 or more objective clinical lesions	• or second clinical attack
• 1 attack	Dissemination in space demonstrated by: • MRI
• 1 objective clinical lesion (monosymptomatic presentation)	• or positive CSF and 2 or more MRI lesions consistent with MS
	Dissemination in time demonstrated by: • MRI • or second clinical attack
Insidious neurological progression suggestive of MS (primary progressive MS)	One year of disease progression (retrospectively or prospectively determined)
	Two of the following: (a) positive brain MRI (nine T2 lesions or four or more T2 lesions with positive VEP) (b) positive spinal cord MRI (two focal T2 lesions) (c) positive CSF

Clinical Features of MS

As multiple sclerosis is defined as a disease whose lesions are disseminated in space within the CNS and over time, the clinical features of the disease need be considered with regard to both the neurologic symptoms and signs that arise from lesions at different sites within the CNS and how these manifest over time. In line with the long-recognized lesions within the white matter tracts of the CNS, individuals affected by MS can show variable combinations of clinical features dependent on the specific tracts affected. Most readily recognized manifestations include disturbance of function of vision (optic nerve), strength (descending motor tracts), sensory dysfunction (ascending sensory tracts), incoordination (cerebellar tracts), and urinary bladder control (usually spinal cord). Most motor deficits reflect involvement of the upper motor neuron pathways and thus manifest with increased tone (spasticity) and exaggerated reflexes. Since MS lesions do not respect anatomical boundaries, combination of dysfunction from involvement of adjacent pathways (e.g., motor and sensory) is common. Severity of the disturbance varies, widely reflecting the extent of insult to the specific pathway. Correlation exists with the extent of demyelination and destruction of the underlying axons. In cases with intact axons but disrupted myelin, aberrant nerve conduction can result in paroxysmal symptoms, e.g., trigeminal neuralgia or exaggerated symptoms such as sensory dysesthesia and Lhermitte's phenomenon. Any myelinated tract or nerve root with a CNS component can be involved including all cranial nerves and spinal motor and sensory nerve roots. A feature of demyelinated nerve is failure to sustain conduction either on a sustained or intermittent basis. Conduction through demyelinated nerve is sensitive to generalized metabolic upsets most readily recognized by effects of increased temperature on

enhancing neurologic deficits (Uhtoff's phenomenon). More complex clinical features of MS are less readily explained by involvement of single pathways or single discrete lesions. The clinical phenotype often reflects a combination of factors including severity of injury at a given site and the effects multiple lesions within the same or different anatomical pathways. For example, impaired balance can reflect involvement of motor, sensory, vestibular, visual, and cerebellar pathways. Cognitive and psycho-affective dysfunction is well recognized to occur in MS but is variable in severity. Depression is the commonest affective symptom but can reflect a reactive component rather than being a direct result of tissue injury. Attributing deficits in specific cognitive tasks to a single anatomic lesion is unusual in MS given that the majority of affected individuals have multifocal white matter lesions as detected by MR-based imaging. Immunohistochemical analyses of MS tissue sections indicate that there can be extensive gray matter lesions. Current in vivo imaging methods remain insensitive to detect many of the gray matter lesions leaving open the question of how much of the cognitive or affective dysfunction in MS can be attributed to such lesions. The incidence of seizures is marginally above the expected.

Differential Diagnosis of MS

At the time of an initial event with neurologic findings that can be localized to a single anatomic site, one needs to exclude other structural lesions (vascular, tumor). MR imaging will both exclude these diagnoses, and in > 50% of cases, there will already be evidence of multifocal lesions. For individuals with multifocal inflammatory lesions, the main differential diagnosis is the presence of systemic inflammatory disorders (e.g., collagen-vascular disorders, sarcoidosis) or multifocal infectious disease of the CNS.

Clinical Spectrum of MS

The combination of clinical and imaging diagnostic criteria has allowed a clearer characterization of the clinical spectrum of MS. The early natural history reports recognized cases in which the initial episodes were followed by an indefinite benign subsequent course with no advance on the disability scale. The fulminant extreme was also recognized. The most characteristic long-term disease course in the pretreatment natural history studies was development of increasing disability without a significant shortening of life span. Negative prognostic factors include a higher initial relapse rate, time to second relapse, development of progression, and multisystem involvement Uncertainty remains about the long-term impact of the immunomodulatory therapies discussed below on long-term disease course, with suggestive evidence that this as well as relapse frequency and relapse-associated disability has been impacted. The natural history registries also demonstrate that the peak age of initial MS symptoms is in individuals in the third and fourth decade with recognition that disease can have onset at both younger and older extremes. Childhood onset MS, i.e., prepuberty, is uncommon and more frequently has large inflammatory lesions with encephalopathic (behavioral/cognitive) features. The onset in the older cohort (fifth and sixth decade) more characteristically features a progressive or spinal cord-centered disease although relapsing/remitting disease has now been well documented with the availability of MR imaging. In this group, differential diagnosis of vascular disease becomes a more frequent challenge. A consistent observation is the increasing incidence of MS in females, whereas the rate in males remains constant. The median time for progression to EDSS 3–4 (restriction of ambulation) for all MS cases as a group varies in different studies from 8 to 12 years, ranging up to 17 years or more in others. Median times to EDSS 6 (needing gait support) ranged from 14 to 28 years in various studies. In SPMS, these figures are slightly shortened, ranging from 8 to over 20 years, whereas for PPMS, these times were shortened to a range of 3–8 years. Finally, estimates of time to EDSS 10 (death) are 33 years for PPMS and up to 40 years in RRMS. Prognosis is affected negatively by early onset of progressive disease, a higher relapse rate, and multiple system involvement. Various geographical and ethnic factors, as

well as age of onset and gender, also affect the natural history.

Pediatric Multiple Sclerosis

In the last decade, MS clinicians and pediatricians have come to realize that MS occurring in patients below the age of 18, although not common, does not merely behave as it does in adults, but have unique clinical, radiological, and pathological features that present challenges diagnostically and therapeutically. Estimates of incidence range from 1% to 10%, of MS patients, but the higher estimate undoubtedly includes some patients in whom it was realized retrospectively that the first symptoms occurred before the age of 18. Studying these cases offers an opportunity for seeing changes (immunological, pathological, and imaging) which may not only aid in earlier therapy for children but also for providing a window into the first stages of the disease in adults. Understanding the disease is complicated by the concurrent development of the nervous, immune, and endocrine systems, and by general growth features. For example, the normal female to male ratio is not evident in prepubertal children. In addition, many of the ethnic and racial distinctions seen in the adult disease are not present in children. Pathologically and on imaging, the lesions appear to be larger, or tumefactive, but biopsies show essentially the same histological and immunohistological features of the more acute lesions seen in adults. Children appear to have an immune makeup which is more activated, not only to CNS-specific antigens such as MOG (myelin oligodendrocyte glycoprotein), but in a more global fashion. EBV virus seropositivity is significantly raised above the normal controls, the difference being more marked than that seen in adults. The most significant differential diagnosis to be ruled out in making a case for MS in a child is whether the patient has ADEM (acute disseminated encephalomyelitis). This disease, particularly common in the young, is a true immune-mediated process, arising in response to a viral infection or postvaccination and probably operating through molecular mimicry and epitope spreading. It is the human equivalent of EAE in animals and shares much of the characteristics of that disease. The pathology may be very difficult to distinguish from acute MS (see below). Although usually monophasic, it may be recurrent, further complicating the differential. However, it usually has prominent encephalopathic features, which are not a feature of MS. Whether it serves, as a substrate for the later development of MS will await the outcome of many long-term studies currently underway.

Neuromyelitis Optica (NMO)

For many years, this condition, presenting with optic neuritis and extensive myelitis, was considered to be part of the MS spectrum. A recently identified disease-specific autoantibody in the CSF, NMO-IgG, which recognizes the K channel, aquaporin 4, in astrocytes, has served to help definitively distinguish this entity from MS. NMO differs from MS showing a longer segment of spinal cord involvement, but less brain involvement. CSF oligoclonal banding is absent in NMO. Pathologically, the cord lesions show more severe and extensive demyelination and necrosis than do MS cases, with polymorphonuclear and eosinophil infiltrates and complement deposition. The optic nerve lesions may also be more necrotizing than those of MS. The antibody localizes to astrocytic foot processes, especially perivascularly, with subsequent cellular necrosis and edema formation. Many cases of so-called opticospinal MS, commonly found in Japanese patients, have now been reclassified as NMO on antibody testing. In addition, variants of NMO are now described, with relapsing forms and cases showing supratentorial lesions being described. The autoantibody nature of the disease lends itself to therapies such as B-cell depletion and plasma exchange.

Genetic Aspects of MS

One of the most important developments in the study of MS over the last two decades has been the understanding of the primal role of genetic makeup in the causation and the

modulation of the disease. The importance of a differing racial incidence in the disease was an early indication that genetic makeup played a large role in causation (see below). Initial observations began with familial studies in Canada, the United States, and Europe, which established that relatives of patients with MS had a much higher incidence of the disease than the general population. For first-degree relatives, this reaches up to 30 times that of normal population. Significantly, the degree of risk was directly related to the closeness of the relationship, with monozygotic twins having almost double the risk of dizygotic twins. Similarly, the latter carry higher risk than normal siblings and half-siblings in order. Landmark Canadian studies on twins, siblings and half-siblings, and adoptees reared together and apart have shown that in the microenvironment of familial MS, the effect of the environment is small. This statement, however, does not hold for whole populations. Recently, awareness of the role of maternal influence has confirmed that maternal transmission is much higher than that of paternal. Indeed, the risk of maternal half-sibs is the same as that of full siblings. In spite of the obvious genetic influences, many people of similar genetic makeup will not contract the disease, and the complex interplay between strong environmental and genetic factors is of critical importance in determining who will or will not get the disease. There has been much discussion as to whether MS is a single gene condition, or one of the polygenic diseases, each of small influence by itself, such as cardiovascular disease. Candidate gene association and linkage analysis showed only one striking association. The HLA gene cluster, particularly the class 11 region, on chromosome 6p21.3 is now recognized to be the dominant single genetic abnormality in MS. HLA-DRB1 and DQB1 are the significant alleles, with DRB1.1501 being of particular importance. These observations were confirmed in large European and Canadian studies using single nucleotide polymorphism technology. Significant in relation to MS, this locus is intimately associated with control of the immune system. More recently, advances in techniques have resulted in multiple genome-wide association studies (GWAS) using significant banks of patient DNA. As might be expected, a small number of non-HLA candidate genes have been discovered, although none with the power of the HLA class 11 locus. This has reintroduced for some workers, although not all, the notion of a polygenic basis for the disease. Most of these genes are related to the immune system and are responsible for a wide variety of cellular functions such as cell adhesion, T-cell signaling, proliferation, differentiation and activation, B-cell proliferation, apoptosis, and regulation of HLA 1 genes to name a few. The genes include the receptors for IL-2 and IL-7, CD58, EVI5, RPL5, as well as others. It must also be remembered that genes may interact with one another (epistasis) and even their DNA may interact with other DNA segments to alter function. Future investigations may clarify the relative importance of these genes. It is very likely that some aspects of the course of the disease may be under genetic control. As noted below, African Americans may have a more aggressive course and Japanese a different form of the disease. However, even within the Caucasian population, genetic background may influence the age of onset, clinical course, and disability progression. It is possible that some of these differences may depend on variations of the immunological mediators, either within the HLA locus or in some of the more recently identified genes.

Markers of Immunological Damage in MS

There are numerous direct indications that the pathogenesis of MS includes a major immune component as described above. The blood-brain barrier (BBB) plays a critical role in maintaining the integrity of the CNS, but is breached early in the development of the disease. The passage of cells through the abnormal barrier and their subsequent migration through the tissues, mediated by integrins and matrix metalloproteinases and guided by chemo-attraction, are very significant features of MS. Studies on human tissues show many indicators of the abnormalities in the vascular system confirming the existence of these processes in MS.

There is an upregulation of endothelial cell adhesion molecules, such as ICAM, VCAM, and ALCAM, which have corresponding ligands on the infiltrating cells. In MS lesions, the chemokines CXCL12, CCR7, CCL19, and others are expressed on various cell types, but each may be specific for different stages of the disease, as well as for specific sites. CCL20, expressed in the choroid plexus, facilitates entry of TH17 cells into the CNS. Pathological examination of MS lesions shows the presence of most of the elements described above. Lymphocytes, mainly T cells; MHC class 11 macrophages; B cells; and activated microglia are all found in the parenchyma and around blood vessels. In some lesions, immunoglobulin and complement deposition may be seen in and around the lesions. These changes are also seen away from the lesions in the socalled normal-appearing white matter (NAWM) and probably correlate with progressive illness. Although CD4 cells are seen early in the perivascular infiltrates, CD8 cells are more prominent where they are exposed to resident antigen presenting cells and can subsequently damage tissues directly. Similarly, the B-cell meningeal follicles may be responsible for ongoing cortical damage in progressive illness. These follicles also contain germinal centers, dendritic cells, and express cytokines such as CXCL13. T cells autoreactive to myelin and other CNS elements may be found in the blood and CSF of both normal people and in MS patients, but in the latter, they tend to be derived from preexisting memory cells and to be available in a more activated state. Recently, the presence of TH17 cells in the CSF of MS cases, and in the blood of patients undergoing relapses, has bolstered the case for their involvement in the pathogenesis of the disease, given their known ability to damage myelin and neurons in culture. The presence of oligoclonal banding in the CSF of MS patients has always suggested a prominent role for B cells and plasma cells underlying IgG antibodymediated damage to the CNS. In addition, they suggest autonomous intrathecal production of antibody. Consistently, the attempts to find single antigens relating to these antibodies have been unsuccessful. However, gene rearrangement and clonal expansion of lesional B cells have pointed toward specific antigens underlying these cellular responses. Myelin-specific antibodies are also found within the lesions. This finding is not universal and is still controversial. Some of the immunoglobulin in the CSF is also IgM and is usually directed at myelin lipid, rather than protein antigens. Some of these antibodies may also be localized to nonmyelin tissue such as the neurons and axons. Finally, gd T cells, known to kill oligodendrocytes in vitro and to a lesser degree NK cells, are also found within MS lesions and CSF. As discussed above, B cells and T cells interact with each other in the generation of pro-inflammatory molecules. However, this interaction is also responsible for the production of anti-inflammatory cytokines such as TNFa , and IL-10, and other active molecules which are also present in MS lesions.

Staging and Timing of Lesion Pathology

MS lesions fall into one of, or a variation of, active/acute, chronic-active and chronic-inactive/classical groups. In discussing, comparing, and defining any lesion, accurate or at least consistent staging becomes very important. The acuity of the lesion as described in different pathological staging schemes is often discordant with the assessment of the acuity of the clinical presentation. Active/acute lesions have traditionally been defined as showing demyelination with inflammatory infiltrates, whereas chronic lesions show demyelination and gliosis with little or no inflammation or myelin breakdown. The subacute or chronic-active lesion is one with a chronic core and active edge, or a plaque with a low level of inflammatory activity. The active edge of plaque may represent continual expansion of a lesion whose core has become inactive, or it could represent new activity around the edge of a preexisting plaque. Cellularity alone may be a misleading sign of acuity, as lymphocytes and macrophages and debris may remain in the tissue for prolonged periods. The contents of macrophages may help to assess the stage of myelin breakdown more accurately. Activated

early macrophages may stain positively for MRP14 and 27E10; reactivity for the minor myelin proteins MOG and MAG disappears within a week or two, but MBP and PLP are retained in macrophages for up to 3–4 weeks. To be fully relevant, future staging classifications should include other important elements, including axonal and cortical damage, the gliotic reaction, and remyelination, both in lesions and in the so-called NAWM.

The Morphology of MS Lesions

The immunopathological aspects of the MS lesions have been mainly covered in the immunology section.

The Chronic or Inactive (Classical) Plaque

This is the commonest type of MS lesion seen at autopsy in patients who die after a relatively protracted course. Grossly, the chronic plaque is seen as a firm grayishbrown, well-circumscribed lesion single or multiple. Common sites include the periventricular centrum semiovale and the corpus callosum (Figs. 90.1 and 90.2) and the cerebellum. Plaques are also found at the corticomedullary junction, in the cortex and other gray matter structures (see below). The spinal cord is often shrunken and gray white following involvement with primary demyelinated lesions as well as secondary (Wallerian) degeneration (Fig. 90.3). The upper cervical and thoracic cord is usually affected especially in the progressive stages of the disease, either primary or secondary. MRI studies of these areas are difficult but have confirmed the atrophy and have shown good clinical correlation with the progressive forms of the disease. Other sites of predilection include the optic nerves and chiasm and the brainstem (Fig.90.4). Besides the obvious plaques, there are diffuse alterations in neighboring white matter, including granularity and discoloration, the newly named "dirty-appearing white matter" DAWM (Fig. 90.1). MRI changes at postmortem have guided the pathologist to otherwise grossly normal regions, the normal-appearing white matter (NAWM) which histologically shows significant pathology. It is apparent that many lesions have been underrepresented in the past, emphasizing a need for the use of imaging in the pathological examination of MS cases. Generalized atrophy is often striking in the brains of MS patients, either focally or diffusely (Figs. 90.1 and 90.2), as manifested by enlargement of the ventricles and shrinkage of structures such as the corpus callosum and the deep white matter, as well as the cortex and, in severe cases, the deep gray matter. This mirrors changes seen on MRI. Histologically, the hallmark of the disease is loss of myelin (Fig. 90.5) with sharp borders between the demyelinated areas and the normal tissue. Within the plaque, there may be varying degrees of myelin preservation. Demyelination may be detected either with conventional stains such as Luxol fast blue, or with immunochemical stains against myelin components such as MBP (Fig. 90.6) and PLP. Often, axons appear to lose their sheaths as they enter the plaque. There may be almost no myelinated fibers present (Fig. 90.7), or axons with either thin or normal myelin sheaths may be present, representing remyelination and myelin preservation, respectively. At times, there is an extension of demyelination following the walls of blood vessels into the surrounding tissue, a feature known as a Dawson's finger. Oligodendrocyte loss, which may be extensive and near total at times, is usually most severe in the center of the lesion and may accompany the loss ofmyelin. In chronic plaques, there is almost invariably no evidence of ongoing oligodendrocyte necrosis or apoptosis. Around the periphery of the lesion, there is often a rim in which there is a greater density of oligodendrocytes, which may be associated with an increase in the number of thin sheaths representing remyelination.

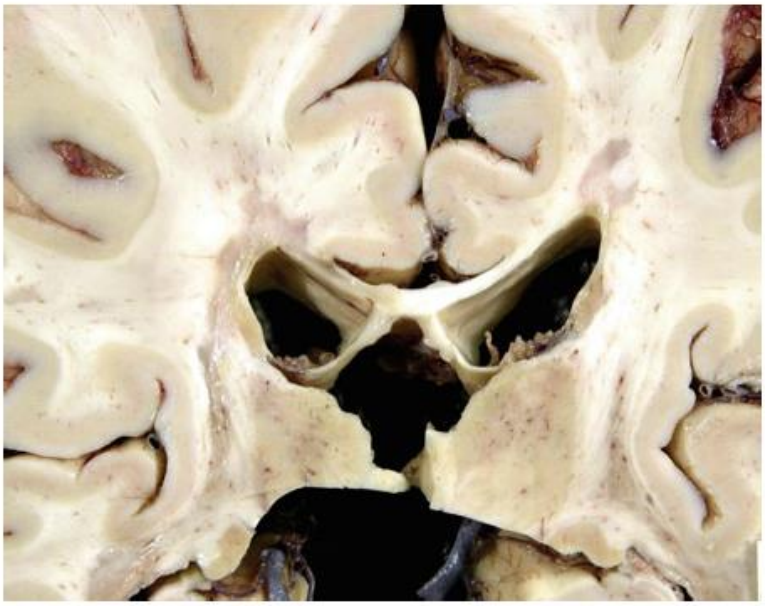

Fig. 90.1 Photograph of a brain with well-demarcated gray/pink MS plaques around the ventricles and extending into the white matter. Adjacent to the plaques, there are areas of less well-defined white matter changes, representing dirty-appearing white matter. Note the atrophy due to myelin and axon loss in the corpus callosum on the left and the ventricular dilatation

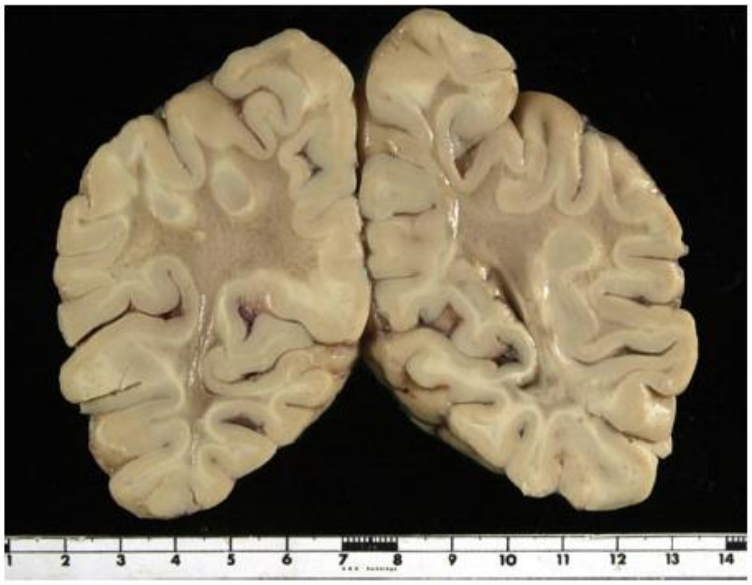

Fig. 90.2 The white matter in the occipital lobes of this brain is almost totally replaced with diffuse gray plaque

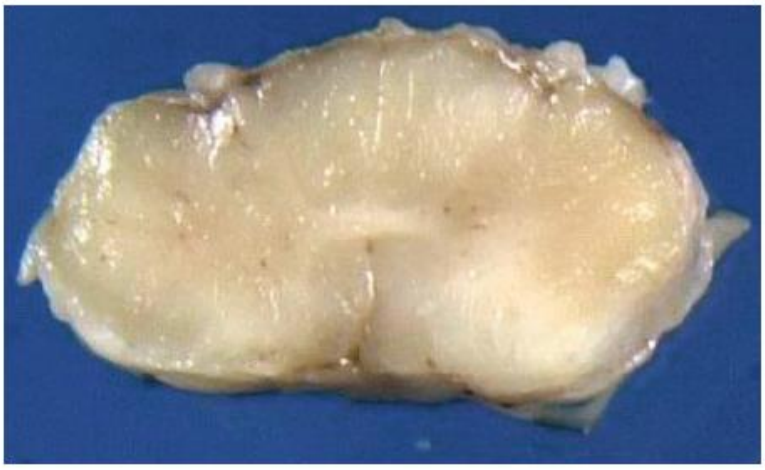

Fig. 90.3 The cervical cord is shrunken and atrophic and largely filled with gray plaque, leaving only the anterior section sector on the right intact

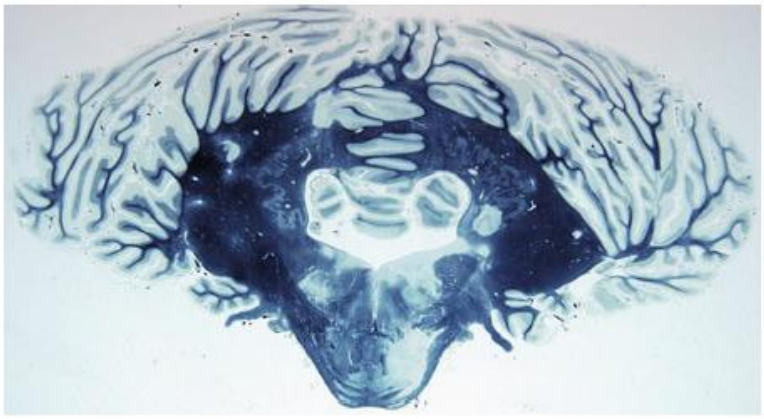

Fig. 90.4 This whole microscopic section of the cerebellum and pons is stained with a *blue* stain for myelin. The base of the pons on the *lower right* shows a large well-defined *white* area, indicative of a demyelinated plaque, and there are other small plaques scattered in the cerebellar white matter

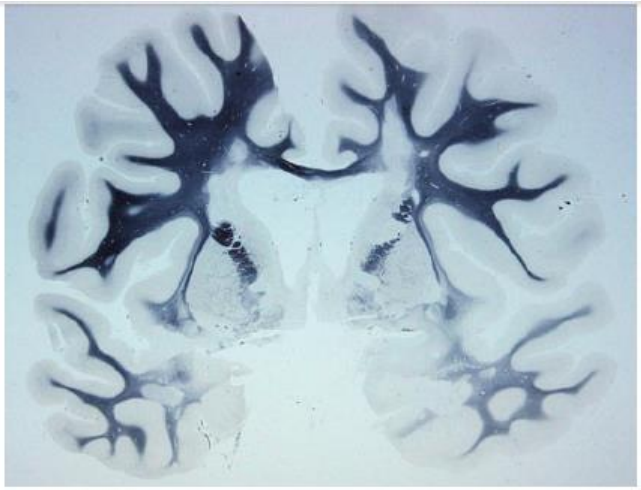

Fig. 90.5 This whole microscopic section of the forebrain, stained as in Fig. 90.5, shows typical plaque distribution around the upper angle of the ventricles. Surrounding the white plaques are regions of less well-stained myelin representing the DAWM

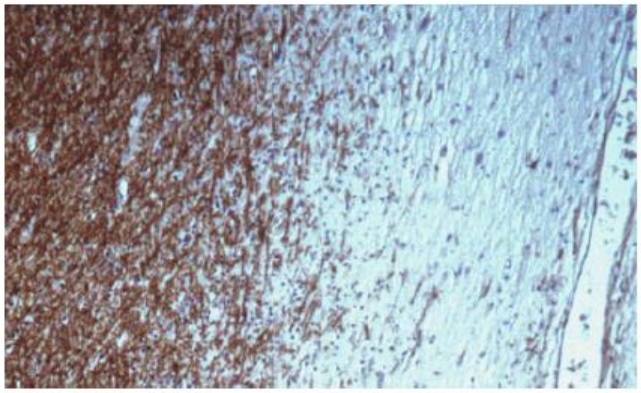

Fig. 90.6 Microphotograph of the edge of a plaque immune stained for myelin basic protein. On the left, the normal myelinated fibers stain *brown*, while on the right, the plaque contains very few fibers. At the rim, some fibers are myelinated

Imaging in MS

MRI permits detection of the focal inflammatory lesions in the white matter of patients with MS with exquisite sensitivity. Thus, it can aid in diagnosis, prognosis, and monitoring of the effectiveness of therapy. The ability to follow the dynamics of white matter lesion formation in vivo has greatly improved our understanding of the pathologic evolution of MS.

Visualizing the Pathology of MS In Vivo

MRI is very sensitive to the presence of focal lesions, the development of new lesions, and the presence of actively inflamed lesions in the white matter of patients with MS. Actively inflamed lesions can be identified because they are associated with increased permeability of the BBB and enhancement after injection of MRI contrast agents, usually gadolinium-based (Gd) chelates (Fig. 90.16). Serial MRI scans show that new white matter lesions develop with a frequency approximately ten times greater than clinical relapse (Fig. 90.17). This implies that the majority of lesions are "clinically silent." This dissociation of MRI lesions from clinical symptoms occurs for several reasons: MRI lesions vary in their destructiveness, most are small, and by chance, most are likely to affect regions of the brain that are not "eloquent" and do not produce symptoms that are immediately evident to the patient. In addition, the brain has the capacity to adapt to injury that is why clinically evident disability may accumulate only after substantial injury has occurred and the capacity to adapt is overwhelmed. Demyelinating lesions in MS can also affect cortical and deep gray matter structures. The cortical demyelinating lesions are much less inflammatory than the white

matter lesions and are usually not visible on conventional MRI scans. Specialized acquisition techniques such as double inversion recovery and phasesensitive inversion recovery increase the visibility of these lesions, but still fail to visualize the majority of them. Very high field strengths (7 T) may be able to provide the contrast and resolution necessary to see these lesions, and a variety of nonconventional acquisition methods such as magnetization transfer ratio imaging may be able to visualize them at more conventional field strengths, such as 3 T. The NAWM is affected by subtle, diffuse pathology that does not show up as "lesion." This be associated with tissue loss and atrophy that can be detected by quantitative image analysis, even at the earliest stages of MS. Nonconventional, quantitative MRI acquisition methods sensitive to a loss of integrity of myelin or axons or both, such as MRS, MTR, and DTI, can also demonstrate this pathology. Quantitative analysis of subtle structural changes that affect the volume of whole brain or specific structures, such as the thalamus, has revealed that diffuse tissue loss occurs early in MS and that the thalamus, a relay nucleus, is particularly affected. MTR imaging uses chemical and magnetization exchange at the molecular level to obtain an estimate of changes in macromolecular content, which is dominated by membrane bound macromolecules that are a marker of myelin content due to the large amount of redundant membranes in myelin. MTR images can be used to obtain semiquantitative estimates of changes in myelin content. This is particularly powerful during the demyelination and remyelination phases of acute lesion formation, when the changes are large and rapid. MRS measures signals from metabolites in the brain, rather than water, and can be used to assess neuroaxonal integrity in vivo due to the fact that one of these metabolites, N-acetylaspartate, is almost exclusively present in neurons and axons and is sensitive to change due to neuroaxonal loss or metabolic dysfunction (Fig. 90.18). DTI also seeks to measure axonal loss based on the fact that the water within axons is restricted in its lateral diffusion (diffusion anisotropy). This technique is less pathologically specific, as the pathological correlates of changes in diffusion anisotropy appear to include other sorts of pathology.

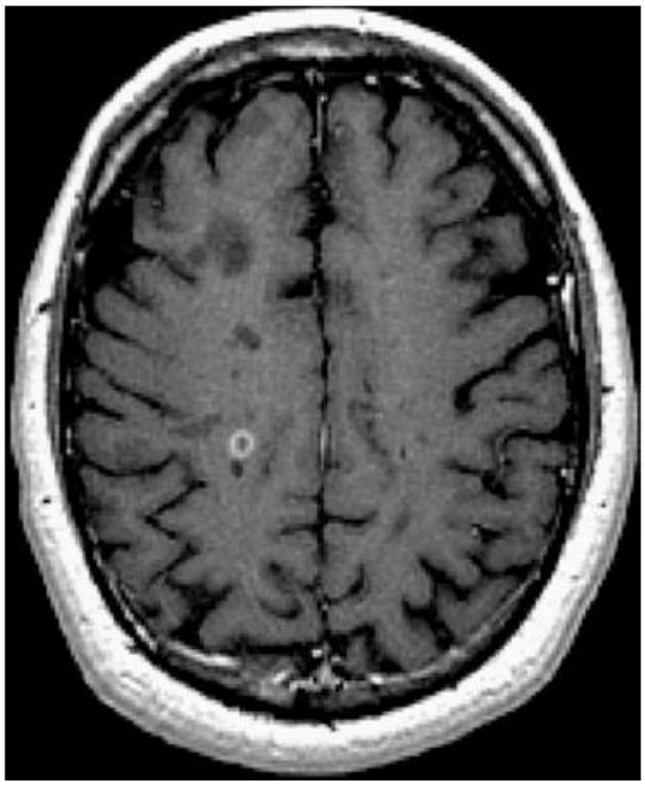

Fig. 90.16 T1-weighted MRI scan showing a *ring-shaped* gadolinium enhancement of one T1-weighted lesion, indicating that this lesion is associated with active inflammation and increased blood-brain barrier permeability. Other hypointense lesions in the slice do not enhance, as they are older and no longer associated with sufficient inflammation and increase in blood-brain barrier permeability

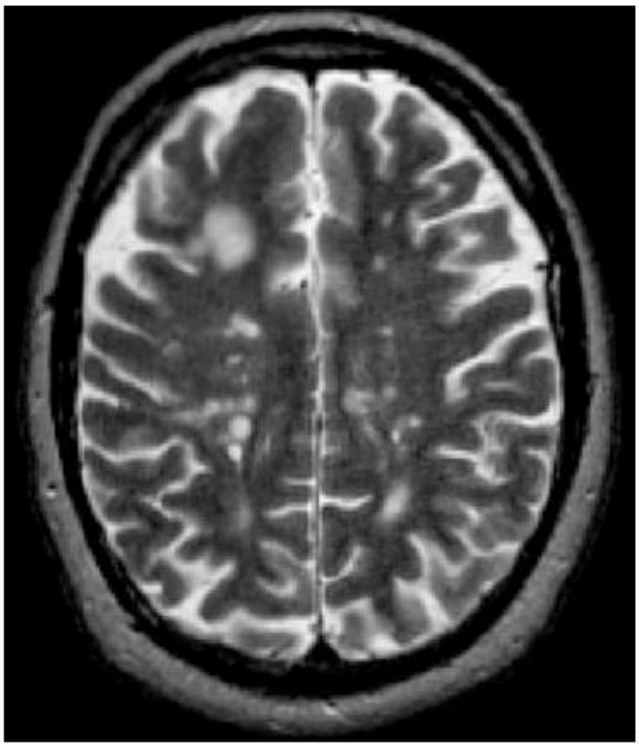

Fig. 90.17 T2-weighted MRI scan showing multiple hyperintense lesions. The T2 hyperintensity reflects increased free water in the lesions associated with either acute or chronic inflammatory injury to myelin and axons and the response to this injury, such as gliosis

Therapy of MS

In his lectures describing the features of MS, Charcot indicated that the time had not yet come to consider therapy for this entity. For the next hundred years, any therapeutic claims were based on treating relatively small group of individuals in a nonrandomized manner (see Therapeutic Claims in MS IFMSS). As potentially cytotoxic immune-suppressant therapies (cyclophosphamide) became available in the 1970s (just preceding the MR imaging era), concern about their toxicity resulted in a strategy in which mainly those with aggressive or advanced disease were treated. A well-controlled clinical trial indicated lack of efficacy of cyclophosphamide in late secondary progressive MS. Based on open-label trials in the 1980s, cyclophosphamide continues to be used as a salvage-type therapy for worsening MS unresponsive to approved therapies. A less toxic agent azathioprine was used for a range of MS patients with only small-scale clinical trial data available. Neither agent was patent protected nor put forward for formal approval for use in MS. Since the 1960s, there has been use of corticosteroids as a therapy to reduce severity of disease relapses and enhance rate of recovery. Initial controlled trials were conducted using ACTH. Subsequent relatively small controlled trials were conducted comparing different corticosteroid preparations, with or without nontreatment groups being included. A current consensus for therapy and one usually built in as the therapy for relapses occurring in clinical trials involves high-dose intravenous therapy (Solu-Medrol 1 g iv daily for 3–5 days) for relapses associated with disability. Whether such therapy has an impact on the eventual extent of recovery remains debated. The modern therapeutic era was initiated in the 1980s with fortuitous coming together of technology to produce recombinant molecules or synthesize new molecules, MR imaging, and progress in design of randomized blinded clinical trials. Since that time, a number of agents have received formal regulatory approval, while a large number of others are moving through the clinical trial process. This chapter describes the agents that have received FDA approval and selective agents from clinical trials that provide insight into the MS disease process.

Regulatory-Approved Agents

Interferon b and Glatiramer Acetate (GA)

Pivotal clinical trial of patients with relapsing-remitting MS led to confirmation of earlier uncontrolled trial results that two classes of agents, interferon b and glatiramer acetate, reduced disease activity as measured by relapse frequency, disability resulting from these relapses, and new MR-defined lesion formation. Each of these agents reduces clinical disease activity by 30–35% in patients with clinically definite MS and pretreatment activity of 1–2 relapses per year. Lack of efficacy with interferon b injections has been linked in some cases with development of neutralizing antibodies. There is extensive data on the mechanisms of actions of interferon b and glatiramer acetate. Both are considered to act as modulators of the immune response within the systemic compartment, with interferon having additional effects on inhibiting migration of lymphocytes across the blood-brain barrier including by inhibiting production of matrix metalloproteinases. Although neither agent is considered to effectively access the CNS, one needs to consider that there may be indirect effects mediated by the lymphocytes whose properties are modulated systemically and then access the CNS. GA is reported to favor anti-inflammatory and neurotrophic molecule production by lymphocytes. Subsequent clinical trials have indicated that both these agents may be more effective when given early in the disease course including prevention of second events when given to patients with CIS. The agents have insignificant effects in patients with progressive forms of MS although intercurrent relapses continue to be responsive. Long-term follow-up (now 20 years) have established the long-term safety of these agents resulting in their indefinite use in patients without any defined "stopping rules." Side effects relate mainly to need for continued subcutaneous or intramuscular injections and systemic "flu-like symptoms" (IFN) and allergic reactions (GA). Data remain suggestive that long-term disability and even survival may be favorably impacted, but such studies are complex to analyze due to selection bias related to who remains on therapy. A current consensus would favor that these therapies when given early are favorable for long-term outcome. As these agents became standard therapy in MS, subsequent therapeutic trials with the next generation of potential therapies were conducted on ever more selected populations including thosewith less active disease. This is reflected in the observation that the control groups in subsequentMS clinical trial have shown a continued decrease in disease activity. One cautions about comparing efficacy across clinical trials.

Natalizumab

This humanized monoclonal antibody delivered intravenously on a monthly basis recognizes the VLA-4 adhesion molecule, interrupting the interaction between lymphocytes and the barriers (endothelial, meningeal) that inhibit cells entry into the CNS. This agent proved more effective than interferon b in head-head clinical trials for relapsing forms of MS. The subsequent recognition that 1:1,000 treated individual would develop progressive multifocal leukoencephalopathy after 2 years of this therapy has resulted in this agent being a second-line choice for those whose disease is uncontrolled by IFN or GA or who cannot tolerate the latter agents. Data are not yet available on any effect of this agent in progressive MS. Other adhesion molecule-directed therapies are currently still in clinical trial stages.

Mitoxantrone

This agent received approval for worsening MS. The cumulative dose-producing cardiotoxicity of the agent limits duration of therapy. There is a lifetime risk of leukemia estimated at 1:500.

Fingolimod (FTY720)

Fingolimod is a sphingosine-1-phosphate (S1P) receptor agonist that acts by enhancing chemokine-directed ingress of lymphocytes bearing corresponding chemokine receptors, mainly CCR7 (naı¨ve and central memory T cells) into regional lymph nodes and inhibiting subsequent S1P-directed lymphocyte (T and B cells) egress from the lymph nodes. This results in peripheral lymphopenia including depletion of the putative disease-mediating population. This agent was approved as a therapy for relapsing forms of MS in 2010 based on

its positive effects both in placebo-controlled and comparator (interferon b 1a) trials. As S1P receptors are expressed on almost all tissues, regulatory guidelines recommend monitoring of effects of fingolimod therapy on heart rate, blood pressure, and pulmonary function. Fingolimod readily enters the CNS leading to ongoing investigations regarding its effects on regulating immune responses within the CNS and tissue protection and repair processes. Clinical trial data indicate that this therapy reduced the rate of tissue loss (MR determine brain volume changes) compared to interferon b 1a therapy. To be answered is whether such results reflect direct CNS effects or indirect effects reflecting overall reduction in CNS inflammation as suggested by observations with other agents (monoclonal antibodies – natalizumab, alemtuzumab, rituximab) that do not access the CNS. Clinical trials with fingolimod for progressive MS are ongoing. Published data from extension phases of clinical trials indicated sustained efficacy of fingolimod, but incidence of rare but serious toxicity cannot yet be determined.

Neurobiologic-Directed Therapies

As mentioned above, current immunotherapies do not impact on established secondary progressive disease. The frequency and severity of initial relapserelated injury has been linked to subsequent progressive disease development and course. Limited data yet exist on use of agents that could protect tissue from effects of initial injury per se or on subsequent disease course. Examples of such agents would be those directed at inhibiting actions of potential neurotoxic molecules such as glutamate. Demyelinated nerve features redistribution of specific ion channels as a means to maintain electrical conduction. A consequence would be altered intra- and extracellular exchange of ions resulting in excess inflow of calcium with potential deleterious effects. Ion channel blockers are studied in experimental models with only limited translation into the clinic. The potassium channel blocker 4-aminopyridine is currently approved for a therapy to promote sustained activity in MS. Additionally, one seeks means to overcome the heavy energy demand required for demyelinated nerve to maintain conduction. Further awaited for translation are agents that are shown in animal models to enhance the capacity of progenitor cells to mediate remyelination. Candidate agents identified in animal studies include neurotrophic factors and hormones such as prolactin and progesterone and agents that target specific receptors that promote or inhibiting progenitor cell differentiation (retinoic acid, anti-LINGO, and NOGO antibodies). Emerging data from the rehabilitation field is that there is greater than previously recognized plasticity of the adult human CNS and that sustained rehabilitation and physical and cognitive training can result in enhanced long-term function. Although there are many reports of benefit of short-term intervention weeks in improving function in MS patients, currently, there are no standardized protocols for long-term management.

Symptomatic Therapy in MS

Individuals with MS experience an array of symptoms that reflect the effects of disruption of normal function of the CNS. Many of these are also encountered in those with other neurologic disease that disrupts CNS pathways. Common problems are spasticity, reduced endurance/fatigue, pain, depression, and bladder/ bowel/sexual dysfunction. Discussion of the complex problem of managing MS patients and optimizing quality of life for the individual and her (his) family is beyond the scope of this chapter.

REFERENCES

1. Davidson's Principles & Practice of Medicine. 20th Edition, Churchill, Livingstone, Elsevier, 413-414, 2006.

2. Bar-Or A, Darlington PJ. The immunology of multiple sclerosis. In: Cohen J, Ruddick R (eds) (2011) Multiple sclerosis therapeutics, 4th edn. Cambridge University Press, New York.
3. Burrell AM, Handel AE, Ramagopalan SVF et al (2011) Epigenetic mechanisms in multiple sclerosis and the major histocompatibility complex (MHC). Discov Med 11:187
4. Compston AS, Confavreaux C, Lassmann H et al (eds) (2006) McAlpine's multiple sclerosis, 4th edn. Churchill Livingstone Elsevier, Philadelphia
5. Degenhardt A, Ramagopalan SV, Scalfari A et al (2009) Clinical prognostic factors in multiple sclerosis: a natural history review. Nat Rev Neurol 12:672–682
6. Koch-Henricksen N, Sorensen PS (2010) The changing demographic pattern of multiple sclerosis epidemiology. Lancet Neurol 9:520–532
7. Maneiro C, Bemmer T, Radding A et al (2009) In vivo imaging of cortical pathology in multiple sclerosis using ultra-high field MRI. Neurology 73:941–948
8. Miller DH (1994) Magnetic resonance in monitoring the treatment of multiple sclerosis. Ann Neurol 36(Suppl):S91–S94
9. Montalban X, Tintore M, Swanton J et al (2010) MRI criteria for MS in patients with clinically isolated syndromes. Neurology 74:427–434
10. Polman CH, Rheingold SC, Edan G et al (2005) Diagnostic criteria for multiple sclerosis. Ann Neurol 58:840–846
11. Raine CS, McFarland H, Hohfeld R (eds) (2008) Multiple sclerosis: a comprehensive text. Saunders Elsevier, New York/Philadelphia