White Matter Diseases

An Update for Neurologists

Massimo Filippi
Maria A. Rocca

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Massimo Filippi
Neurology Unit
IRCCS San Raffaele Scientific Institute
Milano, Italy

Neuroimaging Research Unit
IRCCS San Raffaele Scientific Institute
Milano, Italy

Neurophysiology Unit
IRCCS San Raffaele Scientific Institute
Milano, Italy

Vita-Salute San Raffaele University
Milano, Italy

Maria A. Rocca
Neuroimaging Research Unit
IRCCS San Raffaele Scientific Institute
Milano, Italy

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Introduction

Many neurological conditions affecting young individuals are characterized by the presence of lesions in the white matter (WM) of the central nervous system (CNS). These lesions also occur with aging. The diagnostic workup of neurological diseases characterized by the presence of WM lesions has changed dramatically over the past few years. This is mainly due, on the one hand, to the discovery of specific pathogenetic factors in some of these diseases (e.g., antibodies anti-aquaporin 4 channel in patients with neuromyelitis optica spectrum disorders), on the other, to the optimized use of diagnostic tools, including magnetic resonance imaging (MRI). In this perspective, the increased application of MRI-based technologies has resulted in an improved detection of WM lesions and in the identification of features which can be useful in the differential diagnosis of patients presenting with these abnormalities. Combined with the results of other paraclinical tools (e.g., blood and cerebrospinal fluid analysis), this has led to a significant modification of diagnostic approaches and algorithms in these conditions. Changes have also involved the therapeutic scenario of these WM diseases, where novel drugs have become available and new therapeutic targets for future trials have been identified.

The aim of this book is to provide an up-to-date description of the epidemiology, etiopathogenesis, clinical manifestations, diagnostic procedures, and treatment approaches of the main acquired WM disorders of the CNS in young adults, with a peculiar focus on multiple sclerosis (MS) and other conditions that can mimic MS for type of presentation, patterns of manifestations, and paraclinical findings. By integrating neurological, laboratory, and imaging concepts with the demands of accurate diagnosis, this reference book wishes to provide a state-of-the-art summary of current knowledge in these conditions as well as practical guidelines for their diagnosis and treatment.

The first two chapters of the book discuss MS in adult and pediatric patients. The diagnosis of MS has changed significantly during the past 15 years, following the formal inclusion of MRI findings into the diagnostic criteria of this condition. New pathogenetic mechanisms have been identified, which could become target of treatments. An updated classification of disease clinical course has been proposed. Probably most importantly, many treatments, with different mechanisms of action, have become available.

The third and fourth chapters are focused on neuromyelitis optica spectrum disorders and anti-myelin oligodendrocyte glycoprotein disease, two recently

recognized antibody-mediated conditions for which ad hoc diagnostic criteria have been proposed. Clinical, laboratory, and MRI findings that can guide in the recognition of these diseases are presented. Currently applied treatment strategies are also debated.

Acute disseminated encephalomyelitis, a usually monophasic and self-limiting condition, mostly affecting children, is the subject of the fifth chapter.

The subsequent two chapters examine primary and secondary vasculitides of the CNS, an extremely complex group of neurological conditions in which the CNS can be the primary or secondary target organ. Given that the clinical manifestations of these conditions are often nonspecific and extremely heterogeneous, their diagnosis is challenging. The workup of these diseases relies on the integration of laboratory tests, neuroimaging studies, and tissue biopsies in order to achieve a prompt and accurate diagnosis and start treatment.

The last chapter considers migraine, an extremely frequent condition in which the improved understanding of disease pathophysiology has led to the development of novel migraine-specific and mechanism-based treatments.

Our hope is that this volume is appreciated as a comprehensive source of information and also provides an educational framework for trainees and a reference for practicing neurologists and radiologists seeking direct and authoritative answers to questions. We hope that readers will find this issue of practical relevance and a stimulus to more in-depth reading and investigation in this field.

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1.1 Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS) [1]. It typically affects young adults with an onset between 20 and 40 years of age, although up to 10% of patients experience a disease clinical onset during childhood or adolescence (see Chap. 2). This disorder is typically considered a multifactorial immune-mediated disease caused by a complex interaction among several genetic and environmental factors.

Pathologically, MS is characterized by the accumulation of focal demyelinating lesions affecting both the white matter (WM) and the gray matter (GM) of the brain and the spinal cord, together with inflammation, demyelination, oligodendrocyte loss, reactive gliosis, and neuro-axonal degeneration. These pathological processes determine heterogeneous clinical manifestations, course, and disability progression over time. In the majority of patients, reversible episodes of neurological deficits, usually lasting days or weeks, distinguish the initial phases of the disease [2], whereas a minority of patients (~10–15%) have a progressive course from onset. Over time, the development and progression of irreversible clinical deficits become prominent and affect profoundly MS patients' daily activity and quality of life.

The diagnosis of MS is based on clinical findings and paraclinical tools, requires the exclusion of alternative diagnoses [3] and is based on the demonstration of a pathological process affecting at least two different CNS regions (dissemination in space [DIS]) occurring at different times (dissemination in time [DIT]) [4]. Although the diagnosis can be made on the basis of clinical criteria alone, magnetic resonance imaging (MRI) can support, supplement, or even replace some clinical criteria, allowing an earlier diagnosis of MS, owing to its sensitivity and specificity in demonstrating demyelinating lesions, as well as DIS and DIT. Due to its high sensitivity in revealing disease-related abnormalities, MRI has significantly improved the management of MS patients not only during their diagnostic workup, but also for monitoring the disease course and treatment response, and influencing treatment decisions.

In this chapter, recent knowledge on the epidemiology and etiopathogenesis of MS are summarized. The clinical manifestations of the disease and current diagnostic procedures are also discussed. Finally, current and future treatment approaches are described.

1.2 Epidemiology

MS is the most common chronic inflammatory, demyelinating and neurodegenerative disease of the CNS affecting young adults; it is associated with a high societal economic burden, which has increased over time [5]. Typically, the mean age of onset ranges from 20 to 40 years. Disease onset is rare prior to 10 years, even though up to 10% of MS patients experience their first attack during childhood (<18 years

of age) [6] (see Chap. 2), and 4–10% after 60 years of age [7]. Conversely, MS typically starts later, generally from the fifth decade of age, in patients who experience a progressive course from onset.

Approximately ~2.3 million people have MS worldwide [5]; however, the incidence and prevalence of MS are highly variable, with both genetic and geographical factors playing a role.

The importance of the environment is demonstrated by the peculiar geographic distribution of the disease, with a trend towards a higher prevalence with increasing latitudes [5, 8]. In particular, the highest prevalence is found in northern Europe and North America (typically ~1 case per 1000 individuals but up to 1 case per 400 individuals in some countries with higher latitudes), medium prevalence is reported in southern Europe and southern United States of America (USA) (5–30 per 100,000), while Asia, Africa, and South America have a very low burden of disease (<5 per 100,000) [8]. These geographical variations can in part be attributed to genetic predisposition, given the clearly higher risk in individuals of Western European ancestry. The distribution of the *HLA-DRB1* haplotype might account in part for the latitudinal gradient. Nonetheless, several studies showed that the risk of MS correlates with the country of residence during childhood and that migration from high-risk to low-risk areas in early life leads to a decreased susceptibility, thus highlighting the role of acquired, environmental factors (see below).

Of note, the overall prevalence of MS has increased since the 1950s [5, 8], and this is more evident in women. This finding might be due to improved access to medical facilities, better diagnostic accuracy, and increased life expectancy owing to improved management. However, this cannot explain changes in female preponderance. Of note, although a diffuse gender difference with females being more frequently affected than males has been consistently demonstrated, the female-to-male ratio has increased from 2:1 in the 1950s up to ~3:1 in the 2010s [8, 9]. This might suggest the role of environmental risk factors mainly affecting women (e.g., occupation, increased cigarette smoking, obesity, birth control, and later childbirth) as contributors to such an increase of female MS preponderance [8, 9].

1.3 Etiopathogenesis

Although the causes of MS are still unknown, this disease is likely to be multifactorial, as a result from an interplay between genetic susceptibility and environmental risk factors.

1.3.1 Genetic Susceptibility

Several genetic factors may play a role in MS susceptibility and disease evolution. Pivotal epidemiological studies showed the presence of familial aggregation in MS patients, thus suggesting the role of genetic risk factors. Relatives of people with MS are more likely to develop the disease than the general population, with higher

risk in closer relatedness. The prevalence of familial MS is ~13% for all MS phenotypes [10]. The risk of recurrence within families increases with percentage of genetic sharing [11], ranging from 35% in monozygotic twins to 3% in siblings and first-degree relatives [11]. However, the heritability of MS is polygenic and involves polymorphisms in several genes, each of which contributes with a small increase in disease risk. The first genetic factor found is located in the human leukocyte antigen (HLA) class I region on chromosome 6p21.3 [11, 12]. The HLA cluster encompasses more than 200 genes within 4.5 megabases, with important roles in several immunological processes [11, 12]. Specifically, the strongest association pointed to the so-called "*HLA-DR15* haplotype," including *HLA DRB1*1501* and *DQB1*0602* that are almost invariantly found together in individuals of European ancestry and convey the highest risk for MS [11, 12].

Thanks to the advance in genotyping technologies, which allowed obtaining whole genome information on thousands of individuals, the knowledge of MS genetic architecture has significantly improved in the last few years. Genome-wide association studies have identified over 200 genetic risk variants for MS. Each variant has a small effect on the risk of disease, and different combinations of these variants likely contribute to genetic susceptibility in different patients [13]. Most of these polymorphisms encode molecules involved in the immune system (such as polymorphisms in *IL2R* and *IL7R*) and are associated with a higher risk for other systemic dysimmune disorders. Others are involved in different biological processes, such as vitamin-D metabolism, suggesting that environmental risk factors are likely to interact with MS susceptibility genes [12].

1.3.2 Environmental Risk Factors

Several environmental factors have been shown to increase the risk to develop MS [12], including infective agents, a lack of sun exposure, low vitamin-D levels, feeding habits, and smoking. Some of these risk factors (e.g., obesity) have been suggested to be particularly relevant during childhood and adolescence (see Chap. 2). Their identification might contribute not only to better understand the pathological substrates of the disease, but also to implement future strategies to prevent the onset and limit the progression of the disease, since some of them are modifiable [14].

Due to the immune-mediated pathogenesis of MS, it has been hypothesized that some kind of infections might trigger disease onset. Many pathogens have been proposed to play a role in MS, Epstein–Barr Virus (EBV) being the most consistently and robustly associated [12, 15]. An EBV infection in adolescence or early adulthood, and a history of infectious mononucleosis have been associated with an increased MS risk. A molecular mimicry between EBV and myelin antigens is likely to represent the pathological mechanism.

Sun exposure, and mainly exposure to ultraviolet B radiation, is the major determinant of vitamin-D levels, which tend to decrease with increasing latitudes and thus could contribute to the "latitude effect" found in MS. The active form of vitamin D, 1,25-dihydroxycholecalciferol, has a wide range of effects on the human

organism: the best known is that on calcium homeostasis, but recently a role in immunomodulation has been shown, with a reduction of inflammatory activity [12, 16, 17]. Low vitamin-D intake or serum vitamin-D status are associated with increased risk of developing MS and in MS patients normal vitamin-D levels are correlated with lower disease clinical and MRI activity, suggesting a beneficial effect throughout the course of the disease [12, 17].

Smoking has been consistently demonstrated as a risk factor for MS [12]. The risk of MS is positively correlated with the amount of smoking, both active and passive [12]. Smoking is also associated with an increased risk of early and more severe disability progression and to a faster conversion to secondary progressive (SP) MS [12, 18]. Possible mechanisms for this association include a chronic inflammatory activity in the lung, with a higher activation of the immune system, but also a direct toxic effect of some smoke components on several cells, including neurons and oligodendrocytes.

Recently, several pieces of evidence have also suggested that the gut microbiota, the combination of bacteria that colonize the human intestine, might modulate the activity of innate and adaptive immunity, thus contributing to disease pathogenesis [19].

1.3.3 Pathology

The pathological hallmark of MS is the formation of focal plaques, characterized by areas of demyelination. Such lesions are typically located around post-capillary venules and in the acute phase are associated with the breakdown of the blood–brain barrier (BBB). This promotes the migration of activated innate (e.g., macrophages) and adaptive (T and B cells) immune cells into the CNS, thus causing inflammation and demyelination, which are followed by oligodendrocyte loss, reactive gliosis, and neuro-axonal degeneration [20].

MS plaques occur both in the WM and GM and are typically disseminated throughout the CNS, including the brain, optic nerves, and spinal cord [21–23]. Lesions are frequently active in early phases of the disease, whereas their activity is lower in the later course. These lesions are heavily infiltrated by lymphocytes (mainly $CD8^+$ T cells and $CD20^+$ B cells), activated microglia and macrophages containing myelin debris, and large reactive, sometimes multinucleated, astrocytes [24, 25].

Progressive MS patients are mainly characterized by inactive lesions, which are sharply circumscribed, with reduced axonal and cellular densities, a well-defined limit of demyelination, reactive gliosis, and a variable degree of activated microglia only in the periplaque WM [24–28]. However, inflammation is still present in progressive MS patients. Some of the preexisting plaques, defined as “chronic active” or mixed inactive/active, account for up to 57% of all lesions in patients with progressive MS [29]. These lesions are characterized by iron-laden microglia/macrophages at their edge (diminishing towards their inactive center) [24, 29, 30], a smoldering inflammation promoting a slow rate of ongoing demyelination and axonal transection and a slow, but progressive, expansion in size [31].

Also the WM not affected by focal demyelinating plaques is often characterized by a mild degree of demyelination, macrophage and lymphocyte infiltration, activated microglia, and neurodegenerative phenomena, including astrocyte gliosis and axonal damage and loss [21, 27]. These abnormalities occur from the earliest phases of the disease and seem to occur at least partially independently of the accumulation of focal lesions [21].

GM involvement is also diffuse in MS, occurring from the earliest phases of the disease and being more severe in progressive MS patients [32, 33]. GM demyelinating lesions occur in cortices of the forebrain and cerebellum, in the deep GM nuclei and spinal cord [21, 23, 34–37]. Compared to WM, GM lesions typically have less BBB breakdown and lower inflammatory infiltrates [38]. However, they are also characterized by variable degrees of transected neurites, apoptotic neurons, neuroaxonal and glial loss together with a significant synaptic loss [38–41].

Cortical lesions are predominantly found in cortical sulci and in deep invaginations of the brain surface, frequently affect the most superficial portion of the cortex (the so-called subpial demyelination) [42] and are associated with inflammatory infiltrates in the meninges [43–46] and pro-inflammatory profiles in the cerebrospinal fluid (CSF) [47], suggesting a "surface-in" process, possibly mediated by one or more toxic soluble factors released by meninges or present in the CSF.

A variable degree of neurodegenerative phenomena involving neurons, axons, and glial cells have been also demonstrated in normal-appearing and demyelinated CNS tissues. These substrates are particularly relevant because they can contribute to irreversible clinical disability and disease progression [27]. Different mechanisms, which may occur at different stages of the disease, might drive neurodegeneration as a primary and/or secondary phenomenon [26, 27, 48, 49]. These pathological processes include acute or chronic oxidative stress promoted by active inflammation, mitochondrial dysfunction and iron accumulation, loss of myelin trophic support, hypoxia, altered glutamate homeostasis, and a pro-inflammatory environment, with possible cytotoxic factors and complement activation [26, 27, 48, 50, 51].

Reparative processes have been also described in MS. For instance, remyelination may occur in MS [52–54] and could be a target for future treatments [55]. Such a phenomenon gives rise to the so-called "shadow" plaques, which are characterized by global or patchy remyelination, a sharp demarcation from the surrounding WM, and axons showing thin myelin sheaths and shortened internodes [52, 53, 56, 57]. The extent of remyelination is heterogeneous, is more frequent in GM than in WM lesions and depends on several factors, including patients' age, disease duration, lesion location, the presence of oligodendrocyte progenitors, and the integrity of axonal function [50]. While a significant remyelination is frequently encountered during the earlier phases of MS and in younger subjects, it is more sparse or absent in progressive MS [58].

1.3.4 Immunopathophysiology

The knowledge of the immunopathophysiology of MS has shown a significant evolution during the last years [30]. Although the initial antigenic targets and

mechanisms that trigger the immune response are still unknown, historically, the aberrant activation of effector T cells (CD4+ and CD8+) has been considered the key factor of MS inflammatory disease activity [30]. T-cell activation, possibly promoted by a molecular mimicry with antigens of infectious agents, is then sustained by an imbalance in immune regulatory activity and by a progressive T-cell activation to additional CNS antigens triggered as a consequence of CNS injury ("epitope spreading"), which may contribute to the propagation of chronic immune responses [30].

Although typically considered a "T cell-mediated" disease, recent evidence clearly suggests that MS inflammatory activity includes relevant bi-directional interactions between innate immunity (including myeloid cells) and adaptive immunity (T and B cells), as well as resident CNS cells, such as microglia and astrocytes [30, 59].

In particular, recent pieces of evidence coming from the results of selective B-cell targeting treatments have clearly changed the immunopathophysiology framework of MS [30, 59]. While the original hypothesis for B-cell role in MS was based on the abnormal production of antibodies, it is now clear that other antibody-independent functions are relevant [30, 59]. These include an increased production of pro-inflammatory cytokines, a deficient ability to produce regulatory cytokines, and B-cell contribution as antigen-presenting cells for T lymphocytes [30, 59].

The interplay between peripheral immune cells and CNS-resident cells may promote the setting of a pro-inflammatory environment, with the secretion of a wide range of pro-inflammatory mediators that can increase BBB permeability, thus further promoting the recruitment and activation of inflammatory cells into the CNS and leading to demyelination and neuro-axonal damage [30, 59].

Another conceptual change has been the growing demonstration that different types of inflammatory processes can occur in MS. Beside peripheral inflammatory mechanisms, the role of CNS-compartmentalized inflammation—localized within the CNS or in the meninges—has been suggested to contribute to CNS injury, although it is likely to be poorly targeted by currently available treatments [50, 60, 61].

1.4 Clinical Manifestations

1.4.1 Clinical Features

The clinical manifestations of MS are heterogeneous, with no clinical finding being pathognomonic of MS, and depend on the topography of focal and diffuse CNS damage.

Typically, MS onset is characterized in ~85% of patients by a first acute episode of neurological dysfunction (defined as clinically isolated syndrome—CIS) that can affect the optic nerve, the spinal cord, the brainstem, the cerebellum, or the cerebral hemispheres [62, 63]. This reversible episode of neurological deficits lasts at least 24 h, reaching a peak of severity within 2–3 weeks, and is followed

by spontaneous remission with variable degrees of recovery after a few weeks. During disease course, further episodes, known as relapses [64–66], may occur, developing at irregular intervals, being followed by spontaneous remission with partial or complete recovery; they characterize the relapsing-remitting (RR) form of the disease (see below).

Optic neuritis is the first neurological episode in ~25% of patients with MS and can occur in up to 70% of MS patients along their disease course [67–69]. Optic nerve involvement is characterized by a partial or total visual loss in one eye with a central scotoma and dyschromatopsia. Visual disturbances are often associated with orbit pain that worsens with eye movements [67–69]. If inflammation involves the optic disc, the optic nerve head may show inflammation (papillitis) and disc edema. Optic nerve involvement may be also subclinical and can be demonstrated by afferent pupillary defect or abnormalities at paraclinical tests (visual evoked potentials [VEPs], optical coherence tomography [OCT], or MRI).

Somatosensory symptoms represent the clinical onset of up to 43% of MS patients, typically due to brainstem or spinal cord involvement [70]. These include paresthesias (numbness, tingling and/or pins-and-needles tightness, coldness, or swelling of the limbs or trunk), Lhermitte's sign (a transient electric sensation running through the back and into the limbs promoted by neck flexion), impairment of vibration and joint position sensation, and reduced pain and light touch perception. A transient worsening of these symptoms can occur with increased temperature (Uhthoff phenomenon).

Motor manifestations are the first symptoms in 30–40% of patients, affect the majority of MS patients during disease course and occur due to brainstem, spinal cord, or hemispheric involvement [71]. These include pyramidal signs (Babinski sign, brisk reflexes, clonus, etc.), spasticity, and paresis.

Impairment in ocular movements (such as nystagmus, oscillopsia, and diplopia), ataxia and gait imbalance, dysmetria, complex-movement decomposition, slurred speech, and dysphagia are typical manifestations due to brainstem and cerebellar involvement and can affect up to 70% of MS patients [71].

Sphincter and sexual dysfunctions are also common, especially in progressive MS and in patients with motor disability [72]. They include bladder dysfunction such as urinary urgency, hesitancy, frequency and urge incontinence [72]. Constipation is more common than fecal incontinence, while men with MS often suffer from erectile dysfunction and impotence.

Up to 40–70% of patients with MS have cognitive impairment, starting in the earliest phases of the disease and being more pronounced in progressive MS [73]. Cognitive deficits include impairment in information processing speed, episodic memory, attention, and executive function [73].

Fatigue is another characteristic symptom experienced in up to 75–95% of MS patients. This manifestation can be associated with recent disease activity; however, it can persist after the attack has subsided and can be independent of relapses or the severity of clinical disability.

Affective disturbances occur in up to two-thirds of patients, of which depression is the most common manifestation [74].

Finally, pain is reported in up to 43% of MS patients and includes trigeminal neuralgia, dysesthetic pain, back pain, visceral pain, and painful tonic spasms [75].

1.4.2 Clinical Phenotypes

In 1996, the US National Multiple Sclerosis Society Advisory Committee on Clinical Trials in MS [76] defined four MS clinical courses: RRMS, SPMS, primary progressive (PP) MS, and progressive relapsing (PR) MS (Fig. 1.1a). RRMS is the most common type (approximately 85% of MS patients) and is characterized by the occurrence of relapses [64–66], followed by spontaneous remission with variable degrees of recovery. In a significant proportion of RRMS patients, increasing with age and disease duration, the course of MS converts to SPMS, characterized by a progression of irreversible disability occurring independently of relapses [76]. Conversion to SPMS occurs at a rate of ~2–3% of patients per year [77]. About 10–15% of patients present a PP clinical phenotype, characterized by an insidious disease progression from the onset, resulting in gradual, progressive, and unremitting accumulation of neurological deficits for more than 1 year, without preceding relapses and remissions [76, 78]. Finally, PR was an additional rare clinical course distinguished by progressive disease from the onset, with acute relapses, with or without full recovery, and periods of continuing progression between relapses [76].

An update of the definitions of these MS clinical phenotypes was proposed in 2013, with the introduction of relevant changes (Fig. 1.1a, b) [2]. CIS has been included in the spectrum of MS phenotypes to denote those patients with a first clinical presentation of the disease with characteristics of inflammatory demyelination that could be MS, but do not yet fulfill DIT criteria [2]. Moreover, for each MS subtype, a classification of the disease as "active" or "not active" has been added, defined by clinical assessment of relapse occurrence or lesion activity detected by MRI. Another important modification has been the inclusion for the progressive stages of whether disability has progressed over a given time period, thus identifying progressive patients with or without disability progression [2].

1.5 Diagnostic Procedures

1.5.1 MRI

MRI has a high sensitivity in detecting macroscopic abnormalities in the brain and spinal cord of MS patients. Specific features have been described to identify typical MS lesions [79], which are defined as areas of focal hyperintensity on a T2-weighted (T2, T2-FLAIR, or similar) or a proton density (PD)-weighted sequence (Fig. 1.2). Typical MS lesions are round to ovoid in shape and range from a few millimeters to more than one or two centimeters in diameter. While lesions can occur in any CNS region, MS lesions tend to affect specific WM regions, such as the periventricular and

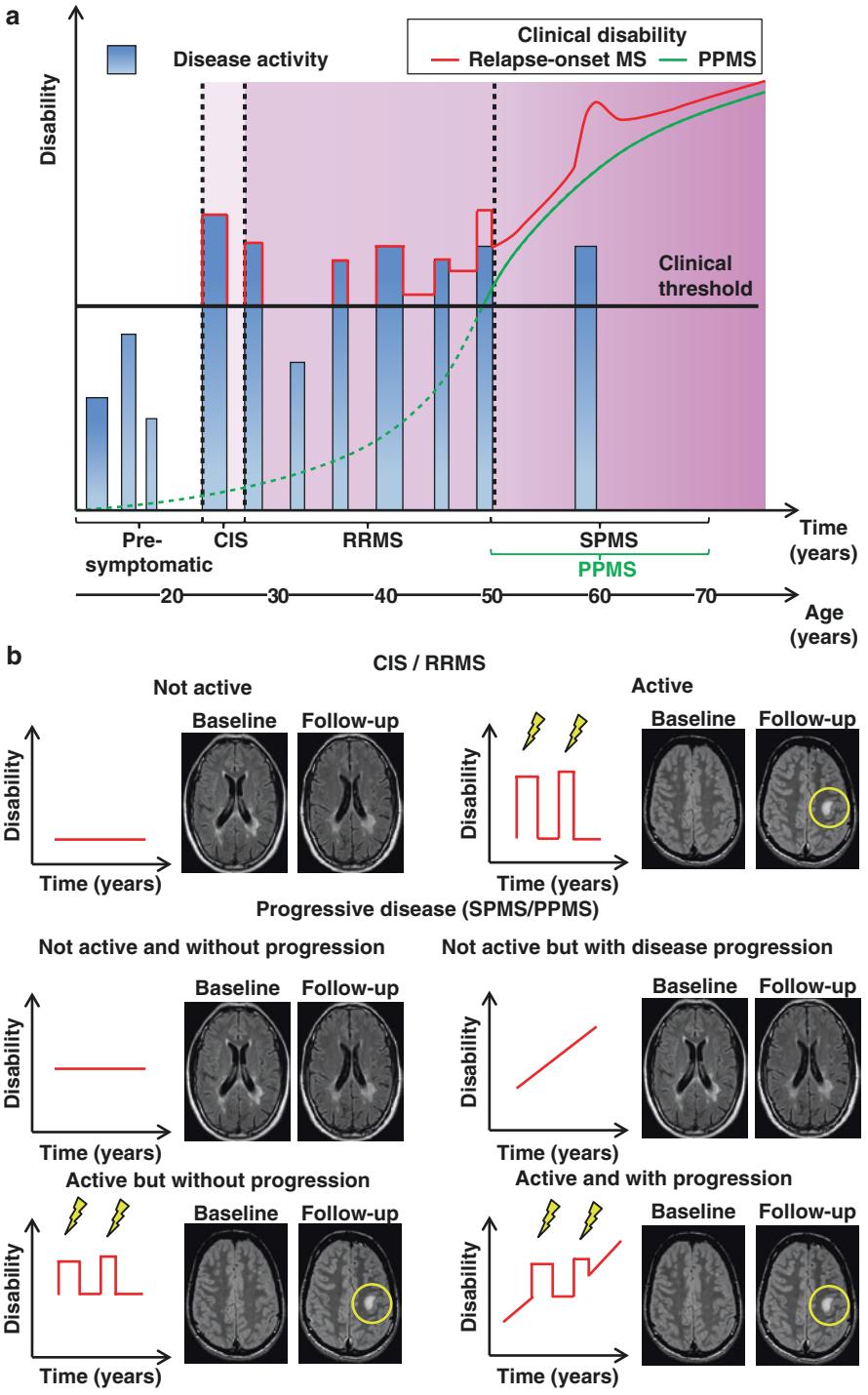

Fig. 1.1 (**a**) Clinical courses of MS and (**b**) new definitions included in the 2013 revision [2] of the MS clinical course

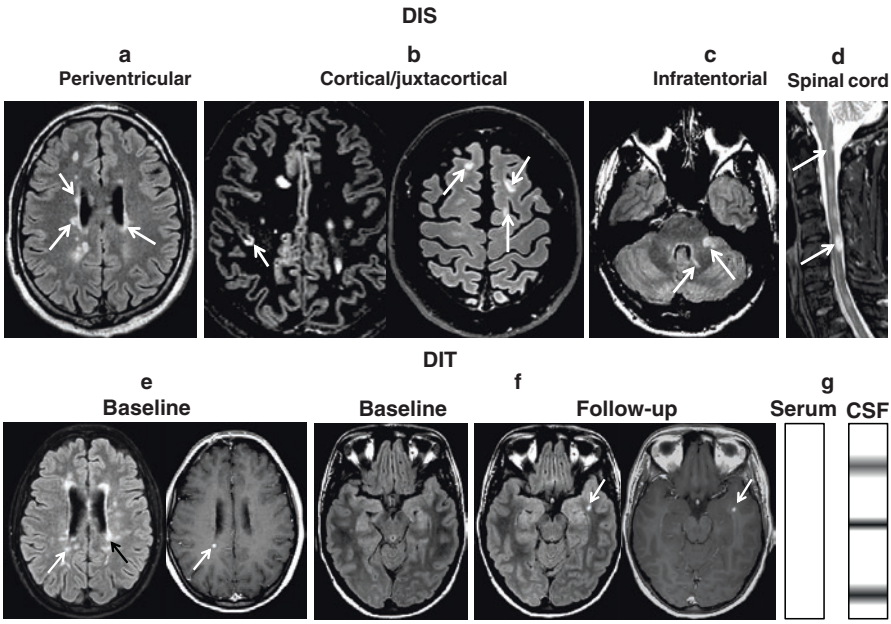

Fig. 1.2 Typical multiple sclerosis lesions and the 2017 McDonald Criteria for demonstration of dissemination of space (DIS) and time (DIT) in patients with a clinically isolated syndrome suggestive of MS [4]. Typical MRI examples (arrows) of (**a**) periventricular, (**b**) cortical/juxtacortical, (**c**) infratentorial, and (**d**) spinal cord MS lesions. DIS can be demonstrated by ≥1 T2-hyperintense lesions in ≥2 of 4 typical areas of the central nervous system. DIT can be demonstrated by (**e**) a simultaneous presence of gadolinium (Gd)-enhancing (white arrows) and non-enhancing (black arrow) lesions at any time; (**f**) a new T2-hyperintense and/or Gd-enhancing lesion on follow-up MRI (arrows), with reference to a baseline scan, irrespective of the timing of the baseline MRI; or (**g**) the presence of cerebrospinal fluid (CSF)-specific oligoclonal bands (OCBs). For the definition of both DIS and DIT, the distinction between symptomatic and asymptomatic lesions has been removed in the 2017 revision of the McDonald criteria

juxtacortical WM, the corpus callosum, infratentorial areas (especially the pons and the cerebellum), and the spinal cord (preferentially the cervical segment) (Fig. 1.2).

The administration of gadolinium-based contrast agents and the acquisition of post-contrast T1-weighted images allow to distinguish active from inactive lesions. Signal enhancement, which underlies active lesions, occurs due to increased BBB permeability and corresponds to areas with ongoing inflammation. Lesions that persistently appear hypointense on post-contrast T1-weighted images (so-called black-holes) are associated with more severe tissue damage, suggestive of demyelination and axonal loss, compared with lesions that do not appear dark on such images. In the diagnostic criteria for MS, MRI is used to confirm DIS or DIT for RRMS, and it has been included in the criteria for a diagnosis of PPMS (see below) [4]. Recommendations aimed at optimizing and standardizing the use of MRI in clinical practice have been given [80, 81].