Chapter 1
The Spectrum of Demyelinating Inflammatory Diseases of the Central Nervous System

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Abstract Multiple sclerosis (MS) is, by far, the most common inflammatory demyelinating disease of the central nervous system (CNS), but it is not the only CNS inflammatory demyelinating disease and there is a broad spectrum of disorders with varied clinical course, imaging features, epidemiological characteristics, regional distribution of pathological abnormalities, and pathology. Other syndromes associated to MS are clinically isolated syndromes and radiologically isolated syndromes. MS variants included active MS (Marburg type), Schilder's disease, and Baló lesions. Neuromyelitis optica spectrum, idiopathic acute transverse myelitis, acute disseminated encephalomyelitis, chronic inflammatory myelopathy, and chronic relapsing inflammatory optic neuritis must be distinguished from MS.

Keywords Multiple sclerosis • Clinically isolated syndromes • Radiologically isolated syndromes • Neuromyelitis optica • Baló concentric sclerosis • Schilder's disease • Transverse myelitis • Chronic relapsing inflammatory optic neuritis • Marburg disease

Introduction

Multiple sclerosis (MS) is, by far, the most common inflammatory demyelinating disease of the central nervous system (CNS) affecting probably more than two million people worldwide [1]. However, MS is not the only CNS inflammatory demyelinating disease, and there is a broad spectrum of disorders with varied clinical course, imaging features, epidemiological characteristics, regional distribution of pathological abnormalities, and pathology.

Table 1.1 presents a classification of these disorders based on lesion location and clinical course.

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Table 1.1 Classification of inflammatory (not infectious) demyelinating diseases

Name	Lesion distribution	Typical course	Comment
Multiple sclerosis (MS) spectrum			
Clinically isolated syndromes (CIS) of the type seen in MS without dissemination in time			
Optic neuritis	Optic nerve	Monophasic, recovery is usual, with or without sequelae	Idiopathic, presumably autoimmune
			Absence of dissemination in time. Limited dissemination in space possible
Acute partial myelitis	Spinal cord	Monophasic, recovery is usual, with or without sequelae	Idiopathic, presumably autoimmune
			Absence of dissemination in time. Limited dissemination in space possible
Other CIS	Brainstem, cerebellum, brain hemispheres, uni- or multifocal	Monophasic, recovery is usual, with or without sequelae	Idiopathic, presumably autoimmune
			Absence of dissemination in time. Limited dissemination in space possible
Progressive syndrome mimicking primary progressive MS			
Chronic progressive inflammatory myelopathy	Spinal cord	Chronic, progressive	Inflammatory CSF usual and lesions of the inflammatory type on cord MRI. No dissemination in space outside the cord
Multiple sclerosis			
McDonald MS (or "active CIS")	Clinically CIS (optic neuritis, partial acute myelitis, brainstem, or others) but multifocal lesions (dissemination in space)	One episode and imaging evidence of dissemination in time	Clinical presentation indistinguishable from idiopathic CIS
			Usually evolves toward RRMS
Relapsing-remitting MS	Multifocal, disseminated	Relapsing-remitting	According to clinical (relapses) and imaging activity, it could be classified as active RRMS or inactive RRMS
			Frequently evolves toward SPMS

(continued)

Table 1.1 (continued)

Name	Lesion distribution	Typical course	Comment
Secondary progressive MS	Multifocal, disseminated	Progressive accumulation of disability after initial relapsing course	According to clinical (relapses) and imaging activity, it could be classified as active SPMS or inactive SPMS and with or without progression
Primary progressive MS	Multifocal, disseminated	Progressive accumulation of disability from onset	According to clinical (relapses) and imaging activity, it could be classified as active PPMS or inactive PPMS and with or without progression
Other syndromes associated with MS			
Radiologically isolated syndromes	Multifocal, disseminated	Clinically silent	Imaging abnormalities typical of MS
Marburg variant Schilder's disease	Multifocal, disseminated, extensive lesions	Rapidly evolving course. Fatal.	Very rare
Neuromyelitis optica (NMO) spectrum			
NMO (Devic's disease)	Mainly optic nerve and spinal cord (LETM), possible brainstem and diencephalon involvement	Relapsing (very rare secondary progression has been described)	Positive anti-aquaporin-4 antibodies in the majority of cases
Seropositive isolated LETM or optic neuritis	Cord (LETM) or optic nerve	One episode. High risk of evolution toward relapsing NMO	Positive anti-aquaporin-4 antibodies required
Unusual high-risk syndromes	Brain, infra- or supratentorial	One episode. High risk of evolution toward relapsing NMO	Positive anti-aquaporin-4 antibodies required
Recurrent syndromes	Recurrent myelitis (usually LETM) or optic neuritis	Several episodes in the same location. High risk of evolution toward relapsing NMO	Positive anti-aquaporin-4 antibodies required
Other inflammatory demyelinating diseases			
Isolated monophasic syndromes with clinical presentation usually not mimicking MS			
Acute disseminated encephalomyelitis	Brain, cord, multifocal, disseminated	Monophasic (rarely multiphasic and rare relapsing forms reported), recovery is usual, with or without sequelae	Frequently postinfectious; frequent in children; frequent gray matter involvement

(continued)

Table 1.1 (continued)

Name	Lesion distribution	Typical course	Comment
Acute hemorrhagic leukoencephalomyelitis (Hurst type)	Brain, cord, multifocal, disseminated, occasionally focal	Monophasic, hyperacute, frequently fatal	Extremely rare
Idiopathic transverse myelitis	Spinal cord (usually longitudinally extensive transverse myelitis (LETM))	Monophasic	Severe course. Negative anti-aquoporin-4 serology required
Other relapsing inflammatory diseases not mimicking MS			
Chronic relapsing inflammatory optic neuritis (CRION)	Optic nerve	Recurrent	Negative anti-aquoporin-4 serology required. Response to steroids and relapse on withdrawal or dose reduction

Multiple Sclerosis Spectrum

In many countries, MS is the most frequent disabling neurological condition that affects young adults [2]. About 5 % of MS patients are diagnosed before the age of 18 [3]. Its prevalence varies according to geographical location, with a relative north-south gradient in the north hemisphere, and ranges from 40 to 300 cases per 100,000 inhabitants [2, 4]. In nearly 85 % of patients, the disease initially follows a relapsing-remitting (RR) course and is called RRMS [5]. The remainder 15 % of cases has primary progressive MS (PPMS), which is characterized by a gradually progressive clinical course from the onset [5, 6]. In many cases, patients with RRMS experience after several years a gradual worsening after an initial relapsing disease course, with or without acute exacerbations, and are diagnosed as having secondary progressive MS (SPMS) [5, 7, 8]. A consensual classification of these clinical phenotypes has been established [9] and has been recently updated [10] (Table 1.2).

Relapsing-Onset MS

RRMS typically begins in the second or third decade of life and has a female predominance [2, 4, 5]. Some evidence has shown that the proportion of women in newly diagnosed RRMS patients increased in the last 20 years reaching more than 70 % in recent studies [11, 12]. RRMS is characterized by acute neurological episodes typically evolving over a period of several days, stabilizing, and then often improving, spontaneously or in response to corticosteroids, within weeks [13, 14].

Table 1.2 Clinical phenotypes of MS [9, 10]

1996 MS clinical subtypes [9]		2014 MS phenotypes [10]	
Relapsing disease			
RRMS	With full recovery from relapses	CIS	Not active[a]
			Active[a,b]
	With sequelae/residual deficits after incomplete recovery	RRMS	Not active[a]
			Active[a]
Progressive disease			
Progressive disease	Progressive accumulation of disability from onset with or without temporary plateaus, minor remissions and improvements (PPMS)	Progressive accumulation of disability from onset (PP)	Active[a] and with progression[c]
			Active[a] and without progression[c]
			Not active and with progression[c]
			Not active[a] and without progression[c] (stable disease)
	Progressive accumulation of disability after initial relapsing course with or without occasional relapses and minor remissions (SPMS)	Progressive accumulation of disability after initial relapsing course (SP)	Active[a] and with progression[c]
			Active[a] and without progression[c]
	Progressive accumulation of disability from onset but clear acute clinical attacks with or without full recovery		Not active[a] and with progression[c]
			Not active[a] and without progression[c] (stable disease)

[a]Activity determined by clinical relapses and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually)
[b]CIS active: CIS, if subsequently clinically active and fulfilling current multiple sclerosis (MS) diagnostic criteria, becomes relapsing-remitting MS (RRMS)
[c]Progression measured by clinical evaluation, assessed at least annually. If assessments are not available, activity and progression are "indeterminate"

The usual mode of presentation of RRMS is with a first episode of focal neurologic symptoms which is called a clinically isolated syndrome (CIS) in the absence of previous documented symptoms [13, 14]. A CIS is therefore defined as an acute or subacute episode of neurological dysfunction due to inflammatory demyelination that lasts more than 24 h and occurs in the absence of fever, infection, or encephalopathy [14]. The later criterion is useful to distinguish CIS from acute disseminated encephalomyelitis (ADEM) [15], but encephalopathic signs rarely occur in CIS [14]. A CIS is clinically indistinguishable from relapses that are typically associated with RRMS, except that they are isolated in time clinically (first known episode) [13]. While CIS is closely related to MS, a significant proportion of patients presenting with a CIS typical for MS have a monophasic illness without clinical and imaging dissemination in time even with long-term follow-up, and the diagnosis remains CIS or "isolated idiopathic demyelinating event" [13]. These syndromes account for approximately one third of patients with CIS although the number varies depending on the phenotype, the highest proportion having been observed in patients with optic neuritis (ON) [13]. ON, partial myelitis, and brainstem

syndromes are the most common type of CIS and also of MS relapses [13, 14]. However, cerebellar, hemispheric, and multifocal episodes are possible. In large cohort studies, the proportion of patients with a progressive course among relapsing-onset MS patients is variable from 30 to 60 % [5, 7, 8, 16, 17], the proportion being higher in studies with a longer follow-up. In the British Columbia cohort, about 75 % of patients with more than 30 years of disease duration were classified as having SPMS [7]. Relapses could occur during the secondary progressive phase but their frequency is usually low. SPMS is usually characterized by progressive motor pyramidal or cerebellar impairment leading to a severe disability [5, 7, 8].

Progressive-Onset MS

Contrary to RRMS, there is no female predominance in PPMS (ratio about 1/1) [6, 18]. Usually PPMS begins in the fourth decade and is characterized in more than 80 % of cases by a progressive paraparesis due to spinal pyramidal involvement [8]. Bladder dysfunction is usual. In other cases, progressive hemiparesis or cerebellar dysfunction could occur. Very rare pure optic or cognitive forms of PPMS have been described [8].

Other Signs and Symptoms

Patients with MS frequently experience signs and symptoms that are not usually due to a relapse or the progressive stage, like fatigue, chronic pain, and urogenital dysfunction [19–21]. Psychiatric and cognitive impairment could also frequently occur and will be addressed in other chapters of this book.

Diagnostic Criteria

The diagnostic criteria of MS have been a matter of debates since many years. Various sets of criteria have been proposed on the basis of the principles of dissemination in space and time established by Schumacher [22]. Three versions of the more recent criteria, the so-called McDonald criteria, named after Pr William Ian McDonald, have been published [23–25]. Table 1.3 summarizes the current criteria published in 2011 [25].

These criteria are based on clinical and imaging evidence, the latter being obtained by magnetic resonance imaging (MRI) of the brain and the spinal cord. In relapsing-onset MS, the main challenge is to differentiate RRMS from CIS without dissemination in time as discussed above (Table 1.1). In PPMS, the main differential diagnoses are other causes of progressive myelopathy, in particular hereditary

Table 1.3 Multiple sclerosis diagnostic criteria [25]

Clinical presentation	Clinical evidence	Information needed for MS diagnosis
At least two attacks[a]	Objective clinical evidence of at least 2 lesions	None
		In these cases, MRI is not required for time dissemination but is necessary for differential diagnosis
At least two attacks[a]	Objective clinical evidence of 1 lesion and reasonable[b] historical evidence of a prior attack without other explanation	None
		In these cases, MRI is not required for time dissemination but is necessary for differential diagnosis
At least two attacks[a]	Objective clinical evidence of 1 lesion	Dissemination in space demonstrated by MRI[c]
One attack[a]	Objective clinical evidence of at least 2 lesions	Dissemination in time demonstrated by MRI[c]
One attack[a]	Objective clinical evidence of 1 lesion	Dissemination in space and time demonstrated by MRI[c]
Insidious neurological progression suggestive of MS (PPMS)	One year of disease progression (retrospectively or prospectively determined)	2 of 3 of the following criteria:
		1. Dissemination in space demonstrated by brain MRI[d]
		2. Dissemination in space demonstrated by spinal cord MRI (at least two lesions)
		3. Positive CSF[e]

MS multiple sclerosis, *MRI* magnetic resonance imaging, *PPMS* primary progressive multiple sclerosis, *CSF* cerebrospinal fluid

Notes

[a]Criteria have been proposed for patients presenting with a typical clinically isolated syndrome, including optic neuritis, myelitis, and brainstem syndromes with duration of at least 24 h, in the absence of fever or infection

[b]Some historical events with symptoms and evolution characteristic for MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event, but clinical diagnosis based on objective clinical findings for 2 attacks is most secure

[c]Dissemination in space on MRI requires at least one T2 lesion in at least 2 of 4 MS-typical regions of the central nervous system (periventricular, juxtacortical, infratentorial, or spinal cord), but symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes; dissemination in time demonstrated by MRI requires simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time or a new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, irrespective of its timing with reference to a baseline scan

[d]Dissemination in space demonstrated by brain MRI for PPMS requires at least one T2 lesion in the MS-characteristic (periventricular, juxtacortical, or infratentorial) regions, but symptomatic lesions are excluded from consideration in subjects with brainstem syndromes

[e]Positive CSF means isoelectric focusing evidence of oligoclonal bands and/or elevated immunoglobulin G index

spastic paraplegia and, in rare instances, chronic progressive inflammatory myelopathies which are clinically similar to PPMS and associated with evidence of inflammation on cerebrospinal fluid examination or MRI but without clinical or imaging evidence of dissemination in space [6].

Other Syndromes Associated with MS

The concept of radiological isolated syndromes (RIS) has emerged recently [26, 27]. Patients with subclinical lesions discovered on brain or cord MRI that fulfill the criteria for inflammatory demyelinating lesions suggestive of MS but with the primary reason for the acquired MRI resulting from an evaluation of a condition other than MS could be diagnosed as RIS. It is important to differentiate the lesions from nonspecific white matter hyperintense abnormalities associated with small-vessel pathology (microangiopathy), which are very frequent in patients with high blood pressure and migraine for instance. About 34 % of patients diagnosed with RIS developed neurological clinical signs suggestive of a CIS or, rarely, of PPMS, within a 5-year period from the first brain MRI study [27].

Several variants of MS have been described, including acute MS (Marburg type), Baló concentric sclerosis, and Schilder's disease (diffuse sclerosis). These conditions are very rare, and there are still nosological debates about them. Marburg MS is characterized by rapid progression of a severe demyelinating disease leading usually to death within a short period of time (a few months or a few years) and associated with destructive lesions, sometimes very similar to those found in other MS cases, but sometimes with very extensive widespread areas of demyelination [28]. These latter cases are similar to what have been described as Schilder's disease [29], a rare variant of MS predominating in children and characterized by focal neurological abnormalities, which are atypical for MS, in conjunction with tumor-like white matter lesions on MRI [29]. Peripheral demyelination could be present in acute MS. Baló concentric sclerosis lesions are characterized by alternated rims of demyelination and myelin preservation [30]. The first described cases were observed at autopsy on brain of patients who died from acute or subacute diseases, but concentric lesions have been observed on MRI of patients with typical MS. It is considered nowadays that about 50 % of Baló cases seen on MRI have typical MS lesions, and typical relapses may occur [30]. The typical syndrome is characteristic of intracerebral mass lesions including headache, cognitive impairment, seizures, aphasia, and hemiparesis [30].

Neuromyelitis Optica (NMO) Spectrum

The term neuromyelitis optica was coined by Devic and Gault in 1894 and refers to the co-occurrence of ON and myelitis [31]. NMO was regarded for many years as a clinical variant of MS and has only recently been individualized, when a highly

specific antibody has been discovered [32]. NMO is a rare disease. Its prevalence is estimated to range from less than 1 to 4.4/100.000 [33]. The age at onset is usually during the fourth decade, but onset during childhood or after 60 is possible [34, 35]. Typically, NMO is characterized by episodes of severe ON, frequently bilaterally at the same time or during subsequent relapses, and severe longitudinal extensive transverse myelitis (LETM), leading to severe disability in a few years (blindness and tetraplegia) in the absence of treatment [31, 33–35]. Since the demonstration of the presence of anti-aquaporin-4 antibodies (AQP4 IgG) in the majority of cases of NMO and the absence of this antibody in MS, the diagnostic criteria of NMO has evolved. According to the 2006 criteria, a definite diagnosis can be made when ON, myelitis, and at least two of three supportive criteria (MRI evidence of a contiguous spinal cord lesion in ≥3 segments, brain MRI not diagnostic of multiple sclerosis, and AQP4-IgG seropositivity) are present [36]. The description of new syndromes associated with AQP4 IgG positivity has led to the concept of NMO spectrum disorder (NMOSD) [37]. New diagnostic criteria for NMOSD have been proposed and presented in 2014 at the American Academy of Neurology [38] which include six different core characteristics: ON, acute myelitis, area postrema syndrome (nausea, vomiting, and hiccups), other brainstem syndromes, symptomatic narcolepsy or acute diencephalic syndrome with MRI findings, and symptomatic cerebral syndrome with MRI findings. AQP4 IgG-positive patients need to show at least one of these core characteristics, with no other better explanation for their symptoms. AQP4 IgG-negative patients need to show at least two of the core characteristics, meeting the following requirements: at least one of the core symptoms must be ON, myelitis, or area postrema syndrome; the core characteristics must be disseminated in space and the MRI findings must distinguish NMOSD from MS or other demyelinating disorders.

Patients presenting with a syndrome typical of NMO, such as LETM or severe bilateral ON, and with positive AQP4 IgG but without dissemination in space and time are considered as having a high-risk syndrome [39]. Relapses could occur in patients with high-risk syndromes (recurrent severe ON, recurrent LETM). An immune-mediated optic neuropathy considered distinct from NMO and MS characterized by a recurrent or chronic unilateral or bilateral vision loss has been described under the acronym CRION (chronic relapsing inflammatory optic neuritis) [40]. Steroid responsiveness with a risk of a relapse on withdrawal of steroids is considered as a key diagnostic criterion [40].

Clinical and spinal cord imaging characteristics of patients presenting with LETM associated with NMO and patients presenting an isolated episode of LETM are similar. They are usually characterized by a severe clinical dysfunction attributable to the spinal cord with usually bilateral sensory, motor, and bladder dysfunction, reaching maximal deficit between 4 h and 21 days, with evidence of inflammation on CSF or MRI [39]. Other causes of LETM are idiopathic transverse myelitis and secondary transverse myelitis (caused by infections or associated with a connective tissue disease like systemic lupus erythematosus or Sjögren's syndrome). Acute idiopathic transverse myelitis is characterized by a typical transverse myelitis (LETM) seronegative for AQP4 IgG and without evidence of other cause of myelopathy (vascular, postradiation, MS, connective tissue disease, and NMO) [41].

Acute Disseminated Encephalomyelitis (ADEM)

ADEM is defined as a monophasic ("acute"), multifocal (dissemination of space of the lesions), inflammatory demyelinating disease [15]. ADEM is frequently secondary to infectious events or vaccinations. The absence of dissemination in time is one the main differences with MS, but the clinical characteristics (encephalitic presentation) and the MRI features could help to distinguish the two entities [15, 42, 43]. Indeed, in most cases, ADEM is monophasic, but in some patients, relapses may occur immediately after the onset of the disease. If these relapses are considered to represent part of the same acute immune process, with similar symptoms to those at onset (encephalopathic episodes), the term multiphasic disseminated encephalomyelitis (MDEM) can be used [42, 43]. However, in about 30 % of cases, a typical first episode of ADEM could subsequently evolve to typical MS, with a clear demonstration of dissemination in space and time [43]. In these cases, the relapses are clinically similar to those seen in typical MS and different from the inaugural episode. ADEM is more frequent in children but could be a mode of onset of pediatric MS [42, 44]. On a pathological point of view, ADEM can be distinguished from MS by the presence of sparse demyelination restricted to narrow perivenous sleeves widespread throughout the nervous system, giving rise to large and diffuse or multifocal lesions in MRI [45]. These features differentiate ADEM from MS where inflammation is associated with focal confluent plaques of primary demyelination showing variable degrees of axonal injury and loss. Diagnostic criteria have been proposed to distinguish ADEM from MS in adults and children [42, 43]. In adults, "ADEM corresponds to patients with at least 2 of the following 3 criteria: (1) Clinical atypical symptoms of MS. One or more of the following: consciousness alteration, hypersomnia, seizures, cognitive impairment, hemiplegia, tetraplegia, aphasia, or bilateral optic neuritis; (2) absence of oligoclonal bands in the cerebrospinal fluid; (3) MRI: Grey matter involvement (basal ganglia or cortical lesions)" [43]. Diagnostic criteria for pediatric ADEM have been recently updated [42] in which all the following items are required: "(1) a first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause; (2) encephalopathy that cannot be explained by fever; (3) no new clinical and MRI findings emerge 3 months or more after the onset; (4) brain MRI is abnormal during the acute (3-month) phase; (5) typically on brain MRI: diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter; T1 hypointense lesions in the white matter are rare; deep grey matter lesions (e.g. thalamus or basal ganglia) can be present."

A rare severe variant has been described by Hurst with perivascular hemorrhages and severe brain edema (acute hemorrhagic leukoencephalitis) [46].

Other Inflammatory Disorders of the CNS

Some other inflammatory diseases of the CNS exist and have to be taken into account for the differential diagnosis of MS including infectious diseases, paraneoplastic disorders, and other autoimmune encephalitis. The latter will be detailed in

Chap. 6 of this book. A new syndrome has been recently described with chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) [47]. It is characterized by episodic brainstem symptoms, characteristic punctuate and curvilinear gadolinium-enhancing lesions peppering the brainstem (mainly in the pons) on MRI, responsiveness to steroids, and T-lymphocytic infiltrate with perivascular predominance in brain biopsies.

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