

Chapter

1

Introduction: historical perspective of pediatric multiple sclerosis and related disorders

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Why this book? Why now? We know multiple sclerosis (MS) with onset in childhood is not a newly described disease entity [1], but was in fact reported shortly after it was described in adults [2], and that was well over a century ago (Table 1.1, Figure 1.1). However, it has only been since the early 1990s that major advances in the care of adults with MS have occurred, specifically the ability to diagnosis early in the disease course (using more proficient magnetic resonance imaging (MRI) techniques), and the advent of disease-modifying therapies (DMT) [3–9]. Still, children with MS have received little attention and pediatric MS remains a challenging disease to diagnose and treat (see clinical vignettes). While MS in children is uncommon, there is an increased sense of responsibility to effectively recognize, diagnose, and treat children and adolescents with MS. This chapter briefly summarizes the history of pediatric MS and related diseases, and current clinical and research directions.

Brief history of MS origin

It has been suggested that the first reference to MS probably dates back to the age of the Vikings, with a description of a female with intermittent visual and speech disturbances [10]. Much later, in the nineteenth century, a description of MS was found in the writings of Frederick d'Este (1794–1848) [11]. At about the same time, MS pathologic findings, based on macroscopic observations of the central nervous system, were described in the respective textbooks by Cruveilhier (1793–1873) in France and Carlswell (1793–1857) in England [12,13]. The first clinical description of MS – with pathological confirmation – was proposed in 1849 by Frerichs in Goettingen [14]. Additionally, in 1868, the French neurologist Charcot characterized the disease based on its pathological

hallmark, the plaque, which led to the name “sclérose en plaque disséminée”, later to be named multiple sclerosis [2] (Figure 1.1).

Pediatric MS

Initial reports

Perhaps the first documented case of pediatric MS dates back to the fourteenth century. Lidvina v. Schiedham (1380–1433), a 15-year-old Dutch girl, fell while skating shortly after recovering from an acute illness (presumably from balance and weakness problems; perhaps her first demyelinating episode). She developed recurrent headaches, left-sided visual loss, and left arm paresis. She became a nun and, history tells us, she died at age 53 having experienced recurrent and progressive disease over a 37-year period [15]. It was not until five centuries later, in 1883, that the French neurologist Pierre Marie (Charcot's student) reported the first 13 cases of pediatric MS [1] (Figure 1.1). In 1902, Schupfer, from the Institute of Neurology at Rome, summarized 58 pediatric cases published in the medical literature and added one of his own [16]. In this paper, published in German, he used the pathological criteria of focal sclerosis and disseminated sclerosis to define MS. He critically reviewed each of the 58 reported cases using these criteria, and confirmed the diagnosis in only 3. It appeared that the diagnosis of pediatric MS was inaccurate in most of these cases, since the diagnoses were based solely on clinical grounds with little or no pathological confirmation. One of these cases, Eichhorst's [17], is remarkable since both the mother and her 8-year-old son were affected. They both developed a similar pediatric-onset illness characterized by recurrent weakness and ataxia, in the context of a more complex phenotype including optic nerve involvement

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Table 1.1 Literature milestones of the history of demyelinating diseases in childhood

Inflammatory		Year	Metabolic	
Lucas	"uncommon symptoms succeeding the measles". May be initial reported case of acute disseminated encephalomyelitis (ADEM)	1790		
Marie	"Sclérose en plaques"	1883		
Devic	Neuromyelitis Optica (NMO) (1 adult patient)	1894		
			1885	Pelizaeus "Multiple sclerosis" (Pelizaeus–Merzbacher disease)
Müller	Monograph of 139 pediatric MS cases 1887–1902	1904		
Marburg	Acute MS (3 adult patients)	1906		
			1910	Merzbacher "Aplasia axialis extracorticalis congenita" (Pelizaeus–Merzbacher disease)
Schilder	3 publications on "encephalitis periaxialis diffusa" (diffuse sclerosis)	1912–1924		
			1916	Krabbe "Diffuse cerebral sclerosis" (Globoid cell leukodystrophy)
			1925	Scholz "Diffuse cerebral sclerosis" (Metachromatic leukodystrophy)
Balo	Concentric sclerosis (adult patients)	1928		
Low/Carter	MS in children	1956		
Duquette	125 (2.7%) out of 4632 MS patients with onset before 16 years	1987		
Krupp <i>et al.</i>	First operational definitions of pediatric MS and related disorders proposed by the International Pediatric MS Study Group	2007		

and dementia. The child died within one year, at 9 years of age and the mother at 41 years of age. The diagnosis of pediatric MS was reportedly confirmed by pathology in both cases. The original autopsy report of the mother, issued from the Institute of Neuro-pathology in Zurich (pm: 401/1896) is presented in

Figure 1.2. A posteriori, the final diagnosis remains questionable. The short disease duration (at least in the boy), the clinical severity and complexity of the phenotype, its mode of inheritance, and the pathological observations, are atypical for MS according to current criteria [18].

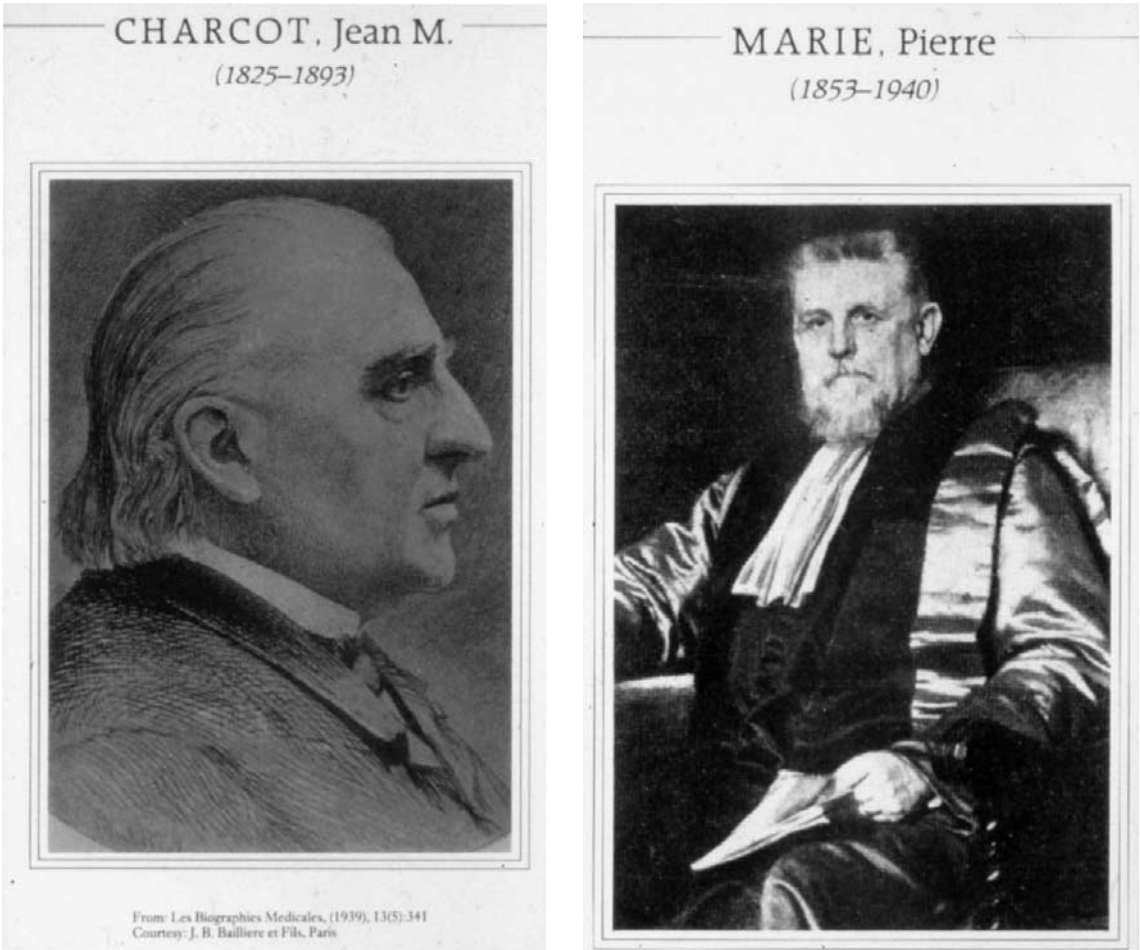


Figure 1.1 Representation of Jean-Martin Charcot and Pierre Marie, two French neurologists of the nineteenth century, who initially characterized multiple sclerosis in adults and children.

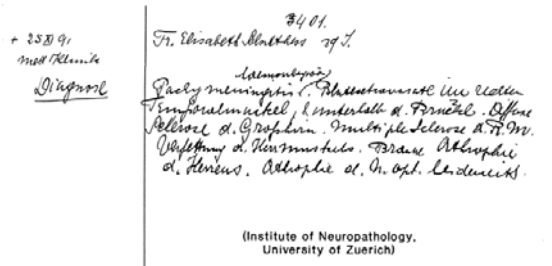


Figure 1.2 Autopsy report of the mother in the case of Eichhorst [17] Translation and interpretation from German by F. Hanefeld: The macroscopic evaluation showed “diffuse sclerosis” of the cerebrum, multiple sclerosis of the spinal cord, bilateral optic atrophy. However on microscopic examination no abnormalities in the cerebrum were discovered, while the spinal cord showed “multiple sclerosis”.

In fact, by the end of the nineteenth century, significant confusion existed concerning the diagnosis of MS in children. Various neurological diseases such as thalamic tumors [19], Leigh’s disease [20], or heterotopias [21] were misdiagnosed as MS. Marie also observed that MS in children might be related to acute infectious diseases, syphilis or trauma, suggesting that at that time, there was already some overlap with infectious or post-infectious central nervous system (CNS) diseases such as acute disseminated encephalomyelitis (ADEM).

Confusion between pediatric MS and leukodystrophies
In the early 1900s, pediatric inherited demyelinating disorders of metabolic origin (leukodystrophies)

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began to be described. This led to even more confusion about the nature of demyelinating diseases, given the clinical and pathological overlap with MS. It was believed that some previously reported cases of MS in children may have, in fact, been leukodystrophies. In particular, both “multiple” and “diffuse sclerosis” were pathological terms used to describe inflammatory as well as metabolic demyelination. For example, the first case of Pelizaeus–Merzbacher disease was reported as MS [22], and the initial cases of Krabbe’s disease and metachromatic leukodystrophy were described as “diffuse sclerosis” [23,24].

Additional confusion resulted from the publications of three pediatric cases by Schilder (between 1912 and 1924) that he termed “diffuse sclerosis” or “encephalitis periaxialis diffusa.” One case was fulminant pediatric MS, another was adrenoleukodystrophy and the third case was subacute sclerosing panencephalitis [25–27]. Despite the confusion, the term “Schilder’s disease” continued to be used until the 1960s, in particular for describing adrenoleukodystrophy [28]. The reclassification of diffuse sclerosis to a metabolic rather than inflammatory etiology may even have caused some to question whether there was such a disease entity as pediatric MS, until resurgence of interest (and recognition) in the late 1950s [18].

Confusion between pediatric MS and ADEM initial events

ADEM is classically described as a monophasic illness (see Section 4), and one that predominantly occurs in childhood, as opposed to MS, a relapsing and remitting disease, which predominantly occurs in young adults. The first clinical description of ADEM probably dates back to the early eighteenth century with the recognition of the temporal relationship to the childhood exanthemata illnesses (small pox and measles) [29]. The association of ADEM with vaccines, particularly rabies vaccine, became evident towards the end of the nineteenth century. Mortality and morbidity were high, and for those who recovered, neurologic sequelae were frequent [30,31]. Clinical, pathological and epidemiological studies established the connection between ADEM and specific viruses (measles) or vaccines in the early twentieth century. Successful immunization programs for measles, mumps and rubella, the eradication of natural smallpox disease, and promotion of vaccines devoid of neural tissue, resulted in a marked decrease in the frequency of ADEM [32,33]. Currently,

although a wide range of infectious illnesses and vaccines continue to be reported in association with the development of ADEM, most cases in the United States follow nonspecific (less identifiable) viral illness in the winter and spring [34].

From a historical perspective, when Marie first described pediatric MS in 1883, he noted the possible relationship to infectious illness [1]. Indeed it is probable that at least some of his 13 cases were misclassified, and were in fact due to direct infectious causes or post-infectious processes (i.e. ADEM). In contrast, Bogaert diagnosed 19 patients with ADEM, 4 of whom ultimately developed MS [35].

With no specific biologic markers, clinical or neuroimaging features, it remains very difficult to definitively distinguish ADEM from MS at disease onset. Many clinicians have acknowledged that some children with a diagnosis of ADEM may go on to have another episode, yet may have as good an outcome as children with monophasic ADEM. The period necessary to be assured of this good and perhaps theoretical outcome was, and still, is unclear. It was also recognized that a proportion of these children would continue to have attacks, and develop the lifelong illness, MS. Review of the literature highlights inconsistencies that have added to the confusion, such as:

- Different descriptions of ADEM based on pathology (perivenous), anamnestic data (post-infection, post-vaccinal) or supposed pathogenesis
- Different terminology used to describe ADEM and “its variants”, often with little or no definition or consensus [36–42]
 - “biphasic ADEM”, representing a protracted single episode rather than a new event
 - “multiphasic or recurrent ADEM” representing repeat episodes, if occurring within the first few months or year(s) of the initial event
 - “steroid-dependent relapse” if the event occurred as steroids were tapered.

The recent renewed interest in pediatric MS

It was only in the late 1950s that MS in the pediatric population resurfaced in the literature [43–45]. The latter half of the twentieth century led to a greater understanding of both inherited leukodystrophies and acquired CNS demyelinating disorders [46]. MRI

transformed the diagnostic process, and dramatically improved early diagnosis and the ability to follow the course of the disease [47] (see Chapter 5). More recent investigations have shown that it is possible to distinguish MS from certain other CNS disorders, such as metabolic diseases or neuromyelitis optica (NMO) [48] (see Chapters 6 and 23), thus offering more specific treatment options. Despite these advancements, for the child who presents with a first CNS inflammatory demyelinating event (or at times, the second), it continues to be a challenge to predict if s/he will remain asymptomatic, or develop MS (Chapters 7 and 19).

In the past, a diagnosis of ADEM would have been considered when a physician saw a previously well child who developed new neurologic signs and symptoms (focal or multi-focal), coupled with neuroimaging evidence of demyelinating lesions (focal or multi-focal) and if cerebrospinal fluid (CSF) and other studies excluded infectious, neoplastic or metabolic etiologies (see Chapters 6, 17, and 18). Treatment with steroids and supportive care would have been recommended (even though there have been no randomized clinical trials to determine the best dose, best route of administration and best treatment duration) (see Chapter 19). Physicians often adopted a “wait and see” approach, since therapy (steroids) was the same whether the illness was labeled ADEM, clinically isolated syndrome (CIS) or MS.

However, clinical trials in adults with MS showed that use of DMT slowed the progression of the disease in some patients and early treatment was recommended [7]. These treatments are now commonly used in children and adolescents, even though they have not been formally tested (see Chapters 10 and 11). Thus, the distinction between ADEM and a CIS inaugurating MS in children and adolescents is no longer a theoretical concern, since recommended early therapy for MS and CIS are markedly different from ADEM (see Chapter 19). Thus, accurate and early diagnosis has become crucial in the pediatric population.

Recent increased interest in the international scientific and medical communities

Awareness of and interest in pediatric MS have increased in the past two decades (Figure 1.3); however, information concerning diagnosis, treatment,

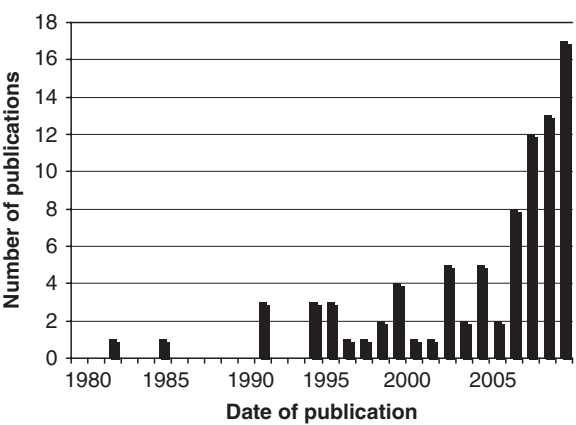


Figure 1.3 Published cases of pediatric MS. This figure represents the number of Medline publications including the term “pediatric MS” or “childhood MS” in the title or abstract over the past 30 years. By definition, this figure does not include all the publications regarding pediatric MS that have been published, but only those with the above-mentioned constraint. In 1993, Bauer and Hanefeld reported that 136 actual pediatric MS cases had been reported before 1980 (including 20 prepubertal cases), and 235 cases between 1980 and 1993 (including 43 prepubertal) [50].

epidemiology, and long-term prognosis is still limited. Since there are relatively small numbers of children in any one geographic area, especially children who develop their first symptoms before puberty (Table 1.2), it is essential to have multi-center, international collaborative efforts in order to further address these issues.

Since 2002, countries such as Australia, Canada, England, France, Germany, Italy, and the US, among others, have developed national collaborative teams of clinicians and researchers to address pediatric MS. In addition, an International Pediatric MS Study Group (IPMSSG) has evolved to include clinicians and researchers from over 18 countries, with support from MS societies throughout the world (www.ipmssg.org). The result of the initial work of the IPMSSG was the peer-reviewed supplement in the journal *Neurology* in April 2007 including a series of nine review articles. This landmark supplement included an article describing working operational definitions for acquired CNS demyelinating disorders in children including MS, CIS, ADEM, recurrent ADEM, multiphasic ADEM, and NMO [49]. These definitions were designed both to improve diagnosis in individuals under the age of 18, and to develop a platform for future research. While it was recognized that these definitions were not perfect and would need to be tested and revised with time, the uniform

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Table 1.2 Early-onset cases of multiple sclerosis published by 1993 (with permission from [50])

Study	Age at onset (years)
Bauer <i>et al.</i> (1991)	3
Bejar and Ziegler (1984)	2
Boutin <i>et al.</i> (1988)	2
Brandt <i>et al.</i> (1981)	2
Bye <i>et al.</i> (1985)	3
Golden and Woody (1987)	3
Haas <i>et al.</i> (1987)	4.5
Hauser <i>et al.</i> (1982)	3
Ishahara <i>et al.</i> (1984)	5
Kesselring <i>et al.</i> (1990)	2
Maeda <i>et al.</i> (1989)	15
Mattyus and Veres	4
Miller <i>et al.</i> (1990)	2
Schneider <i>et al.</i> (1969)	4
Shaw and Alvord (1987)	2.25
Vergani <i>et al.</i> (1988)	2

classification was an important first step to accelerate international research and to advance the understanding and treatment of this disease (see Chapter 2). Today, the IPMSSG is focused on optimizing worldwide care, education and research in pediatric MS and other acquired inflammatory demyelinating disorders of the CNS, through global collaborative research.

Future research directions

Although much has been learned regarding pediatric MS, there are still more questions than answers. MS research and treatment strategies have mainly focused on adult-onset disease. It should be remembered that DMT are currently used *off-label* to treat children and adolescents with MS. Randomized clinical trials have not been conducted in children (see Chapters 10 and 11). Studies are required to better understand safety, efficacy of therapies, possible side effects, and how treatments may impact the developing nervous and immune systems. Multi-centered, prospective studies addressing natural history and long-term prognosis, treatment failures, and how best to make treatment

decisions, are essential. In addition, research is required to identify risk factors, biological and MRI disease markers, prognostic correlates, the effects of puberty, and underlying pathogenetic mechanisms.

The study of pediatric MS provides a unique opportunity to examine factors contributing to MS pathogenesis in general, since in affected children there is a close temporal proximity between the interplay of biological, genetic and environmental factors leading to clinical expression of the disease. Insights into underlying pathophysiologic mechanisms might be gained since disease expression is closer to inciting events. Pediatric MS offers an opportunity to investigate a disease at its onset and, when in the very young patient, during a time when the nervous and immune systems are still maturing (e.g. the effect on myelin damage and repair). This is also a time when exposures to infections may play an important role in the maturation and modeling of the immune system. The timing and role of immunizations as well as infection need to be explored. In addition, there are opportunities to study hormonal influences of puberty and how these may contribute to the expression of MS in this young population.

Summary

While much has been learned in the past decade, our understanding of pediatric MS remains inadequate. Increased research activity will lead to improved clinical care and better characterization of the disease in young children and adolescents. We need to advance our understanding of underlying biological and pathophysiologic mechanisms, in particular of the overlap with ADEM. The aim of this textbook is to review in detail our current knowledge of pediatric MS and related diseases, based on published data or, when unavailable, on common practices. Forty-seven authors from various geographical locations (7 countries represented) contributed to this original collaborative endeavor, including the perspectives of both pediatric and adult specialists. This textbook is written for clinicians and researchers, with an emphasis on clinical care and the most recent scientific advances in the field.

Clinical vignettes

The diagnosis of pediatric MS has been, and in large part remains, difficult at times, as demonstrated by these vignettes.

Case 1

Rosario and his parents moved to Germany from a Mediterranean country. In 1988, when he was five years old, he developed a squint, right arm weakness, and complained of dizziness and blurry vision, which resolved within a few weeks. Symptoms and signs recurred six months and then again one year later. Improvement was noted within a few weeks after each episode. The diagnosis of multiple sclerosis was established, based on clinical course, detection of IgG oligoclonal bands in CSF, and multi-focal white matter lesions visualized on brain MRI. Looking back on the historical evolution of demyelinating disorders, we would imagine that Pierre Marie in 1833 would most likely have considered MS to be the diagnosis. Schilder, in 1913, however, would have suspected diffuse sclerosis; whereas, later yet prior to introduction of CT and MRI, a neurologist might have considered a diagnosis of a metabolic-genetic demyelinating disorder such as adrenoleukodystrophy (considering the child's sex, age, and Mediterranean heritage).

Case 2

In the late 1970s, Katherine, a 14-year-old girl, had been followed in the Department of Child Psychiatry at a university hospital for two years with a diagnosis of conversion disorder (psychogenic gait disturbance). Her illness was characterized by episodes of gait instability and weakness. She used a wheelchair, since she was unable to walk independently. Because of her age, MS was not considered and the remittent and alternating nature of the paresis and ataxia led to a misdiagnosis. After two years, a pediatric neurologist found clear-cut pyramidal and cerebellar signs leading to CSF analysis showing positive IgG oligoclonal bands, and to a cranial CT scan, which led to the correct diagnosis of MS. The lack of awareness that MS can affect children and the frequent diagnosis of psychosomatic disorders in adolescent girls was, and still is, a problem. At the time of Pierre Marie, for example, hysteria might have been considered a possible diagnosis.

Case 3

In 1999, Peter, a four-year-old boy, developed an unsteady gait and clumsiness. Examination showed a mild left facial droop and left leg weakness. The CSF profile was normal, culture and PCR studies (e.g.

herpesviruses) were negative. The provisional diagnosis was viral encephalitis. Signs and symptoms resolved within 10 days. He developed a left hemiparesis 16 days later. CSF examination was unremarkable. Brain MRI showed hyperintense T2 patchy lesions (some fluffy, some confluent) involving the cerebral white matter. The diagnosis of ADEM was made based on the combination of clinical course, CSF, and neuroimaging studies. He received intravenous steroids. Signs and symptoms resolved. Six months later, clumsiness and ataxia developed, lasted for two days and resolved without treatment. The diagnosis of ADEM-variant was considered. No new symptoms ensued and neurological examination remained unremarkable. Routine follow-up MRI performed one year later showed new enhancing lesions. He remained well until April 2002, when he again developed slurred speech and ataxia. The CSF profile was normal. The CSF quantity was insufficient to test for oligoclonal bands. He again received IV steroids followed by a one-month prednisone taper. Recovery was excellent. In June 2002 he had an episode of right-sided weakness. MRI showed multiple rounded ovoid and patchy T2 hyperintensities extensively involving both cerebral hemispheres, the corpus callosum, brainstem, and the cerebral and cerebellar peduncles. Repeat CSF examination showed IgG oligoclonal bands. MS was diagnosed. Neuropsychological evaluation was normal. Disease-modifying therapy was instituted. During the following years he continued to have further episodes. Changes in DMT were made. Although he had been classified as a gifted student at age 9 years he began experiencing academic difficulties necessitating special education resources. This case illustrates the challenges of distinguishing between ADEM and MS onset in children, especially when the second episode occurs within 30 days from onset and there are no IgG oligoclonal bands. It also emphasizes that cognitive problems in children with MS may have a significant impact on academic performance as well as psychosocial issues.

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Chapter

2

Controversies around the current operational definitions of pediatric MS, ADEM, and related diseases

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Pediatric MS has been increasingly diagnosed over the past 20 years. The increased clinical awareness has translated into growing interest in pediatric MS research in the international community, and the number of publications on pediatric MS has grown exponentially from 12 articles reported on the NIH Entrez Medline website in 1998 to 58 articles in 2008. Although diagnostic criteria for pediatric MS and related diseases have evolved in parallel, they are still debated (see Chapter 1). Until 2001, the criteria used to diagnose MS in adults were based on the clinical dissemination of symptoms in time and space [1]. In 2001, consensual MS criteria incorporating MRI findings were published [2] and then refined in 2005 [3]; they have been used in clinical practice and research settings for the past 8 years in adults.

However, these criteria may have a limited applicability in the pediatric population. In fact, MS is a challenging diagnosis in children – especially those who have not yet reached puberty – because of the atypical clinical, biological and MRI presentations, and the broader spectrum of potential differential diagnoses specific to that age range [4]. In particular, differentiating a first episode of MS from acute disseminated encephalomyelitis (ADEM) in children who present with an initial demyelinating event can be an issue for any clinician given the clinical overlap between the two entities and the absence of a reliable biomarker or MRI criteria.

In 2002, a first International Pediatric MS Study Group (subsequently referred to as Study Group) was assembled that made a first attempt to tackle the issue of operational definitions of pediatric MS and related diseases such as ADEM, clinically isolated syndrome (CIS), optic neuritis (ON), transverse myelitis (TM), and neuromyelitis optica (NMO) [5]. The goal was to

improve standardization of the terminology applied to these entities to both facilitate the diagnosis and enhance communication among pediatric MS researchers across the world. This was the first attempt to speak with the same voice about pediatric MS and related diseases. The publication of these definitions in 2007 further increased the awareness of pediatric MS within the medical community and provided a framework for prospective research that could test and refine the proposed definitions [5]. At the onset, the Study Group recognized further studies would be needed to challenge and refine these definitions. As expected, both omissions and blurring of categories were identified by research studies subsequent to the publication of the operational definitions. One concept that has emerged since 2007 is that prepubertal MS patients at the time of their initial demyelinating event can have ADEM-like features even if they go on to subsequent clinical events consistent with MS. Since these MS patients have subsequent relapses, they might be misdiagnosed as multiphasic or recurrent ADEM. Two of the criteria upon which the distinctions between ADEM and MS rely, yet represent the most difficulty, are encephalopathic changes and polyregional/polysymptomatic presentation. In this chapter, we will discuss how these current operational definitions can apply to clinical practice and research settings, and we will emphasize their strengths and limitations.

The Study Group has grown in size and breadth of represented countries since the original pediatric MS and related definitions were proposed. The enlarged Study Group shares the goal to update and revise the 2007 definitions, particularly by incorporating data published since the original definitions were drafted.