Onset symptoms in paediatric multiple sclerosis

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ABSTRACT

INTRODUCTION: Paediatric multiple sclerosis (MS) carries a relatively higher mortality and morbidity than adult MS. Paediatric MS symptoms and paraclinical findings at the first demyelinating event have never before been characterised in a Danish setting. The aim of this study was to compare symptoms and paraclinical findings at the first demyelinating event in paediatric MS with those of an adult MS population.

MATERIAL AND METHODS: A total of 18 subjects with onset of MS relapse before 16 years of age were retrospectively included in the study. Case records were reviewed for symptoms at disease onset, cerebrospinal fluid findings, magnetic resonance imaging (MRI) and evoked potentials at the first demyelinating event. These data were compared with similar nationwide data from adults in Denmark.

RESULTS: The median age was 14 (range 10 to 15) years at the first demyelinating event and the mean time to MS diagnosis was 1.7 years. The majority of children had sensory symptoms (47%; 95% confidence interval (CI): 23-72%) or optic neuritis (35%; CI: 14-62%) as their presenting symptoms. These results did not differ from the findings in adult MS subjects. Pleocytosis was present in 93% (CI: 66-100%) of paediatric MS subjects, 77% (CI: 46-95%) had an elevated IgG index and 85% (CI: 55-98%) had oligoclonal bands in the cerebrospinal fluid. MRI showed characteristic white matter lesions in all children (CI: 80-100%).

CONCLUSION: MS symptoms at the first demyelinating event and diagnostic delay in paediatric MS subjects do not differ significantly from those seen in an adult MS population.

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Multiple sclerosis (MS) is a chronic autoimmune disease in the central nervous system (CNS) characterised by demyelinating lesions and focal neurological symptoms disseminated in time and space [1]. Presentation at an early age is associated with a poorer prognosis regarding morbidity and mortality, and early treatment of paediatric MS is considered to reduce morbidity in terms of cognitive dysfunction and physical disability [1]. The prevalence of MS in Denmark was 154 per 100,000 in 2005 and has increased during the past decades owing to improved survival and a higher incidence of MS [2]. The overall incidence of MS in Denmark (per 100,000 person years) was six for males and 12 for females in 2002 [3]. It has been estimated that 3-5% of MS subjects have their first relapse before their 16th year of age [1] meaning that the expected incidence of paediatric MS should be around 20 subjects annually in Denmark (population approximately 5,500,000). In our opinion, this number exceeds the estimated number of referrals of paediatric MS subjects to Danish MS centres for immunomodulatory treatment. One of our concerns in this regard is that early diagnosis and treatment of MS in children could be delayed, possibly due to presentation with atypical onset symptoms and paraclinical results.

The objective of this study was therefore to retrospectively evaluate the first demyelinating event of paediatric MS in a Danish MS centre and compare our findings with those of an adult MS population in order to characterise the diagnostic procedures and the diagnostic delay.

MATERIAL AND METHODS

Eighteen subjects with MS fulfilling the diagnostic Poser MS criteria [4] with onset of MS before their 16th years of age were included in the study. The subjects were identified retrospectively in a clinical database at the Danish Multiple Sclerosis Centre (DMSC), Rigshospitalet, which provides care for approximately 2000 MS patients. The subjects were all referred from paediatric departments with a characteristic clinical and paraclinical presentation of demyelinating CNS disease. A final diagnosis of MS was made in the DMSC according to the formal criteria before the data were entered into the MS database. Case records were reviewed for onset symptoms, time to diagnosis, magnetic resonance imaging (MRI) findings, cerebrospinal fluid (CSF) findings and evoked potentials at first demyelinating event.

The symptoms at the first demyelinating event were grouped into five categories based on a large cohort study of Danish subjects with MS [5] that describes onset symptoms in an adult population as follows:
1. Cerebellum; 2. Optic neuritis (ON); 3. Diplopia;
4. Motor symptoms from long motor tracts; 5. Sensory symptoms from long sensory tracts.

The statistical evaluation included Clopper and Pearson exact confidence interval calculations for proportions. In this way, our results were compared to the results of the adult cohort study mentioned above.

Trial registration: not relevant.

ORIGINAL ARTICLE

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TABLE 1

Age characteristics for the paediatric subjects in our study.

	Median	Range	Mean
Age at onset, yrs	14	10-15	13.1
Age at diagnosis, yrs	15	11-19	14.8

TABLE 2

Clinical presentation for the paediatric multiple sclerosis subjects in our study and for an adult cohort study of Danish multiple sclerosis patients [5].

	Paediatric subjects (N = 18)		Adult cohort study (N = 4,833)	
	n	% (95% CI)	n	% (95% CI)
Cerebellum	2	12 (1-36)	769	16 (15-17)
Optic neuritis	6	35 (14-62)	965	20 (19-21)
Diplopia	0	0 (0-19)	379	8 (7-9)
Symptoms from motor long tract	1	6 (0-29)	1,183	24 (23-26)
Symptoms from sensory long tract	8	47 (23-72)	1,537	32 (31-33)

CI = confidence interval.

RESULTS

The majority of paediatric MS subjects had their first demyelinating event between the age of 12 and 15 years. The median age at disease onset was 14 years (range 10-15 years) (**Table 1**). The median age at time of diagnosis was 15 years (range 11-19 years), and the mean time from the first demyelinating event to the time of diagnosis was 1.7 years.

Paediatric subjects presented with symptoms from four of the five symptom categories (**Table 2**): cerebellum 12% (95% confidence interval (CI): 1-36%), ON 35% (CI: 14-62%), symptoms from long motor tracts 6% (CI: 0-29%) and symptoms from long sensory tracts 47% (CI: 23-72%). These results do not differ from adult presentation (Table 2) although there was a trend towards a more frequent presentation with visual loss and less frequent presentation with motor symptoms.

MRI showed characteristic white matter lesions in 100% (CI: 80-100%) of the paediatric MS subjects (**Table 3**). 73% (CI: 45-92%) had more than nine lesions on MRI. Only 54% (CI: 25-81%) were given intravenous gadolinium contrast, but of these 86% (CI: 42-100%) had at least one enhancing lesion (Table 3). Only 8% (CI: 0-45%) of diagnostic MRI examinations were assessed according to the now prevailing McDonald criteria.

CSF analysis showed that 93% (CI: 66-100%) of paediatric MS subjects had mononuclear pleocytosis, 77% (CI: 46-95%) had an elevated IgG index and 85% (CI: 55-98%) had IgG oligoclonal bands (OCB) in the CSF. No subjects had elevated protein concentrations in the CSF (Table 3).

Visual evoked potentials (VEP) and sensory evoked potentials (SEP) were abnormal in 77% (CI: 46-95%) and 50% (CI: 19-81%) of the paediatric MS subjects (Table 3).

DISCUSSION

Our study shows that symptoms at the first demyelinating event and diagnostic delay did not differ significantly in the paediatric MS subjects compared with the adult population [5]. However, our results indicate that visual loss might more often lead to diagnostic work up rather than symptoms from long motor tracts (Table 2). A possible explanation could be that loss of vision is more easily measured and expressed by the child compared to e.g. a slight or moderate motor dysfunction for which there could be many reasons and for which the child can compensate. In this way caregivers may be more inclined to observe for spontaneous improvement of motor symptoms than improvements of visual loss. In a large French cohort study, 23% of the paediatric MS subjects had ON as their first demyelinating event and 38% had either long sensory or motor tract symptoms [6], which is also consistent with the MS onset pattern seen in adults.

Another discrepancy between our results and the literature is that acute demyelinating encephalomyelitis (ADEM) is consistently reported as a presenting symptom in paediatric MS populations [7-9]. In a prospective study with 296 subjects under 16 years of age, 29% of the children with an initial diagnosis of ADEM had a second relapse and were hereby classified as clinically definite MS [8]. The diagnosis of ADEM was defined as a poly-symptomatic onset with mental status change and suggestive brain MRI (poorly limited lesions, associated at the time with thalamus and/or basal ganglia lesions).

TABLE 3

Baseline characteristics for the paediatric subjects in our study.

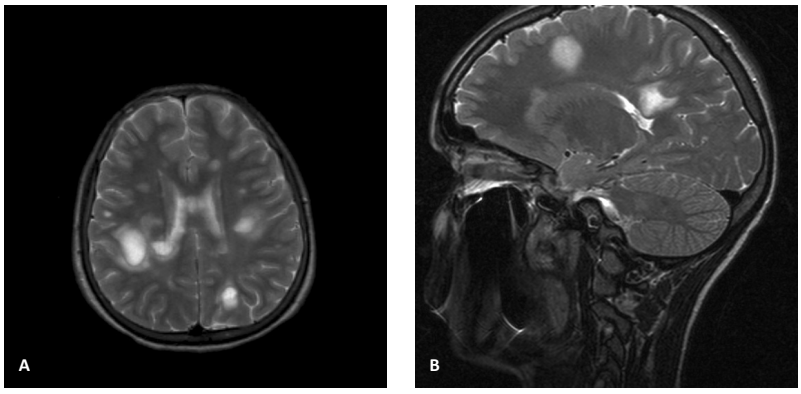
	Positive results	
	n	% (95% CI)
Cerebrospinal fluid examination		
Pleocytosis (N = 14)	13	93 (66-100)
Oligoclonal bands (N = 13)	11	85 (55-98)
Elevated IgG index (N = 13)	10	77 (46-95)
Elevated protein (N = 6)	0	0 (0-46)
Magnetic resonance imaging		
Lesions typical for MS (N = 17)	17	100 (80-100)
> 9 lesions (N = 15)	11	73 (45-92)
Intravenous contrast agent given (N = 13)	7	54 (25-81)
Gadolinium-enhancement (N = 7)	6	86 (42-100)
Assessment of McDonald criteria (N = 13)	1	8 (0-45)
Electrophysiology		
Visual evoked potential (N = 13)	10	77 (46-95)
Somatosensoric evoked potential (N = 10)	5	50 (19-81)

CI = confidence interval; MS = multiple sclerosis.

Our study could not corroborate these findings since none of our subjects presented with ADEM. This could be coincidental due to the small number of subjects in our study, but another and more likely explanation may be that the vast majority of the subjects in our study were adolescents at presentation, whereas ADEM patients tend to present at an even younger age [8, 10]. Another explanation may be that the revised 2010 McDonald criteria for MS diagnosis in children with an ADEM-like first attack require confirmation by two or more non-ADEM like attacks, or one non-ADEM attack followed by accrual of clinically silent lesions [9]. As for the above mentioned study by Mikaeloff et al [8] cases of ADEM that had a second relapse were classified as clinically definite MS, although a presentation of ADEM followed by a single non-ADEM relaps does not fulfill the revised 2010 McDonald criteria for progression from ADEM to a diagnosis of MS. In this way, there is an inconsistency in the literature that confounds a direct comparison of conversion rates from ADEM to MS.

Still, the fact that we did not encounter a single child with a previous history of ADEM is consistent with the notion that paediatric ADEM in children older than 11 years is a rare onset symptom of MS, but it also indicates that further investigation of children with ADEM in our clinical setting may be warranted.

Our data do not suggest that there should be a considerable difference between clinical presentation and diagnostic delay in children and adults, at least in adolescents for whom the clinical presentation appears to be comparable to that observed in adult onset MS. The low number of children referred for immunomodulary treatment in an adult MS setting may well reflect the actual incidence of paediatric MS. This is furthermore supported by recent studies which show an incidence of paediatric MS of 0.15-0.5/100,000 in children under 18 years of age [11, 12], and 0.3/100,000 in children under 16 years [13]. Extrapolating these data to a Danish population with a population size of children under 16 and 18 years of approximately 1 and 1.2 million, the incidence of paediatric MS in Denmark would be two to six new cases annually, which is substantially lower than the previously suggested figures of 3-5% of MS cases [1]. The CSF findings show that the majority of the paediatric MS subjects had pleocytosis and intrathecal IgG synthesis. Other studies reported that 39-66% had pleocytosis, 83-92% had OCB, and 64-87% had an elevated IgG index [14-16]. CSF analysis is helpful in distinguishing MS from ADEM since only 4-10% of ADEM subjects have OCB; and 13-15% have an elevated IgG index at the first demyelinating event [14, 17]. These findings indicate that routine CSF examination and OCB analysis are relevant in the diagnosis of paediatric MS and support the use of these modalities in the diagnostic evaluation.



Magnetic resonance imaging showing characteristic multiple sclerosis (MS) white matter lesions in a child with MS. Horizontal (**A**) and sagittal view (**B**).

Our MRI data show that all paediatric MS subjects had characteristic MS lesions on T2-weighted images at the first presentation, and the majority had more than nine cerebral lesions. We have little information regarding fulfilment of the diagnostic McDonald criteria since only 8% of our subjects were assessed in this regard. This is mainly due to the fact that the McDonald criteria were not implemented in paediatric clinical practice when most of our subjects were diagnosed. The clinical impact of diagnostic MRI criteria has been thoroughly discussed in the literature, and it has been argued that only 54% of paediatric MS subjects with clinically definite MS meet the diagnostic McDonald criteria of dissemination in space (DIS) at the first demyelinating event and only 67% at the time of the MS-defining relapse [18]. Different approaches have been suggested in order to improve the diagnostic accuracy in paediatric MS. In particular the Callen criteria have been applied. These criteria differentiate demyelinating from non-demyelinating disease with 98% specificity and 85% sensitivity [19]. Recently, a study by Sadaka et al [10] demonstrated that applying the revised 2010 McDonald criteria [9] in children older than 11 years without an initial diagnosis of ADEM and using clinical relapsing disease as the gold standard resulted in high specificity and sensitivity (100% and 86%, respectively) after an observation period of 4.3 years. The revised 2010 McDonald criteria are therefore the current recommendation for use in paediatric MS although caution is recommended when applying these criteria in children under 11 years and in children with an initial diagnosis of ADEM [10]. The diagnostic differentiation between MS and ADEM is primarily based on clinical findings, although the revised 2010 McDonald criteria, as well as the former Callen criteria, clearly separate these two pathological entities.

A pitfall regarding fulfilment of the revised 2010 McDonald criteria is the reluctance to administer gadolinium (Gd) contrast, which in some instances can be decisive for an accurate diagnosis. In our study, only 54%

were given Gd contrast at clinical presentation, which may delay diagnosis and early treatment of MS, although 86% had at least one enhancing lesion. The reasons for not using Gd contrast is supposedly not based on rational arguments and we strongly recommend that intravenous contrast is applied in routine MRI in the diagnostic workup of children with symptoms of demyelinating disease.

Visual evoked potentials (VEP) and somatosensory evoked potentials (SEP) were abnormal in 77% and 50%, respectively, of the children in our study. The use of evoked potentials is important since children may be less likely to meet the diagnostic criteria of DIS at the first demyelinating event, and evoked potentials may contribute to fulfilment of these criteria [18]. In a retrospective study, evoked potentials detected clinically silent lesions in 46% of the paediatric MS subjects [20] and VEP detected 36% of these lesions. We therefore recommend that children with symptoms of demyelinating disease should also be assessed with at least VEP and SEP in the diagnostic workup.

CONCLUSION

Our study shows that MS symptoms at the first demyelinating event and the time to diagnosis in our cohort did not differ significantly in children with MS compared with an adult MS population. Furthermore, our study does not support the notion that a major part of the paediatric MS subjects older than 11 years initially present with ADEM. It is currently unknown whether this is merely due to the small number of subjects in our study, reduced clinical vigilance in children with ADEM, or referral bias. We find that MRI is the most important paraclinical investigation in the diagnosis of MS in children and suggest that the revised 2010 McDonald criteria should be applied in children who are 11 years and older at presentation. In all children with ADEM, diagnostic procedures should be thoroughly implemented and followed up according to the revised 2010 McDonald criteria in order to reveal early signs of MS. Furthermore, the diagnostic assessment of paediatric MS subjects should include CSF analysis as well as evoked potentials (VEP and SEP).

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