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ORIGINAL PAPER

Paediatric multiple sclerosis and acute disseminated encephalomyelitis in Germany: results of a nationwide survey

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Abstract The aim of this study was to evaluate the incidence of paediatric multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM) in Germany. In a prospective nationwide survey carried out between 1997 and 1999, all registered new cases of paediatric MS and ADEM with an onset before the age of 16 years were evaluated using a standardised questionnaire. A total of 132 patients with suspected or definite MS and 28 patients with an assumed diagnosis of ADEM were reported. Among these, 82% of the MS patients were 10 years of age or older, as opposed to 18% in the ADEM-cohort. The female-to-male ratio was 1.2:1 in the MS-cohort and 0.8:1 in the ADEM-cohort. Manifestation was polysymptomatic in 67% of the MS patients compared to 86% of the ADEM patients. The most frequent primary symptoms in the MS-cohort were cerebellar (44%), sensory (39%) or visual (36%), followed by brainstem (30%), pyramidal (29%) and cerebromental (22%) complaints. *Conclusion*: The incidence of paediatric MS in Germany is more than fourfold higher than that of paediatric ADEM; in addition, it shows a strikingly different age-distribution. With an estimated minimum of 50 new cases per year, the incidence of paediatric MS in Germany is much more frequent than previously believed.

Keywords Acute disseminated encephalomyelitis · Age distribution · Gender ratio · Incidence · Multiple sclerosis

Abbreviations

ADEM	acute disseminated encephalomyelitis
CSF	cerebrospinal fluid
EP	evoked potentials
ESPED	Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland (German Surveillance Unit for Rare Paediatric Disorders)
MRI	magnetic resonance imaging
MS	multiple sclerosis

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Introduction

Multiple sclerosis (MS) is still widely considered to be a disease of adulthood, whereas acute disseminated encephalomyelitis (ADEM) is judged to occur more frequently in children and adolescents. However, the results of several retrospective studies have shown that disease onset before the age of 16 occurs in about 5% of the whole MS population [7, 8, 28]. Data on the frequency of ADEM are lacking, as are exact diagnostic criteria. It is thus assumed that many cases of paediatric MS either remain undiagnosed or are possibly misdiagnosed as ADEM and that affirmative diagnosis of MS is often delayed until

adulthood. In order to evaluate the frequency as well as clinical and paraclinical characteristics of newly diagnosed paediatric MS and ADEM we conducted a nationwide survey that included all paediatric departments in Germany.

Methods

A prospective nationwide survey was performed during a 3-year period (January 1, 1997 to December 31, 1999) in cooperation with the German Surveillance Unit for Rare Paediatric Disorders ["Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland" (ESPED)] [31]. Inquiries were sent monthly to all Departments of Paediatrics and Paediatric Hospitals asking about possible newly diagnosed MS or ADEM patients with a disease manifestation before the age of 16 years. When a positive reply was received, an anonymised, standardised detailed questionnaire was sent to the reporting institution aimed at evaluating the presumed diagnosis, family and medical history, age at onset, primary symptoms, paraclinical findings and course of the disease. Two years later, a second questionnaire was sent out asking for information on the observed disease course and a possible change of diagnosis.

Calculations on the reported incidences were performed on the basis of demographical data of the Federal Statistical Office of Germany (Table 1).

The study was approved by the ethics committee of the Medical Faculty, Georg-August-University Göttingen, Germany.

Results

Inquiry return rate and number of notifications

The return rate of the monthly inquiry cards was 95% in 1998 and 94% in 1997 and 1999. A total of 235 initial notifications from 110 paediatric departments were received during the 3 study years: 72 in 1997, 75 in 1998 and 88 in 1999. Standardised questionnaires were sent to all reporting physicians, and 204 questionnaires were returned (87%). Twenty-one duplicate reports of the same patients, 12 patients with other diagnoses (mostly encephalitis) and 11 patients with an age over 15 years at disease manifestation were excluded from further evaluation, resulting in 160 questionnaires for the final analysis.

In the follow-up study 2 years after the first evaluation, 68 questionnaires (43%) were returned: 55 for the MS-cohort (42%) and 13 for the ADEM-cohort (46%).

Table 1 Demographic data of Germany during the survey period

Population				
	Total	<16 years	<10 years	10–15 years
1997	82,057,379	14,025,867	8,530,229	5,495,638
1998	82,037,011	13,883,539	8,343,911	5,539,628
1999	82,163,475	13,797,064	8,199,237	5,597,827

Diagnoses

The diagnoses of the 160 patients, as reported by the treating physicians, were definite MS in 48 patients, suspected MS in 84 patients, ADEM in 19 patients and suspected ADEM in nine patients. In the following analysis, the patients with suspected and definite MS will be analysed as the "MS-cohort" (n=132) and those with ADEM and suspected ADEM as the "ADEM-cohort" (n=28).

Incidence

With 132 patients reported within a 3-year period the per-year incidence of paediatric MS in Germany was 0.3 per 100,000 children under 16 years of age. For children under 10 it was only 0.1, which is in stark contrast to the 0.6 reported for adolescents between 10 and 15 years of age.

The incidence of paediatric ADEM in Germany is 0.07 per year per 100,000 children under 16 years. It is threefold higher in the group of children under 10 years than in the group of children between 10 and 15 years of age (0.09 versus 0.03 per 100,000 children of the respective age group).

Age and gender distribution

In the MS-cohort, the number of reported cases increases with age, with a steep rise in 13- to 15-year-old children (Fig. 1), especially in girls (Fig. 2a).

The female-to-male ratio changes with age: it is 0.9:1 in the group with manifestation of MS before the age of 14 years and 2.2:1 in the group with a disease onset at the age of 14 or 15 years (Fig. 2a). The female-to-male ratio for the whole group is 1.2:1.

In the ADEM-cohort, incidence peaks in the 3- to 8-year-old children, who represent 75% of all patients (Fig. 1). Slightly more boys than girls with ADEM were reported (ratio: 1.3:1), but there is no detectable difference in the gender distribution in the different age groups (Fig. 2b).

Family history

Data on the family history were available for 123 of the 132 patients of the MS-cohort. Six of these children (5%) had family members with MS, but only two of them had first-degree relatives with MS (in both cases, the father).

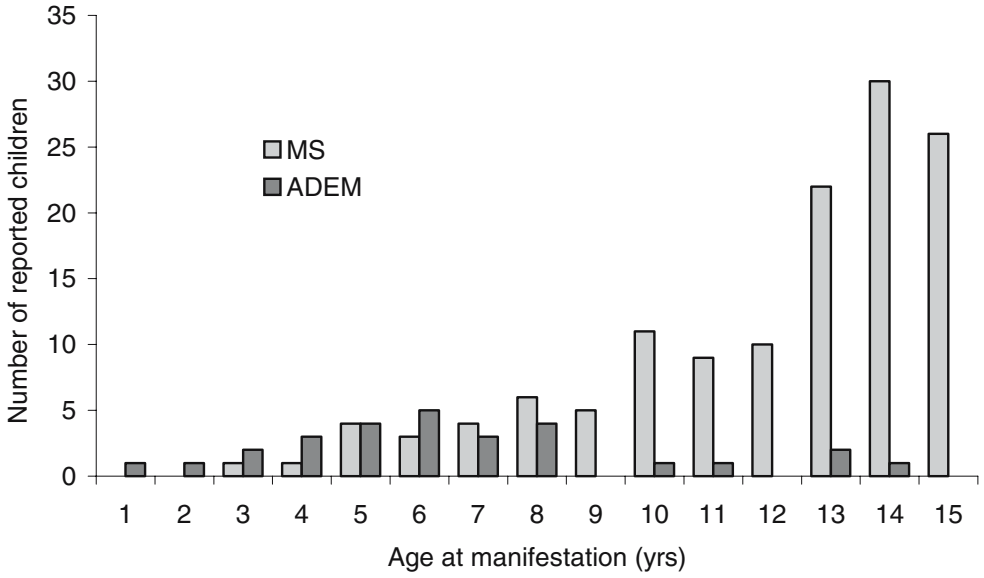

Fig. 1 Number of reported children with MS or ADEM according to age at manifestation

Data on the family history were available for 27 of the 28 patients of the ADEM-cohort. Of these children, none had a relative with ADEM, but one child had a second-degree relative with MS.

Associated diseases

An associated second disease was reported for 19 patients of the MS-cohort (14%), with the most frequent being an

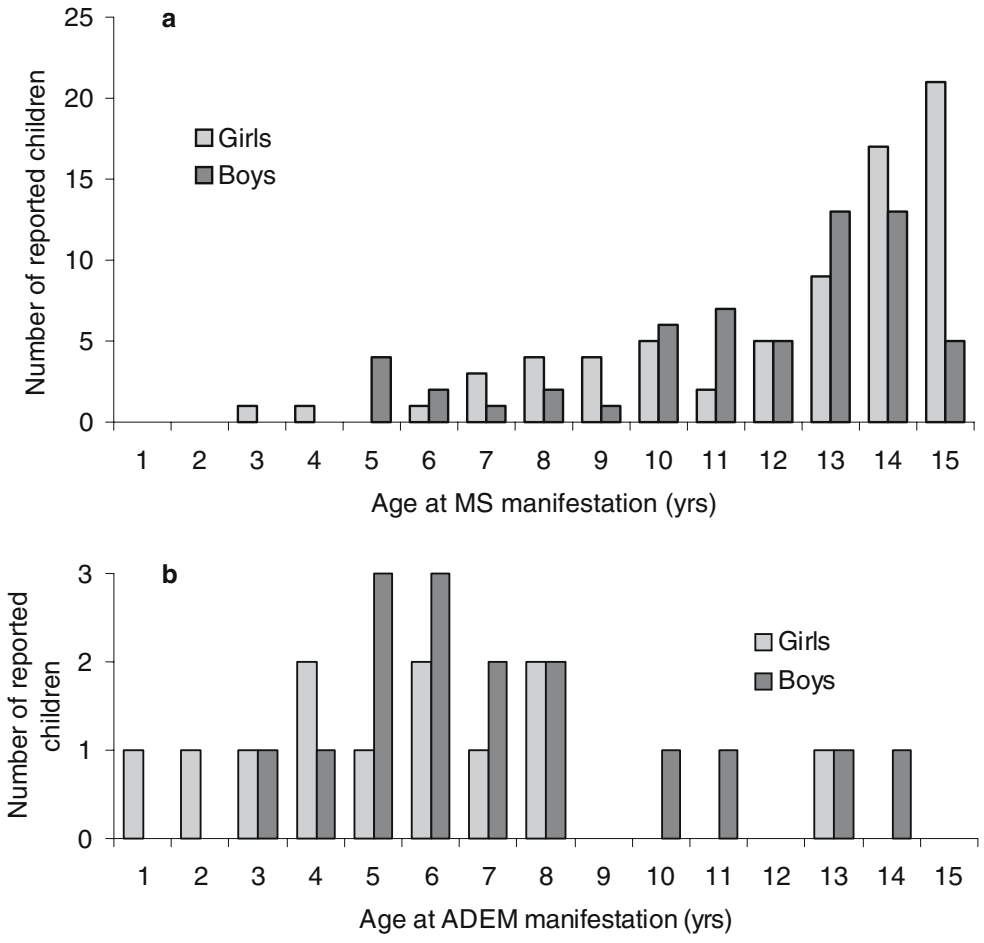

Fig. 2 Gender distribution of reported children with MS (**a**) or ADEM (**b**) according to age at manifestation

allergy (n=9). Three children had concomitant autoimmune diseases, two of them insulin-dependent diabetes, one a juvenile chronic arthritis.

Of the 28 children of the ADEM-cohort two had associated diseases: one, an idiopathic thrombocytopenic purpura, and one, a nephrotic syndrome.

Primary symptoms

In the MS-cohort, 67% of the patients had a polysymptomatic manifestation, most frequently with cerebellar (44%), sensory (39%) or visual (36%) symptoms, followed by brainstem (30%), pyramidal (29%) and cerebromental (22%) complaints (Fig. 3).

Within the group of the monosymptomatic patients, the presenting symptoms were most often visual (42%), followed by brainstem (21%), sensory (16%), cerebellar (9%), cerebromental (7%) and pyramidal (5%) symptoms.

There were no significant differences between the primary symptoms of girls and boys or between the different age groups.

In the ADEM-cohort, a polysymptomatic onset was reported for 86% of the patients. The most frequent symptoms were cerebellar, cerebromental or pyramidal, followed by brainstem and sensory disturbances (Fig. 3).

Table 2 provides an overview of the main features of the paediatric MS and ADEM patient cohorts.

Table 2 Outline of main features of the paediatric MS and ADEM patient cohorts

	MS	ADEM
Age (years)		
Range	3–15	1–14
Mean	12.1	6.6
Median	13	6
Female-to-male ratio	1.24:1	0.75:1
Polysymptomatic onset [*n* (%)]	88 (67%)	24 (86%)
CSF [*n* (%)]		
Pleocytosis	72 (55%)	17 (65%)
Oligoclonal IgG	89 (67%)	5 (19%)
MRI pathology [*n* (%)]		
Total	122 (92%)	28 (100%)
Supratentorial	116 (88%)	24 (86%)
Infratentorial	68 (52%)	18 (64%)
EP pathology [*n* (%)]		
Total	68 (62%)	8 (57%)
Visual EP	50 (45%)	5 (36%)
Somatosensory EP	31 (28%)	4 (29%)
Brainstem auditory EP	14 (13%)	1 (7%)

Paraclinical results

Analyses of cerebrospinal fluid (CSF)

In the MS-cohort, CSF data were available for all 132 patients. CSF leukocyte counts ranged from 0 to 200/μl (median: 7/μl) with a generally mild CSF pleocytosis in 72 children (55%). CSF protein ranged from 100 to 1120 mg/l (median: 320 mg/l), with 21 children (16%) showing values >500 mg/l. CSF oligoclonal immunoglobulin G (IgG) was reported in 89 patients (67%).

In the ADEM-cohort, CSF data were available for 26 of the 28 children (93%). CSF leukocyte counts ranged from 1 to 360/μl (median: 28/μl), with a CSF pleocytosis in 17 patients (65%). CSF protein ranged from 170 to 750 mg/l (median: 400 mg/l), with four children (15%) showing values >500 mg/l. CSF oligoclonal IgG was reported in five children (19%).

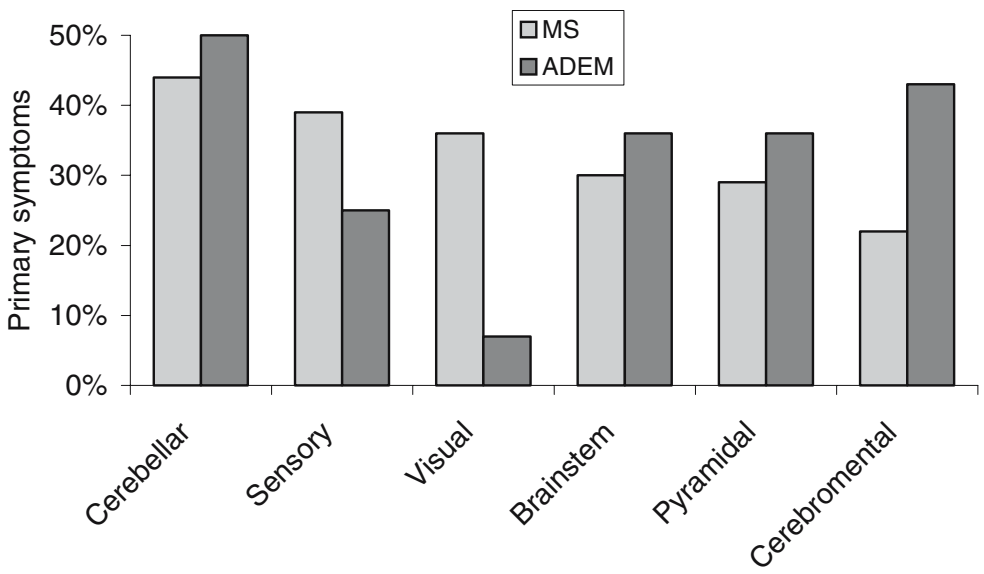

Fig. 3 Presenting features of the patients reported with MS or ADEM

Magnetic resonance imaging (MRI)

In the MS-cohort, 122 of the 132 children (92%) were reported to have MRI scans that revealed pathology, with supratentorial lesions in 116 patients (88%), infratentorial lesions in 68 patients (52%) and lesions in both regions in 64 patients (48%). Subgroup analyses of girls and boys as well as of children under the age of 10 years and from 10 to 15 years revealed no significant differences.

In the ADEM-cohort, all of the 28 children had MRI scans that revealed pathology, with supratentorial lesions reported in 24 patients (86%), infratentorial lesions in 18 patients (64%) and lesions in both regions in 16 children (57%).

Evoked potentials (EP)

Evoked potentials were examined in 110 of 132 children of the MS-cohort. Abnormal EP findings were reported in 68 of these 110 children (62%), with 50 children (45%) showing pathologic visual EP, 31 children (28%) with pathologic somatosensory EP and 14 children (13%) exhibiting pathologic brainstem auditory EP. Of the 50 patients with pathologic visual EP findings, only 29 (58%) were reported to have acute or anamnestic visual complaints.

Evoked potentials were analysed in 14 of 28 children of the ADEM-cohort. Pathologic EP findings were reported in eight of these patients (57%), among them five children with pathologic visual EP (36%), four patients with pathologic somatosensory EP (29%) and one child with pathologic brainstem auditory EP (7%).

Follow-up evaluation

In the follow-up study 2 years after the first evaluation, 68 questionnaires (43%) were returned, 55 for the MS-cohort (42%) and 13 of the ADEM-cohort (46%).

Diagnosis Of the 68 children for whom there were available follow-up data, 51 were reported to have a diagnosis of MS or suspected MS and 13 to have ADEM or suspected ADEM. The initial diagnosis was changed in 14 of the 68 children of the follow-up group – in five children from MS to ADEM, in three children from MS to recurrent optic neuritis, in one child from MS to Myasthenia gravis and in five children from ADEM to MS.

Disease course Of the 51 children with the follow-up diagnosis of MS or suspected MS, 48 (94%) were reported to have a relapsing-remitting disease course and three children (6%) to have a primary progressive course. No child with secondary progressive MS was reported. The patients with a primary progressive course were two boys (age 11 and 14 years) and one girl (age 15 years), all showing polysymptomatic manifestation with pyramidal and cerebellar symptoms, CSF oligoclonal IgG, pathologic visual EPs and combined supra- and infratentorial lesions as diagnosed by MRI.

Attack rate The 48 patients with relapsing-remitting MS had a mean attack rate of 2.1 (range: 1–5) in the first year of disease manifestation and of 0.7 (range: 0–4) in the second year. During the first 2 years of the disease, seven patients (15%) had three to four relapses and two patients (4%) had more than four relapses.

Relapse symptoms Frequent relapse symptoms were cerebellar (54%), sensory (54%), visual (50%), pyramidal (48%), and brainstem (46%) disorders. Concomitant cerebromental symptoms were reported in 35% of the patients.

Attack recovery Data concerning the recovery from attacks within the first 2 disease years were available for 43 of the 48 relapsing-remitting MS patients of the follow-up group. Of these patients, 27 (63%) showed complete recovery in the inter-attack-intervals. Residual deficits were reported in 16 (37%) patients. The group of patients with residual deficits showed a trend to more attacks during the first 2 disease years compared to the group of patients with full recovery (4.6 vs. 2.8 attacks).

Discussion

This prospective survey carried out in Germany provides the first national-level data on the incidence of paediatric MS and ADEM, and reveals an unexpectedly high incidence of paediatric MS in Germany. An average of 44 new paediatric MS patients per year were reported, and this number probably underestimates the true incidence of paediatric MS due to referral, diagnostic and reporting biases: some children, especially adolescents, are cared for in adult neurology departments, which were not covered by this survey, while others might have escaped our survey by receiving outpatient treatment without hospitalisation (referral bias). Our own experience shows that a large number of paediatric MS cases are still misdiagnosed or misclassified as ADEM (diagnostic bias). The return rate of our questionnaire was only 87% and, additionally, not all diagnosed cases of ADEM or MS are likely to have been reported (reporting bias). In similar ESPED studies, the reporting rates estimated by capture-recapture analysis were in the range of 30–80%. For these reasons, the figure of 44 new paediatric MS cases per year represents a minimum estimate of the incidence in Germany.

In contrast, the number of reported paediatric ADEM patients was low, with an average of only nine children per year in Germany. Although the real number of ADEM patients might be higher, the underestimation is probably lower than that for paediatric MS patients: paediatric ADEM patients were reported to be significantly younger than paediatric MS patients, which minimises the probability that these children have been treated in adult neurology departments that were not covered by our survey. In addition, ADEM presents often polysymptomatic with encephalopathy, making an exclusively ambulant treatment unlikely. Consequently, the underestimation of incidence would be less pronounced for paediatric ADEM than for paediatric MS, thereby further accentuating the strikingly higher frequency of paediatric MS. A recent study in San Diego County, California, found an incidence of ADEM of 0.4/100,000 per year among persons <20 years, with a peak incidence of 0.8/100,000 per year for the age strata of children between 5 and 9 years old [16]. While this incidence peak is in accordance to our findings, the total incidence is about tenfold higher than the reported incidence in Germany. This may point to geographical differences in the incidence of ADEM that could be in favour of an environmental factor triggering the disease. Further studies are needed to look for a possible north-south-gradient, which might be inverse to the prevalence gradient of MS.

There was a peak incidence for MS in 13- to 15-year-old adolescent group, whereas the reported incidence of MS in preschool children was very low. The absolute numbers of reported MS and ADEM cases were nearly identical in the under 9-year-olds, whereas there was a steep rise of MS and a decline of ADEM incidence in older children. This phenomenon may only partly be explained by the fact that older patients are more likely to be diagnosed with MS as a consequence of a longer time-frame for relapse. Even if all reported ADEM cases were in fact MS patients, the remaining increase of MS incidence during puberty would still be noticeable. Remarkably, the female-to-male ratio was balanced up to the age of 13 years, but more than twice as many girls than boys were reported in the 14- to 15-year-old group of children. This frequency distribution has also been observed by others [3, 7–9, 11, 27, 28] and points to the disease-enhancing effects of hormonal factors acting in puberty.

Studies in adult MS patients have revealed that 15–20% have affected family members with MS [24]. This percentage is strikingly higher than the 5% found in our survey. Other studies on paediatric MS have also reported a rather low prevalence of a positive family history for MS, ranging from 6 to 23% [1, 5, 7, 19, 27]. Hence, the genetic burden does not seem to be higher in paediatric onset MS than in adult onset MS. However, the low rate of affected family members may also be an underrepresentation, given the young age of paediatric MS patients: their siblings have not yet reached the peak incidence age of MS (20–40 years), and even many of their parents and second-degree relatives are in a high-risk age and may still develop the disease.

The incidence of reported associated autoimmune diseases in German paediatric MS patients was high compared to the low prevalence rate in the general paediatric population: two children (1.5%) had diabetes type 1 (age-matched prevalence in Germany: 0.09–0.14%) [23], and one patient (0.8%) was suffering from juvenile chronic arthritis (age-matched prevalence in Germany: 0.015–0.02%) [15, 30]. However, due to the low numbers, our findings may simply be coincidental.

Although it has been pointed out that paediatric MS and adult onset MS are principally the same disease [13], our survey revealed some differences with regard to the clinical characteristics. In adult onset MS patients, a polysymptomatic manifestation is observed in only 35–43% of the MS patients [1, 25, 27], whereas it was reported in 67% of the ESPED paediatric MS-cohort. Other studies on paediatric MS have shown lower frequencies, ranging from 10 to 44%, but these studies were mostly retrospective [3, 8, 9, 11, 27]. Remarkably, recently published preliminary results of a prospective study on paediatric MS in Canada reported a monosymptomatic presentation in only 36% of the patients, which is close to the 33% of our study [1].

Relative to findings on adult MS in Germany, this study revealed similar frequencies of symptoms at primary manifestation, with the exception of a higher frequency of cerebellar symptoms and a lower frequency of pyramidal symptoms [22]. In accordance with these findings, a study has just been published in which cerebellar and brainstem symptoms were reported to be the most frequent initial presentation of paediatric MS, appearing significantly more frequently in paediatric MS patients than in a control adult onset MS population [27]. Additionally, several studies of paediatric MS point to a lower incidence of primary motor symptoms in paediatric MS patients than in adult onset MS [3, 7, 8, 11, 19, 27, 28].

The CSF findings in the MS-cohort show leukocyte counts comparable to those reported in other studies of paediatric MS. In contrast, the reported frequency for oligoclonal IgG of only 67% is strikingly lower than the 92% we detected in the CSF specimens studied in our department, and also lower than the 75–91% frequencies that have been reported by others [7, 9, 19, 20, 26, 28]. Since the methods of CSF analysis were not evaluated in our questionnaire, the application of low-sensitivity methods cannot be excluded. It is now well known that the

"state of the art method" of immunoblot after isoelectric focusing is about twice as sensitive as agarose gel electrophoresis [17]. In the ADEM-cohort, CSF oligoclonal IgG was reported in only 19% of the patients. This finding is in accordance to the low frequencies found in other studies [4, 6, 10, 14, 16, 18, 29].

As many as 62% of the children in the MS-cohort were reported to have pathologic EPs. Visual EPs were the most frequently observed pathologic EP, which is in accordance with previous studies of paediatric MS patients [12, 19, 21]. Optic neuritis as an initial symptom in early onset MS has been reported with frequencies ranging from 14 to 23% in larger studies [3, 7, 27]. In view of the ESPED findings of 45% of paediatric MS patients showing pathologic VEP after their first attack, with only 58% of these patients complaining of prior visual disturbances, optic neuritis could be an underreported symptom in childhood MS. A possible explanation for this phenomenon is a less precise recognition of visual acuity loss, especially in younger children. In unilateral optic neuritis in particular, the functional impact is generally low and not easily recognisable by parents.

Only three (6%) of the reported MS paediatric patients had a primary progressive course, in comparison to approximately 20% in an adult MS population. No primary progressive courses were registered below the age of 10 years. These findings are in agreement with most cohort studies on paediatric MS, which have reported low frequencies for primary progressive courses ranging from 0 to 7% [1, 3, 9, 11, 19, 26–28]. An age-dependent increase in the rate of primary-progressive courses is well known in the adult MS population [2, 32]. Taken together, these data point to a continuum of an age-dependent increase in the rate of primary progressive courses, starting with a very low frequency when the disease onset is before puberty and reaching a maximum after the fifth decade of life.

In comparison to other studies on paediatric MS, the reported attack rate of the MS-cohort was low. Interestingly, regional differences in the relapse rate of paediatric MS patients have already been described: a comparison between cohorts from Moscow and Vancouver showed significantly more relapses in the Russian than in the Canadian children. During the first 2 years of the disease, 73% of the Russian, but only 48% of the Canadian patients had two or more relapses [11]. A low initial relapse rate is associated with a better prognosis in paediatric MS [3, 27].

Conclusion

In summary, the incidence of paediatric MS in Germany is much higher than previously expected. Although it is principally the same disease as MS in adults, some important differences exist, especially with respect to gender distribution (balanced before the age of 14) and course (few primary chronic cases). The number of reported paediatric ADEM in Germany is low, possibly reflecting regional differences in the incidence of ADEM. Further studies are needed to look for a possible north-south-gradient that may be inverse to the prevalence gradient of MS. Follow-up studies on the course and outcome of paediatric MS in Germany are currently in progress.

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