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Clinical and magnetic resonance imaging features of children, adolescents, and adults with a clinically isolated syndrome

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Abbreviations: acute disseminated encephalomyelitis, ADEM; cerebrospinal fluid, CSF; clinically definite multiple sclerosis, CDMS; clinically isolated syndrome, CIS; dissemination in space, DIS; dissemination in time, DIT; expanded disability status scale, EDSS; fluid-attenuated inversion recovery, FLAIR; gadolinium enhancement, Gd+; magnetic resonance imaging, MRI; multiple sclerosis, MS; negative predictive value, NPV; neuromyelitis optica spectrum disorders, NMOSD; oligoclonal bands, OCB; positive predictive value, PPV.

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1. Introduction

Pediatric multiple sclerosis, defined as the onset of the disease before the age of 18 years, accounts for 3–5% of multiple sclerosis (MS) cases,[1–3] whereas the pre-pubertal onset of MS is even more uncommon, accounting for 20–30% of pediatric MS cases.[4] While it is unclear whether the pathogenesis of the disease is the same in all age groups, several differences between children and adults with respect to clinical course, magnetic resonance imaging (MRI) parameters, and cerebrospinal fluid (CSF) findings have been reported.[5–11] However, direct comparisons of imaging features between children and adults are rare and have shown divergent results.[8,12] More recent data have suggested even greater clinical, imaging, and laboratory differences between pre-pubertal children and adolescents than between adolescents and adult MS patients, with the onset of puberty playing a critical role.[4,13] For example, younger children present more often with a polyfocal onset,[14] tumefactive lesions that vanish over time,[15] and polynuclear cells in the CSF,[16] while post-pubertal patients show features comparable to those seen in their adult counterparts.[4] We therefore compared the clinical, CSF, and imaging features in a cohort of 113 patients with a clinically isolated syndrome (CIS) classified into three age groups: pre-pubertal children; adolescents; and adults. We further compared in these patients the value of the revised 2010 McDonald MRI criteria with respect to the development of clinically definite MS (CDMS) in the respective age groups.

2. Patients and methods

2.1. Patients

We performed a retrospective analysis of 57 pediatric and 56 adult patients with typical features of a CIS (e.g. optic neuritic, transverse myelitis, brainstem/cerebellar syndrome or symptoms attributed to the cerebral hemipheres, like hemiparesis or hemyhypästhesia) according to the consensus criteria for children[17] and adults.[18] The pediatric patients (with disease onset before 18 years) were recruited from seven participating centers in Austria and Germany. They were divided into two groups: one group with disease onset prior to age 13, i.e., puberty[19,20] (pre-pubertal children, n = 11) and one group with disease onset between 13 and 18 years (adolescents, n = 46). The adult patients (age 18 years or older, n = 56) were selected from the database of the Department of Neurology, Medical University of Vienna. All patients were diagnosed and seen between September 2000 and June 2015. Only patients with an initial brain and spinal cord MRI scan obtained within three months after symptom onset were included in the study. Patients who presented with clinical features of acute disseminated encephalomyelitis (ADEM)[17,21] or with neuromyelitis optica spectrum disorders (NMOSD)[22] and/or antibodies against AQ-4 were excluded. MOG-antibody testing was not routinely performed in the patients. We did not exclude patients presenting with optic neuritis or with transverse myelitis and with normal brain or spine MRI. Thus, a total of 6 children/adolescents had no lesions on brain MRI and 1 out of those had no spinal cord lesions. In 3 of these patients there was no spinal MRI available. A total of 5 adult patients had no lesions on brain MRI and 2 out of them had no spinal cord lesions. In 1 adult patient there was no spinal MRI available.

The presence of oligoclonal bands (OCB) in the cerebrospinal fluid (CSF) was recorded. Disability was measured according to the Expanded Disability Status Scale scores (EDSS).[23]

The study was approved by the local institutional review board.

2.2. MR imaging

A standardized MRI protocol was not used, as this was a retrospective study based on scans performed for clinical practice. All MRI examinations were obtained on 1.5 or 3T MR scanners, and with variable pulse sequence parameters. Minimum protocol for the inclusion in the study required the following sequences[1]: for the brain scans, T2-weighted or fluid-attenuated inversion recovery (FLAIR) in at least two orthogonal planes, and T1-weighted sequences before and

after intravenous gadolinium administration; and[2] for the spinal cord scans, sagittal T2-weighted and T1-weighted sequences before and after intravenous gadolinium administration. Axial T2-weighted spinal cord scans were reviewed when they were available. The slice thickness had to be no more than 5 mm. Only lesions with a diameter ≥3 mm were counted. Lesions with gadolinium enhancement (Gd+) were also detected on T2-weighted or FLAIR sequences.

Altogether, we collected 11 brain scans and nine spinal cord scans (seven scans of the entire spine, one scan of the cervical and upper thoracic spine, and one scan of the thoracic and lumbar spine) in the group of pre-pubertal children, 46 brain scans and 39 spinal cord scans (28 scans of the whole spine, six scans of the cervical and upper thoracic spine, four scans of only cervical spine, and one scan of the thoracic and lumbar spine) in the group of adolescents, and 56 brain scans and 41 spinal cord scans (21 scans of the entire spine, 17 scans of the cervical and upper thoracic spine, three scans of only cervical spine) in the group of adult patients.

On the brain scans, we assessed the following parameters: the percentage of patients with abnormal examinations; the overall number of focal T2-weighted hyperintense lesions; the presence and number of Gd+ lesions; the presence of confluent or giant (≥2 cm diameter[24]) lesions; and the lesion distribution according to the MS characteristic locations[25] (i.e., periventricular, juxtacortical, infratentorial, as well as corpus callosum lesions). On the spinal cord scans, we evaluated the percentage of patients with an abnormal examination, the number and size of focal T2-weighted lesions, the distribution of focal lesions according to the spinal cord segment, the presence of diffuse abnormalities and of longitudinally extensive transverse myelitis (demonstrating involvement of ≥3 spinal cord segments), the presence and number of Gd+ lesions. All scans were scored by one radiologist (RI.M.) blinded to the clinical outcome and reviewed by an experienced neuroradiologist (D.P.).

The diagnostic performance of the revised 2010 McDonald MRI criteria for conversion to CDMS was also compared between the three groups. The term "CDMS" was used for patients with two or more clinical attacks (pre-pubertal children: n = 3, adolescents: n = 31 and adults: n = 33). Only patients who developed a second attack and/or were followed-up for at least 24 months were included (pre-pubertal children: n = 8, adolescents: n = 40 and adults: n = 43) into the analysis of the McDonald criteria, regardless of the use of immunomodulatory treatment. For the evaluation of the 2010 McDonald criteria for dissemination in time (DIT), we only used the initial scan if imaging was performed after the application of gadolinium.

2.3. *Statistical analysis*

All calculations and statistical analyses were performed by an independent statistician (M.W.) using IBM SPSS Statistics version 22.0. Categorical variables are presented as absolute numbers frequency and percentages, continuous variables as means ± standard deviation if normal distributed or medians and range (given skewed data). In order to compare the three groups either Kruskal–Wallis tests (for metric but skewed data) or chi^2 tests (for categorical data) were used. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy, with corresponding 95% confidence intervals, were calculated for the performance of the 2010 McDonald criteria. P values equal or less than 0.05 were considered indicative of a significant difference.

3. Results

3.1. *Clinical features*

The demographic and clinical characteristics of the three groups are summarized in Table 1 and Fig. 1. Pre-pubertal children were more likely to present with brainstem and cerebellar syndromes (45.5%) than adolescents (17.4%) or adults (17.9%), while adolescents and adults predominantly presented with optic neuritis (34.8% and 28.6% vs. 9.1% for children), but the difference did not reach statistical significance. There was a trend towards a constantly increasing first interattack interval in the pre-pubertal children (six months), to adolescents (9.9 months) and adults (17.9 months), even if the difference did not reach statistical significance.

Table 1 – Clinical characteristics.

Parameters	Children (<13 y)	Adolescents (13–17 y)	Adults (≥18 y)	p
Total number of patients	11	46	56	
Mean age at first attack, years ± SD	11.2 ± 1.4	15.2 ± 1.3	30.2 ± 7.6	<0.0001
Gender, female, n (%)	6 (54.5)	28 (60.9)	32 (57.1)	0.887
Mean time from first attack to second attack, months ± SD (range)	6 ± 3 (3–9)	9.9 ± 11.7 (2–48)	17.9 ± 16.3 (2–62)	0.084
Mean time from first attack to first brain MRI, months ± SD (range)	0.8 ± 1.1	0.5 ± 0.9	0.5 ± 0.7	0.603
Mean time from first attack to first spinal MRI, months ± SD (range)	1.1 ± 1.2	0.6 ± 0.9	0.6 ± 0.8	0.459
CSF OCB-positive, n (%)	8 (72.7)	41 (89.1)	37 (72.5)	0.077
EDSS at most recent clinical visit, median (range)	0.0 (0.0–3.0)	1 (0.0–3.0)	1 (0.0–4.0)	0.278
Mean follow-up time, months ± SD	35.5 ± 29.2	38.8 ± 24.5	55.7 ± 44.9	0.304
Presentation at onset				
Optic neuritis, n (%)	1 (9.1)	16 (34.8)	16 (28.6)	.344
Transverse myelitis, n (%)	3 (27.3)	9 (19.6)	19 (33.9)	
Brainstem/cerebellar, n (%)	5 (45.5)	8 (17.4)	10 (17.9)	
Cerebral hemispheres, n (%)	1 (9.1)	8 (17.4)	8 (14.3)	
Multifocal, n (%)	1 (9.1)	5 (10.9)	3 (5.4)	

CSF: cerebrospinal fluid; OCB: oligoclonal bands; EDSS: Expanded Disability Status Scale.

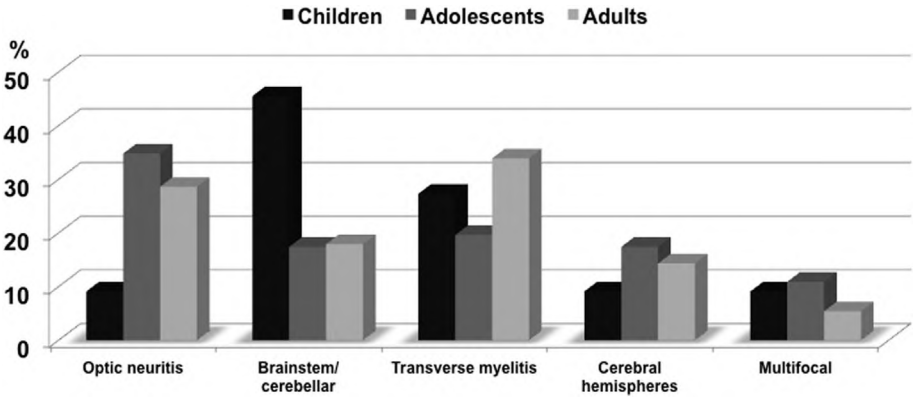

Fig. 1 – Clinical presentation at onset.

There were no statistically significant differences between the three groups regarding gender ratio, proportion of patients with positive OCB, or disability scores.

3.2. *Patterns of initial brain MRI findings*

The characteristics of brain MRIs are presented in Table 2 and Fig. 2. In all groups, the majority of patients presented with an abnormal initial brain MRI, with at least one T2-hyperintense lesion (72.7%, 93.4%, and 91%, respectively). In children juxtacortical and callosal lesions were less common ($P = 0.028$ and .007, respectively).

In contrast, there were no significant differences between the three groups regarding the total number of T2-hyperintense focal lesions, the number of supratentorial and infratentorial T2-hyperintense lesions, the number of Gd+ lesions, and the proportion of patients with periventricular, confluent, and giant lesions.

3.3. *Patterns of initial spinal cord MRI findings*

The MRI features of the spinal cord lesions are presented in Table 2 and Fig. 3. There were nine children ($n = 8$ focal lesions), 39 adolescents ($n = 65$ focal lesions), and 41 adults ($n = 53$ focal lesions) who received initial spinal cord examinations. The proportion of patients with an abnormal initial spinal cord scan did not differ significantly between the three groups, $P = 0.452$. The majority of lesions were focal lesions. Diffuse spinal cord abnormalities tended to be more common in children. There were 2 children, 4 adolescents and 2 adults with LETM. Of these, only one child had normal brain MRI at onset and only the 2 children did not present with OCB in CSF. In all three groups, the majority of lesions were located in the cervical spine (Fig. 3). There were no lumbar lesions observed in children or adult patients. There were no significant differences between the groups regarding the number and size of focal lesions, Gd+ lesions, and lesion distribution.

3.4. *Evaluation of 2010 McDonald criteria*

We evaluated the performance of the 2010 McDonald criteria with regard to the development of CDMS, based on the initial brain and spinal cord MRI scans (Table 3). We identified eight children, 40 adolescents, and 43 adult patients who developed a second attack or who had a follow-up of 24 months or more. Dissemination in space (DIS) was found in all these patients, while dissemination in time (DIT) could be detected in only eight children, 38 adolescents, and 36 adult patients because not all patients received contrast at the initial scan. Altogether, three (37.5%) children, 31 (81.5%) adolescents, and 33 (91.6%) adults developed CDMS over a period of 24 months.

Most of the patients fulfilled the DIS criteria (75% of the children, 90% of the adolescents, and 90.7% of the adults), while only 50% of the children, 52.6% of the adolescents, and 41.6% of the adults fulfilled the DIT component at the initial MRI scan. DIT was never positive in patients who were DIS negative; therefore, for the combined DIS and DIT components, the results were similar to those for the fulfillment of DIT alone.

The 2010 McDonald criteria for DIS showed a high sensitivity in all three groups (100% in children and adolescents and 96.8% in adults), but a low specificity (40% in children, 44.4% in adolescents, and 25% in adults). The DIT component of the McDonald criteria showed a lower sensitivity (66.7% in children, 65.5% in adolescents, and 50% in adults, respectively), but a higher specificity (60% in children, 88.9% in adolescents, and 87.5% in adults, respectively) compared to the DIS criteria. Again, for both DIS and DIT, the results were similar to those obtained for the DIT criteria alone. Both the DIS and DIT components demonstrated high PPV in adolescents and adults (95% and 93.3%, respectively), but this was considerably lower in younger children (50%). NPV demonstrated decreasing values for children (75%), adolescents (44.4%), and adults (33.3%).

4. Discussion

In the present study, we compared the initial clinical presentation, CSF results, and neuroimaging findings, as well as the performance of the 2010 McDonald criteria between prepubertal children, adolescents, and adults with a CIS who were at risk for MS. The landmark of 13 years, dividing pre- and postpubertal patients, was defined according to published data that reported an average age for the onset of puberty of

Table 2 – MRI characteristics on the initial scan.

Parameters	Children (<13)	Adolescents (13–17 y)	Adults (≥18 y)	p
Brain MR imaging findings (n)	11	46	56	
Patients with abnormal examinations, n (%)	8 (72.7)	43 (93.4)	51 (91)	.121
Total number of focal T2 lesions, median (range)	4 (0–32)	13 (0–67)	9.5 (0–68)	.217
Number of supratentorial lesions, median (range)	6.5 (0–30)	12 (0–63)	9 (0–67)	.358
Number of Gd+ lesions, median (range)	0 (0–8)	1 (0–35)	1 (0–23)	.887
Number of infratentorial lesions, median (range)	1 (0–2)	0.5 (0–8)	0 (0–7)	.185
Patients with Gd+ lesions, n (%)[a]	4/11 (63.4)	22/42 (52.4)	25/48 (52.1)	.687
Patients with periventricular lesions, n (%)	7 (63.6)	41 (89.1)	46 (82.1)	.110
Patients with juxtacortical lesions, n (%)	6 (54.5)	41 (89.1)	44 (78.6)	.028
Patients with infratentorial lesions, n (%)	6 (54.5)	23 (50)	19 (33.9)	.167
Patients with lesions of corpus callosum, n (%)	2 (18.2)	32 (69.6)	34 (60.7)	.007
Patients with confluent lesions, n (%)	2 (18.2)	5 (10.9)	4 (7.1)	.407
Patients with giant lesions (Ø ≥ 2 cm), n (%)	4 (36.4)	8 (17.4)	14 (25)	.325
Spinal cord imaging findings (n)	9	39	41	
Patients with abnormal examinations, n (%)	3 (33.3)	22 (56.4)	24 (58.5)	.452
Number of focal T2 lesions, median (range)	0 (0–5)	1 (0–10)	1 (0–7)	.459
Patients with LETM, n (%)	2 (22.2)	4 (10.3)	2 (4.9)	.165
Size of focal T2 lesions (mm), mean ± SD	15.12	13.0	13.0	.135
Patients with diffuse abnormalities only, n (%)	1 (11.1)	2 (5.1)	0 (0)	.082
Patients with Gd+ lesions, n (%)[b]	0 (0)	7/32 (21.9)	12/35 (34.3)	.105
Number of Gd+ lesions, median (range)	0	0 (0–8)	0 (0–3)	.148
Lesion distribution, n (%)				
Cervical spine	1 (25)	10 (45.5)	12 (50)	.243
Thoracic spine	1 (25)	1 (4.5)	5 (20.8)	
Cervical and thoracic spine	2 (50)	8 (36.4)	7 (29.2)	
Cervical, thoracic and lumbar spine	0 (0)	3 (13.6)	0 (0)	

Gd+: gadolinium enhancement; LETM: longitudinally extensive transverse myelitis.
[a] Four adolescents and eight adult patients did not receive gadolinium.
[b] Seven adolescents and six adult patients with spinal cord scans did not receive gadolinium.

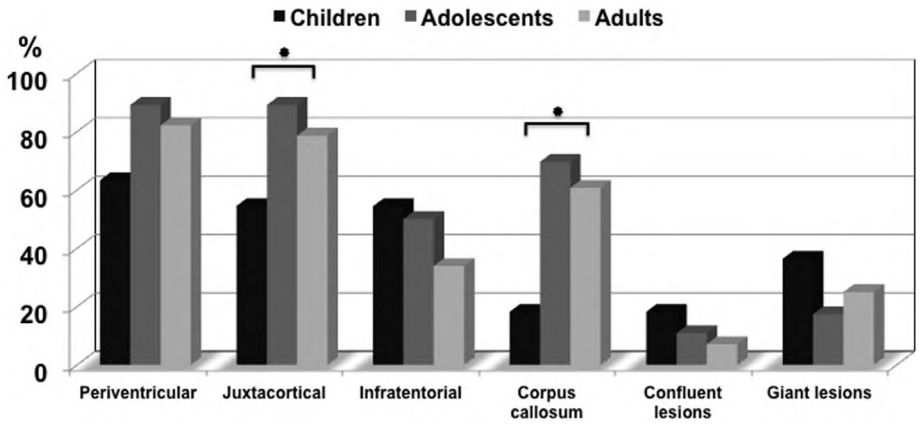

Fig. 2 – Distribution and morphology of cerebral lesions.

12.4 years in MS females[20] and a mean menarchal age of 12–13 years in developed countries.[19]

We found distinct clinical and imaging features in the different age groups, thus suggesting that puberty may influence these phenotypic differences. Optic neuritis tended to be less common in younger children, while brainstem/cerebellar involvement tended to be more common in this age group, as suggested previously.[2,26] Several studies showed that young children tend to present more with polyfocal clinical symptoms,[26,27] a finding which we could not confirm in our cohorts. We also observed an increasing time interval between the first to the second clinical attack with age progression, which confirms previous data that children have a higher annual relapse rate in the initial phase of the disease compared to adults,[7,27] which appears to reflect increased inflammatory activity in children.[27] Also van der Vuurst de Vries et al. found the highest annual relapse rate in 1-10-year-old children with MS.[27] Our results are, however, in contrast with the findings of Huppke et al., who observed a similar first inter-attack interval between pre-pubertal and adolescent patients with a relapsing-remitting disease course.[26] Sex ratios did not differ significantly between our groups, with an even gender ratio before puberty (54.5%), and a slight female preponderance in the adolescent (60.9%) and adult (57.1%) patients. The data

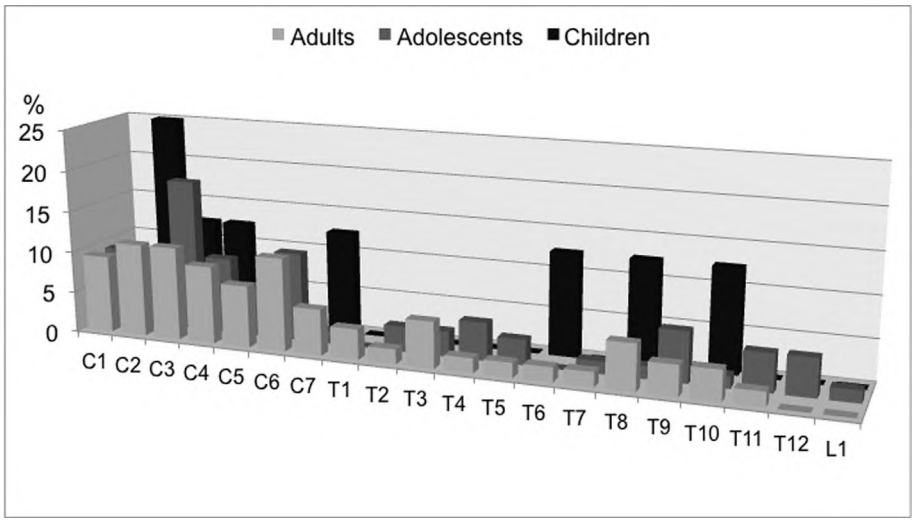

Fig. 3 – Distribution of focal spinal cord lesions according to the vertebral segment.

Table 3 – Performance of the 2010 McDonald criteria for CDMS.

2010 McDonald Criteria	Children (<13 y)	Adolescents (13–17 y)	Adults (≥18 y)	p
DIS positive, n (%)	6 (75)	36 (90)	39 (90.7)	.413
DIT positive, n (%)	4 (50)	20 (52.6)	15 (41.6)	.634
DIS and DIT positive, n (%)	4 (50)	20 (52.6)	15 (41.6)	.634
Sensitivity				
DIS (%, 95% CI)	100.0 (43.8–100)	100.0 (89–100)	96.8 (83.8–99.4)	1.000
DIT (%, 95% CI)	66.7 (20.8–93.9)	65.5 (47.3–80.1)	50.0 (32.6–67.4)	.514
DIS and DIT (%, 95% CI)	66.7 (20.8–93.9)	65.5 (47.3–80.1)	50.0 (32.6–67.4)	.514
Specificity				
DIS (%, 95% CI)	40.0 (11.8–76.9)	44.4 (18.9–73.3)	25.0 (8.9–53.2)	.569
DIT (%, 95% CI)	60.0 (23.1–88.2)	88.9 (56.5–98)	87.5 (52.9–97.8)	.493
DIS and DIT (%, 95% CI)	60.0 (23.1–88.2)	88.9 (56.5–98)	87.5 (52.9–97.8)	.493
PPV				
DIS (%, 95% CI)	50 (18.8–76.9)	86.1 (71.3–93.9)	76.9 (61.7–87.4)	.152
DIT (%, 95% CI)	50 (15.5–85.0)	95 (76.4–99.1)	93.3 (70.2–98.8)	.077
DIS and DIT (%, 95% CI)	50% (15.5–85.0)	95% (76.4–99.1)	93.3% (70.2–98.8)	.077
NPV				
DIS (%, 95% CI)	100 (34.2–100)	100 (51.0–100)	75 (30.1–95.4)	.980
DIT (%, 95% CI)	75 (30.1–95.4)	44.4 (24.6–66.3)	33.3 (17.2–54.6)	.334
DIS and DIT (%, 95% CI)	75 (30.1–95.4)	44.4 (24.6–66.3)	33.3 (17.2–54.6)	.334
Accuracy				
DIS (%, 95% CI)	62.5 (30.6–86.3)	87.5 (73.9–94.5)	76.7 (62.3–86.8)	.197
DIT (%, 95% CI)	62.5 (30.6–86.3)	71.1 (55.2–83)	58.3 (42.2–72.9)	.526
DIS and DIT (%, 95% CI)	62.5 (30.6–86.3)	71.1 (55.2–83)	58.3 (42.2–72.9)	.526

DIS: dissemination in space; DIT: dissemination in time; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

regarding gender distribution of MS patients is controversial, with some reports describing an increased female: male ratio in pediatric MS, including pre-as well as post-pubertal onset,[5] while others reporting an equal sex ratio in cases with pre-pubertal onset and an increased female risk after puberty.[2,27–29] These findings raise the question of whether female pubertal sex hormones represent a risk factor for developing MS.[30] Finally, the CSF analysis revealed no difference in the detection rate of OCB between the groups at the time of the first attack, a finding previously reported also by Reiber et al., who showed that the neuroimmunological patterns of CSF in pediatric MS do not differ qualitatively from the CSF patterns in adults.[11]

There is sparse and diverging published data regarding the quantitative differences in lesion burden and activity on MRI at the initial stage of disease between pediatric and adult onset MS,[8,12] and, to our knowledge, no direct comparison between children, adolescents, and adults has been so far performed. While the groups differed with respect to the presence of juxtacortical and callosal lesions, we otherwise found a similar pattern of lesion distribution and activity in all age groups, supporting a common initial biology of disease. Consistent with data published by Chabas et al.,[15] the overall number of brain lesions was comparable between pre-pubertal children and adolescents, as well as adults. We also noticed that confluent lesions in children were more

frequently present, even if our results did not reach statistical significance. Our results did not show significant differences between the three groups regarding the number of supratentorial, infratentorial lesions or Gd+ lesions. These results are in contrast with former observations that showed a predilection for infratentorial lesions and gadolinium-enhancing lesions in pediatric patients.[8,9] Regarding the lesion distribution typical for MS, we found that significantly fewer prepubertal children showed juxtacortical lesions, compared with adolescents, and corpus callosum lesions, compared with adolescents and adults.

The type and distribution of spinal cord lesions was comparable in our cohorts with predominantly focal lesions preferentially involving the cervical region, similar to previous reports.[31,32] Consistent with the data of Verhey et al., we also noticed the presence of diffuse lesions more often in children than in adolescents and adults; however, we did not find a significant difference between the groups.

Based on the results with regard to number, distribution, and Gd-enhancement of brain and spinal lesions in our cohorts, we further compared the performance of the revised McDonald criteria 2010[25] between the three groups. In all three groups of patients, the 2010 criteria for DIS were sensitive, but less specific, whereas the DIT component was less sensitive, but more specific. Combining DIS and DIT criteria yielded same results as those obtained for the DIT criteria.

The revised McDonald criteria 2010 have been established in adult patients with a typical CIS, and have also been applied in pediatric patients. The already published data show that, in children, the revised 2010 criteria were met in around 60% of patients on the initial scan[33,34] and the criteria showed a 63–100% sensitivity and an 80–100% specificity for CDMS,[31,35] with a better performance in adolescents compared to prepubertal children.[35] The low sensitivity of the DIT component in our results may also be due to the fact that we analyzed only the baseline scan and it has been shown that the sensitivity of DIT can increase on follow-up scans.[33,34] Given the low specificity of the DIS criteria and the sensitivity of DIT criteria in our cohorts, it seems, therefore, that a diagnosis of MS based on the findings of a single scan is not recommended. Despite comparable sensitivity and specificity, PPV of the 2010 criteria was lower in pre-pubertal children compared to adolescents and adults, even if it did not reach statistical significance, possibly because of the small sample size. Similar findings were also reported by Sadaka et al.,[35] thus suggesting caution when applying the 2010 criteria in young children.

The limitations of this study include its retrospective nature, the small cohort of young children; the great proportion of adolescents and adults who developed MS, thus not being able to evaluate the 2010 McDonald criteria in patients with monophasic inflammatory demyelination; the lack of contrast administration and the lack of entire spinal cord imaging in all patients at the initial MRI scan; the administration of disease-modifying therapy before the second attack in some patients; and the use of different scanners and imaging protocols in the various institutions.

In summary, we could show that, at the initial stage of the disease, there are subtle phenotypic differences in prepubertal patients compared to post-pubertal and adult patients, with respect to clinical and neuroimaging features, thus suggesting that puberty may influence these differences. Furthermore, our results on the performance of 2010 McDonald criteria suggest that they should be applied with caution in pre-pubertal children.

Conflict of interest

The authors report no conflict of interest.

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