European Journal of Paediatric Neurology 41 (2022) 8–18

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

journal homepage: www.journals.elsevier.com/european-journal-of-paediatric-neurology

Re-examining the characteristics of pediatric multiple sclerosis in the era of antibody-associated demyelinating syndromes

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ARTICLE INFO

Keywords:
Pediatric multiple sclerosis
Anti-MOG-IgG
Anti-AQP4-IgG
Antibody
Demyelinating

ABSTRACT

Background: The discovery of anti-myelin oligodendrocyte glycoprotein (MOG)-IgG and anti-aquaporin 4 (AQP4)-IgG and the observation on certain patients previously diagnosed with multiple sclerosis (MS) actually have an antibody-mediated disease mandated re-evaluation of pediatric MS series.
Aim: To describe the characteristics of recent pediatric MS cases by age groups and compare with the cohort established before 2015.
Method: Data of pediatric MS patients diagnosed between 2015 and 2021 were collected from 44 pediatric neurology centers across Türkiye. Clinical and paraclinical features were compared between patients with disease onset before 12 years (earlier onset) and ≥12 years (later onset) as well as between our current (2015–2021) and previous (<2015) cohorts.
Results: A total of 634 children (456 girls) were enrolled, 89 (14%) were of earlier onset. The earlier-onset group had lower female/male ratio, more frequent initial diagnosis of acute disseminated encephalomyelitis (ADEM), more frequent brainstem symptoms, longer interval between the first two attacks, less frequent spinal cord involvement on magnetic resonance imaging (MRI), and lower prevalence of cerebrospinal fluid (CSF)-restricted oligoclonal bands (OCBs). The earlier-onset group was less likely to respond to initial disease-modifying treatments. Compared to our previous cohort, the current series had fewer patients with onset <12 years, initial presentation with ADEM-like features, brainstem or cerebellar symptoms, seizures, and spinal lesions on MRI.

Abbreviations: MOG, myeline oligodentrocyte glycoprotein; AQP4, aquaporine 4.

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https://doi.org/10.1016/j.ejpn.2022.08.006
Received 22 May 2022; Received in revised form 13 July 2022; Accepted 22 August 2022
Available online 1 September 2022

The female/male ratio, the frequency of sensorial symptoms, and CSF-restricted OCBs were higher than reported in our previous cohort.
Conclusion: Pediatric MS starting before 12 years was less common than reported previously, likely due to exclusion of patients with antibody-mediated diseases. The results underline the importance of antibody testing and indicate pediatric MS may be a more homogeneous disorder and more similar to adult-onset MS than previously thought.

1. Introduction

Multiple sclerosis (MS) is a chronic immune-mediated demyelinating disorder of the central nervous system (CNS). It usually presents in early adulthood, but in 3–7% of cases, symptoms begin before the age of 18, representing pediatric MS [1–4]. Onset before puberty is even rarer: only 2% of MS cases begin before age 10 [1,2]. After its first description by Charcot in 1868 [5], nearly all recurrent CNS demyelinating syndromes had been classified under the umbrella diagnosis of MS until recently paraclinical markers became widely available. However the large variability in clinical presentation, response to treatment, and outcome of MS, particularly among pediatric patients, is well established. The description of anti-aquaporin 4 (AQP4)-IgG and anti-myelin oligodendrocyte glycoprotein (MOG)-IgG supports the possibility of misdiagnosed cases within previous MS series. The diagnosis is even more challenging in very young patients, for whom genetic and metabolic investigations are often needed to exclude certain MS mimics. Advances and availability of diagnostic methods in the last decade justify the evaluation of recent pediatric MS cases. We examined the characteristics of pediatric MS diagnosed after 2015 with the participation of nearly all pediatric neurology centers across Türkiye and compared them with our previously published pediatric MS cohort diagnosed before 2015 [6]. We also examined data for differences between children <12 years of age and those aged 12–17 years at onset of symptoms.

2. Material and methods

Demographic, clinical, laboratory and neuroimaging data of MS patients who experienced their first symptoms before the age of 18 years were collected from 44 pediatric neurology centers in 25 cities, which constitute more than 95% of pediatric neurology centers in Türkiye. Data were entered into the SPSS data editor by one of the researchers who had either evaluated the patients or reviewed the medical records. To avoid duplicate records, treating physicians were asked about patients' date of birth and sex. The study was approved by the Institutional Ethical Committee (No: 2021/20–04).

Pediatric MS was defined as the onset of first symptoms before the age of 18 years, in line with the consensus of International Pediatric MS Study Group, and the cut off for earlier- and later-onset pediatric MS was defined as 12 years of age based on the validity of the McDonald criteria (2010) after this age and similar studies in the literature [3,4,7–10]. The revised 2017 McDonald criteria were used for the diagnosis [11,12]. The diagnosis and differential diagnosis were made by the treating pediatric neurologists at each center according to current practice and based on clinical and imaging features and antibody status [4,11–13]. Tests for MOG-IgG and AQP4-IgG antibodies were performed whenever needed for differential diagnosis, using the immunofluorescence cell-based assay (CBA-IFA) with fixed transfected human cells, patient serum at 1:10 dilution and a fluorescein-labeled secondary antibody according to the manufacturer's instructions (Euroimmun, Lubeck, Germany).

The following variables were recorded: sex, age at first attack, interval between the first and second attacks, course (relapsing-remitting or progressive), family history of MS (first degree: parents; second degree: siblings and grandparents; and others), history of breastfeeding, smokers at home, infection within one month or vaccination within two months prior clinical onset, initial diagnosis of acute disseminated encephalomyelitis (ADEM), functional sites involved during the first episode, disability, and disease-modifying therapies (DMTs). Onset was classified as mono- or poly-symptomatic depending on clinical features' compatibility with one or more CNS lesions respectively. ADEM was defined as a first polysymptomatic presentation associated with encephalopathy (altered consciousness/behavior) not attributable to fever.[4] In patients with an initial diagnosis of ADEM, the diagnosis of MS was made only if they experienced a nonencephalopathic clinical event associated with new MRI lesions fulfilling 2017-McDonald criteria at an interval of at least three months [11]. Neurologic disability was scored by the mean expanded disability status scale (EDSS) score which was calculated at least two months after the last relapse. DMTs were grouped as moderate efficacy (interferon-beta, glatiramer acetate, teriflunomide), high efficacy (dimethyl fumarate, rituximab, ocrelizumab, natalizumab, fingolimod, cladribine) and others (azathioprine, cyclophosphamide) treatments.

Paraclinical variables: cerebrospinal fluid (CSF) analyses, serum 25-hydroxyvitamin D concentration (deficiency:<20 ng/ml), magnetic resonance imaging (MRI) and visual evoked potential (VEP) results. The initial and latest brain and spinal cord MRI findings were reviewed by the radiologists of each center. Oligoclonal IgG bands (OCBs) were assessed by isoelectric focusing, and were considered positive when at least two discrete bands were demonstrated in CSF only (pattern 2) or when the CSF had at least two more bands than serum (pattern 3). A protein level >45 mg/ml was classified as "elevated". CSF cell count <5/μl mononuclear cells was considered as normal. For the purpose of this study, VEP was defined as abnormal when the P100 wave was delayed or absent.

Response to DMTs was defined as the absence of any relapse for at least 12 months during the treatment period. An intent-to-treat analysis was employed, and patients who discontinued DMTs for any reason (ineffectiveness, non-compliance, or adverse effects) were counted as non-responders. Patients who had been on treatment for less than 12 months were excluded from the efficacy analysis.

Data were described as mean ± standard deviation or median (minimum – maximum) for continuous variables. Earlier vs. later-onset groups, and previous vs. current cohorts were compared by Pearson's chi-square or Fisher's exact tests for categorical and *t*-test or Mann Whitney *U* test for continuous variables. The EDSS scores at different times of the study (baseline and the 1st, 2nd, 3rd, and 4th years) were analyzed by the Friedman test with a Bonferroni post hoc correction. Missing data were excluded from analysis for that particular case. Significance was set at $p < 0.05$ (SPSS for Windows, version 20.0, Chicago, IL).

3. Results

The cohort consisted of 634 patients (456 girls), mean age of onset 14.1 ± 2.51 years (range: 3–17) after exclusion of patients who were found to have anti-MOG (n = 102) or anti-AQP4 antibody diseases (n = 30), even if they met the 2017 diagnostic criteria for MS. Only 89/634 (14%) were <12 years old at onset. Distribution of patients across sex and age groups is presented in Fig. 1. Medical history revealed the presence of a family member with MS in 8.7% of the patients, breastfeeding for more than six months in 77.5%, and history of smoke exposure at home in 52.7%. An infection or vaccination preceding the initial episode was described in 3.4% and 0.3% of patients, respectively.

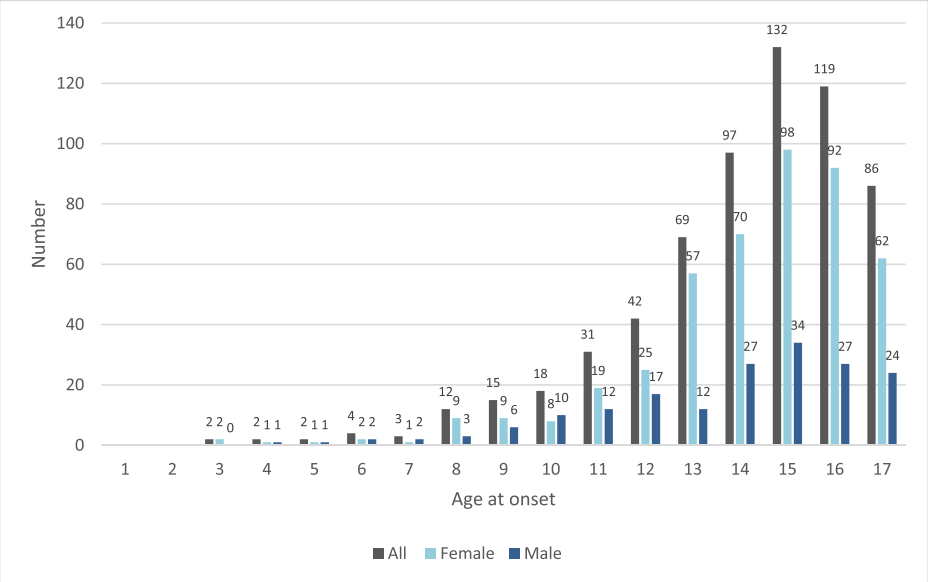

Fig. 1. Distribution of pediatric MS patients according to sex and age groups.

Presentation was monofocal in 46.8% of patients. The most common initial symptoms were sensorial (53.9%), followed by motor symptoms (36%), optic neuritis (30.6%), brain-stem (23%) and cerebellar symptoms (21.1%) (Table 1). During median 24 months of follow up, the total number of attacks was two on average, with a mean interval of 10 months between the first two attacks while 39% of patients had a single episode. No progressive course was observed.

3.1. Comparison of earlier and later-onset pediatric MS (Tables 1 and 2)

General demographic, clinical, and paraclinical characteristics were compared between earlier and later onset groups. The earlier-onset group had lower female/male ratio and more frequent infection/vaccination history preceding the first episode. The likelihood of an initial diagnosis of ADEM was higher and MS, lower; brainstem symptoms were more frequent and sensorial symptoms, less frequent at onset in earlier-onset group. This group had longer interval between the first two attacks. On MRI, periventricular white matter and spinal cord involvement were less frequent in earlier-onset patients, as were CSF-restricted OCBs and elevated IgG index. Lumbar puncture was repeated in median eight months in 17 patients who did not have CSF-restricted OCBs at the first episode, and were detected in 10/17.

3.2. Incidence (Fig. 2)

Since nearly all pediatric neurology centers in Türkiye participated in the study, we calculated the incidence of pediatric MS in Türkiye using the Turkish Statistical Institute's open access data on population by age and sex [14]. The incidence was calculated as 6.77 per million children. It was higher in girls and in children 12 years of age and older.

3.3. Treatment (Tables 3 and 4)

One DMT was started in 550 children at the time of diagnosis. The most commonly used initial DMTs were interferon beta 1-a (65%), followed by interferon beta 1-b (7.4%) and teriflunomide (4.9%). High efficacy DMTs were used as the initial therapy in 41 children (dimethyl fumarate in 16, fingolimod in 15, ocrelizumab in 5, rituximab in 3, and natalizumab in 2 patients). Four patients were initially treated with monthly intravenous immunoglobulin. Average time from the first symptoms to beginning of treatment was longer in the earlier-onset group. Initial DMTs were found to be effective in 43.6% of patients, and the frequency of response was significantly higher in the later-onset group (46.1%) compared to earlier-onset group (27.1%).

3.4. Outcome (Tables 1, 5 and 6)

The mean EDSS score was 0.52 at the end of the 4-year follow-up period. Although not significantly different, mean EDSS score changed in opposite directions in the two age groups increased from 0.49 at baseline to 0.83 at year 4 in the earlier-onset group compared to 0.51 at baseline to 0.40 at year 4 in the later-onset group. Academic performance was reported as average or higher in 95.4% of the patients.

3.5. Comparisons of current and previous[6] cohorts (Table 6)

In the current cohort, the mean age at first clinical event was higher. While the frequency of onset <12 years, history of infection/vaccination prior to initial episode, initial presentation mimicking ADEM or featuring brainstem signs, cerebellar signs, sphincter disturbances, seizures, and MRI showing spinal lesions were lower, the frequency of CSF-restricted OCBs, elevated IgG index, sensorial symptoms, and female/male ratio were higher than reported in our previous cohort. Mean EDSS scores over 3 years' follow-up did not differ between the two cohorts.

4. Discussion

This large multicentric study covering nearly all pediatric MS centers in Türkiye documents the general characteristics of the disease and compares two decades. The differences we observed in the current series can be attributed in part to the use of revised 2017 criteria which were not available at the time of our previous study. Although the 2010 criteria have high sensitivity, specificity, and positive predictive value for children older than 12 years of age, the positive predictive value for <11 year olds was estimated as low as 55%, and not applicable to cases with ADEM-like presentation [15].

4.1. Incidence

Most studies report an incidence less than 1.0 and a pooled global incidence reaching 0.87 per 100,000 children while overall incidence ranged from 0.05 to 2.85 according to two recent meta-analyses [16,17]. Very limited data are available for trends over time: an increase in incidence was reported from Netherlands (from 0.15 between 2007 and

Table 1
Comparison of demographic and clinical characteristics between patients with earlier and later-onset pediatric multiple sclerosis.

Characteristics	All patients	Earlier-onset <12 yrs	Later-onset 12–17 yrs	P
Number, %	634	89 (14.0)	545 (86.0)	
Female:Male	2.56	1.41	2.87	**0.002**
Age at first clinical attack, years	14.1 ± 2.51, 5 (3–17)	9.22 ± 2.00, 10 (3–11)	14.9 ± 1.49, 15 (12–17)	**<0.001**
Duration of follow up, months	28.4 ± 22.3, 24 (1–96)	34.6 ± 27.6, 24 (1–96)	27.4 ± 21.2, 23 (1–84)	**0.005**
Patients with at least 12 months' follow up	454 (71.6)	68 (76.4)	386 (70.8)	0.279
Total number of attacks	2.09 ± 1.33, 2 (1–12)	2.26 ± 1.28, 2 (1–6)	2.06 ± 1.34, 2 (1–12)	0.199
Number of attacks per month during follow-up	0.15 ± 0.22	0.13 ± 0.14	0.16 ± 0.23	0.273
Patients with a single attack				
All patients	247 (39.0)	27 (30.3)	220 (40.4)	0.072
Patients with at least 12 month-follow up, n = 454	121 (26.7)	14 (20.6)	107 (27.7)	0.220
Interval between first two attacks, months				
All patients	10.3 ± 10.9, 7 (1–84)	13.8 ± 16.2, 8 (1–84)	9.70 ± 9.55, 6 (1–53)	**0.006**
Patients with at least 12 months of follow up, n = 320	11.3 ± 11.4, 7.5 (1–84)	15.5 ± 16.8, 8 (1–84)	10.6 ± 10.0, 6 (1–53)	**0.004**
<12 months interval between the first two attacks in patients with at least 12 months of follow up, n = 454	212 (46.7)	30 (44.1)	182 (47.2)	0.644
Coexistence of other autoimmune disorders, n = 561	33 (5.9)	2 (2.9)	31 (6.3)	0.412
Family history of MS, n = 553	48 (8.7)	3 (4.4)	45 (9.3)	0.182
Breastfeeding ≥6 months, n = 414	321 (77.5)	41 (75.9)	280 (77.8)	0.816
Smoking at home, n = 391	206 (52.7)	29 (64.4)	177 (51.2)	0.093
Infection/vaccination preceding initial episode, n = 624	23 (3.7)	8 (9.3)	15 (2.8)	**0.008**
Infection	21 (3.4)	8 (9.3)	13 (2.4)	
Vaccination	2 (0.3)	0	2 (0.4)	
Relapsing-remitting course	634 (100)	89 (100)	545 (100)	
Initial diagnosis				
Relapsing-remitting MS	452 (71.3)	50 (56.2)	402 (73.8)	**0.001**
Clinically isolated syndrome	159 (25.1)	26 (29.2)	133 (24.4)	0.332
Acute disseminated encephalomyelitis	23 (3.6)	13 (14.6)	10 (1.8)	**<0.001**
Presenting clinical phenotype, monofocal	297 (46.8)	37 (41.6)	260 (47.7)	0.282
Functional systems involved during initial attack				
Optic neuritis	194 (30.6)	25 (28.1)	169 (31.0)	0.580
Unilateral	160 (25.2)	20 (22.5)	140 (25.7)	
Bilateral	34 (5.4)	5 (5.6)	29 (5.3)	
Motor	228 (36.0)	33 (37.1)	195 (35.8)	0.813
Sensory	342 (53.9)	37 (41.6)	305 (56.0)	**0.012**
Brainstem	146 (23.0)	31 (34.8)	115 (21.1)	**0.004**
Cerebellar	134 (21.1)	21 (23.6)	113 (20.7)	0.540
Myelopathy	33 (5.2)	10 (11.2)	23 (4.2)	**0.016**
Sphincter dysfunction	3 (0.5)	1 (1.1)	2 (0.4)	0.365
Seizure	9 (1.4)	3 (3.4)	6 (1.1)	0.120
EDSS				
Baseline, n = 541	0.51 ± 0.76, 0 (0–4)	0.49 ± 0.75, 0 (0–4)	0.51 ± 0.76, 0 (0–4)	0.817
Year 1, n = 376	0.46 ± 0.75, 0 (0–4)	0.47 ± 0.74, 0 (0–4)	0.46 ± 0.75, 0 (0–4)	0.985
Year 2, n = 223	0.42 ± 0.76, 0 (0–6)	0.57 ± 0.58, 1 (0–2)	0.39 ± 0.79, 0 (0–6)	0.208
Year 3, n = 112	0.43 ± 0.70, 0 (0–3)	0.66 ± 0.68, 1 (0–2)	0.37 ± 0.69, 0 (0–3)	0.084
Year 4, n = 64	0.52 ± 0.83, 0 (0–4)	0.83 ± 1.03, 1 (0–4)	0.40 ± 0.71, 0 (0–2.5)	0.061
Academic performance, n = 495				
Adequate/excellent	472 (95.4)	60 (93.8)	412 (95.6)	0.521
Excellent	246 (49.7)	33 (51.6)	213 (49.4)	
Average	226 (45.7)	27 (42.2)	199 (46.2)	
Poor	23 (4.6)	4 (6.2)	19 (4.4)	
Failed	18 (3.6)	3 (4.7)	15 (3.5)	
Special education	3 (0.6)	–	3 (0.7)	
Unable to attend school	2 (0.4)	1 (1.6)	1 (0.2)	

Data are number (%) or mean ± SD, median (minimum-maximum), unless otherwise specified.
S.D: Standard deviation; MS: multiple sclerosis; EDSS: Expanded Disability Status Scale; yrs: years; F: female; M: male.
"n" on the first column is the number of subjects who have data for the specific parameter on that line.

2010 to 0.26 between 2011 and 2016, per 100,000 children) and from Kuwait (from 0.3 in 1994 to 2.1 in 2013, per 100,000 children).[16] Our study showed a clear increase in the incidence of MS per 100,000 children from 0.21 in 2015 to 0.68 in 2021. Possible causes for this observation include: 1) an increase in the number of pediatric neurologists and pediatric neurology centers in recent years leading to improved diagnosis during childhood; 2) development of new diagnostic criteria in 2017 allowing early diagnosis during initial symptoms: indeed 71.3% of patients had been diagnosed during their initial attack; 3) environmental factors including COVID-19 pandemic activating autoimmune

Table 2
Comparison of paraclinical characteristics between patients with earlier and later-onset pediatric multiple sclerosis.

	All patients	Onset <12 yrs	Onset 12–17 yrs	P
Anti-MOG-IgG*	0/483	0/75	0/408	
Anti-AQP4-IgG*	0/437	0/65	0/372	
MRI lesions at onset				
Cortical/Juxtacortical, n = 624	519 (83.2)	76 (88.4)	443 (82.3)	0.165
Periventricular white matter, n = 624	594 (95.2)	77 (89.5)	517 (96.1)	**0.014**
Infratentorial, n = 624	394 (63.1)	60 (69.8)	334 (62.1)	0.170
Spinal cord, n = 624	288 (46.2)	27 (31.4)	261 (48.5)	**0.003**
Total T2-lesion number, n = 607				0.815
1–3	61 (10.0)	7 (8.3)	54 (10.3)	
4–9	271 (44.6)	37 (44.0)	234 (44.7)	
≥10	275 (45.3)	40 (47.6)	235 (44.9)	
Gd-enhancing lesion number, n = 562				0.931
None	115 (20.5)	14 (19.2)	101 (20.7)	
1–3	288 (51.2)	36 (49.3)	252 (51.5)	
4–9	112 (19.9)	16 (21.9)	96 (19.6)	
≥10	47 (8.4)	7 (9.6)	40 (8.2)	
VEP latency abnormalities				
At onset, n = 400	211 (52.8)	29 (65.9)	182 (51.1)	0.064
Patients with a history of ON, n = 133	114 (85.7)	12 (100)	102 (84.3)	0.138
Patients without a history of ON, n = 267	97 (36.3)	17 (53.1)	80 (34.0)	**0.035**
At the last follow up, n = 415	236 (56.9)	33 (66.0)	203 (55.6)	0.164
Patients with a history of ON, n = 169	142 (84.0)	17 (94.4)	125 (82.8)	0.202
Patients without a history of ON, n = 246	94 (38.2)	16 (50.0)	78 (36.4)	0.141
Cerebrospinal fluid				
OCBs** restricted to CSF, at onset, n = 577	468 (81.1)	51 (63.8)	417 (83.9)	**<0.001**
OCBs restricted to CSF, at the last visit, n = 577	478 (82.8)	56 (70.0)	422 (84.9)	**0.001**
Conversion of CSF-restricted OCBs from negative to positive, n = 17	10 (58.8)	5 (71.4)	5 (50.0)	0.622
Conversion duration of CSF-restricted OCBs from negative to positive, months, n = 10	11.3 ± 9.5, 8 (3–30)	12.6 ± 11.3, 10 (3–30)	10.0 ± 8.3, 6 (3–24)	
Elevated IgG index, at onset, n = 502	365 (72.7)	33 (55.9)	332 (74.9)	**0.002**
Elevated IgG index, at the last visit, n = 504	374 (74.2)	38 (62.3)	336 (75.8)	**0.023**
Lymphocytes in CSF ≥5/ml, n = 489	68 (13.9)	14 (21.9)	54 (12.7)	**0.048**
CSF Protein, mg/dl, n = 541	34.1 ± 15.2, 31 (5–91)	29.5 ± 12.1, 27 (10–78)	34.8 ± 15.5, 31 (5–91)	**0.006**
Elevated CSF protein (>45 mg/dl), n = 541	68 (13.9)	6 (8.6)	85 (18.0)	**0.048**
25-hydroxyvitamin D, ng/mL				
Serum levels at onset, n = 549	16.3 ± 9.47, 14 (3–88)	18.2 ± 9.1, 15.5 (4–48)	16.0 ± 9.5, 14 (3–88)	0.087
Patients with low serum levels (<20 ng/mL) at onset, n = 549	401 (73.0)	45 (68.2)	356 (73.7)	0.343
Serum levels at the last visit, n = 368	25.1 ± 12.2, 22 (4–86)	25.0 ± 11.7, 21 (9–68)	25.1 ± 12.3, 23 (4–86)	0.966
Patients with low serum levels (<20 ng/mL) at the last visit, n = 368	154 (41.8)	20 (42.6)	134 (41.7)	0.916

* Tests for MOG-IgG and AQP4-IgG antibodies were performed using the immunofluorescence cell-based assay (CBA-IFA) with fixed transfected human cells, patient serum at 1:10 dilution and a fluorescein-labeled secondary antibody according to the manufacturer's instructions (Euroimmun, Lubeck, Germany).
** OCBs were assessed by isoelectric focusing, and were considered positive when at least two discrete bands were demonstrated in CSF only (pattern 2) or when the CSF had at least two more bands than serum (pattern 3).
Data are number (%) or mean ± SD, median (minimum-maximum), unless otherwise specified.
S.D: Standard deviation; MRI: magnetic resonance imaging; yrs: years; MOG: myelin oligodendrocyte glycoprotein; AQP4: aquaporin 4; IgG: immunoglobulin G; VEP: visual evoked potentials; ON: optic neuritis; CSF: cerebrospinal fluid, OCBs: oligoclonal bands.
"n" on the first column is the number of subjects who have data for the specific parameter on that line.

mechanisms or triggering symptoms, as addressed in a recent review [18].

4.2. Demographics

Onset before age 12 years is rare, accounting for 12–28% of all pediatric MS cases, lower (12–13%) in previous and higher (25–28%) in recent studies [1–3,9,10]. Compared with 23.3% in our previous cohort [6], and the more recent figures cited above, the proportion of MS in children under 12 years of age was lower in this study (14.0%). This may be due to more accurate exclusion of other demyelinating disorders or neurometabolic diseases mimicking MS. In particular, MOG-IgG associated disease is more frequent in young children and the availability of MOG-IgG testing may be the main factor affecting the incidence in this age group.

The female:male ratio is almost equal (1:1 to 1.5:1) in children younger than 12 years, whereas a marked female predominance (1.24:1–3.4:1) is observed in 12 years and older [2,9,10,16,19–21]. In the present study, the female:male ratio was higher than in our previous cohort [6] and similar to adult ratios [2,3]. This may also be attributed to the lower percentage of children <12 years old in the current cohort.

4.3. Risk factors

The incidence of family history of MS in the current series, 8.7%, is consistent with previous studies including ours [5–16]. [6,9,22] Environmental factors such as vitamin D deficiency, viral infections, exposure to smoke, and obesity are thought to play a role in the development of pediatric MS, with the strongest associations with Epstein-Barr virus infection, infectious mononucleosis, smoking, and reduced serum vitamin D concentrations [22–24]. Vitamin D deficiency has also been associated with increased rates of relapse, new T2 and gadolinium-enhancing lesions, and subsequent disability [25,26]. In the current series, low vitamin D levels were found at similar frequency with our previous cohort (73% vs. 68.5%), and higher than reported for vitamin D deficiency and insufficiency in Turkish children (<20 ng/mL in 8% and 20–29 ng/mL in 25.5%) [27]. Treatment of any vitamin D insufficiency and regular supplementation is recommended [24,25,28].

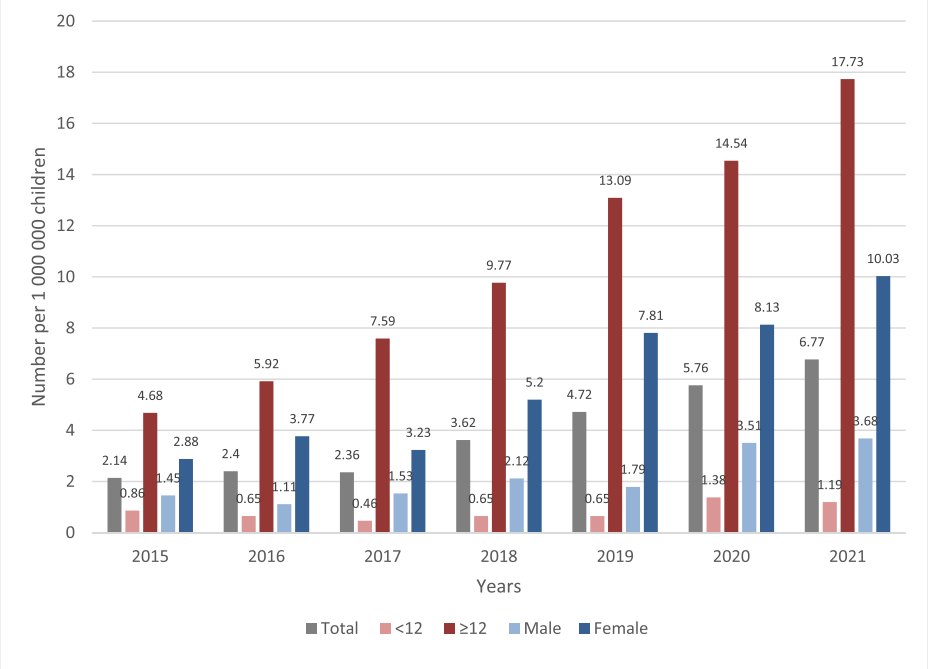

Fig. 2. Estimated incidences of pediatric multiple sclerosis according to years, sex and age groups. The incidence per million children increased from 2.14 in 2015 to 6.77 in 2021. It was higher in girls than boys, and higher in disease onset ≥12 years than <12 years of age.

Table 3
Disease modifying therapies in patients with pediatric multiple sclerosis.

Disease-Modifying Therapies	First DMT n = 634	Second DMT n = 158	Third DMT n = 32	Fourth DMT n = 6
Moderate efficacy	505 (79.7)	47 (29.9)	4 (13.3)	–
Interferon beta 1-a	412 (65.0)	13 (8.3)		
Interferon beta 1-b	47 (7.4)	7 (4.4)	1 (3.1)	
Glatiramer acetate	15 (2.4)	16 (10.1)		
Teriflunomide	31 (4.9)	11 (7.0)	3 (9.4)	
High efficacy	41 (6.5)	109 (69.0)	26 (86.7)	6 (100)
Dimethyl fumarate	16 (2.5)	26 (16.5)	5 (15.6)	1 (16.7)
Fingolimod	15 (2.4)	57 (36.1)	13 (40.6)	1 (16.7)
Ocrelizumab	5 (0.8)	13 (8.2)	5 (15.6)	3 (50.0)
Rituximab	3 (0.5)	4 (2.5)		
Natalizumab	2 (0.3)	8 (5.1)	3 (9.4)	1 (16.7)
Cyclophosphamide	–	1 (0.6)		
Cladribine		1 (0.6)		
Others				
IVIG (monthly)	4 (0.6)	–		
Pulse MPS (monthly)			1 (3.1)	
Azathioprine	–	1 (0.6)	1 (3.1)	
Cyclophosphamide		1 (0.6)		
Unknown	23 (3.6)			
No medication	61 (9.6)			

IVIG: intravenous immunoglobulin; MPS: methyl prednisolone, DMT: Disease-Modifying Treatment.

Indeed, serum 25-hydroxyvitamin D concentrations increased from an average 16 ng/mL at onset to 25 ng/mL at the last visit, and the rate of vitamin D deficiency decreased from 73% to 42%, likely due to vitamin D supplementation.

A history of infection prior to and possibly triggering the initial event was reported in only 3.4% of children in the current series, mostly in children under 12 years of age. This rate is lower than previously published reports, including ours (15.7%) and may be explained by better exclusion of children with ADEM [6,9,10,21]. Vaccination in general is not a risk factor for MS; on the contrary, a recent large case-control study revealed its association with lower likelihood of receiving the diagnosis of MS within the next five years [29]. A recent review concluded any vaccines for COVID-19 are likely safe for MS patients and protection from the infection outweighs the risk of a relapse [30]. However three cases of reactivation or new-onset demyelinating disease after vaccination with Oxford-AstraZeneca COVID-19 recombinant adenovirus (ChAdOx1 nCoV-19; AstraZeneca) [31], and one case with first manifestation of MS after immunization with the Pfizer-BioNTech COVID-19 vaccine [32], were reported recently. In our series, two children had been immunized with Pfizer-BioNTech COVID-19 vaccine 20 and 50 days prior to their initial MS symptoms. Therefore, whether COVID-19 vaccines pose a risk factor for the development or relapse of MS remains to be elucidated by meta-analyses of large studies.

The increased risk of MS in children exposed to parental smoking is proportional to the duration of exposure [33]. In our series, such exposure was 52.7%, similar to our previous cohort (55.8%) [6], and to the recently published prevalence of passive smoking in children younger than 15 years of age in Turkey (55.9%) [34]. These figures do not reinforce smoking as an additional risk factor for MS.

Studies on breastfeeding show conflicting results: some support a protective effect of breastfeeding for at least one week to four months, while others fail to confirm this finding [35–38]. Breastfeeding for at least 6 months was recorded in 77.5% of our patients, comparable to our previous report of 70.8%,[6] and to the Turkish Statistical Institute's figures on the general population between 2014 and 2019 (72.0%) [39]. We therefore did not demonstrate any role of breastfeeding on the development of MS.

4.4. *Clinical findings*

Presenting symptoms in pediatric MS vary widely. In the current series, sensorial symptoms were the most common, followed by motor, visual, brainstem and cerebellar disturbances. Sensorial symptoms were more frequent than previously reported whereas brainstem, cerebellar, sphincter problems and seizures were less frequent in the current study [6,9,10]. The higher rate of sensorial symptoms might be related to more patients over 12 years of age in the current series, young children being less able to describe sensorial symptoms. On the other hand, lower rate of sphincter disturbance and seizures as well as ADEM-like initial

Table 4
Effectiveness of disease modifying therapies in patients with pediatric multiple sclerosis.

	All patients	Onset <12 yrs	Onset 12–17 yrs	P
Initial Disease-Modifying Therapies, n = 634				
Moderate efficacy	505 (79.7)	70 (78.7)	435 (79.8)	0.460
Interferon beta 1-a	412 (65.0)	60 (67.4)	352 (64.6)	
Interferon beta 1-b	47 (7.4)	6 (6.7)	41 (7.5)	
Glatiramer acetate	15 (2.4)	–	15 (2.8)	
Teriflunomide	31 (4.9)	4 (4.5)	27 (5.0)	
High efficacy	41 (6.5)	4 (4.5)	37 (7.8)	
Dimethyl fumarate	16 (2.5)	–	16 (2.9)	
Fingolimod	15 (2.4)	–	15 (2.8)	
Ocrelizumab	5 (0.8)	1 (1.1)	4 (0.7)	
Rituximab	3 (0.5)	3 (3.4)	–	
Natalizumab	2 (0.3)	–	2 (0.4)	
IVIG (monthly)	4 (0.6)	4 (4.5)	–	
Unknown	23 (3.6)	4 (4.5)	19 (3.5)	
No medication	61 (9.6)	7 (7.9)	54 (9.9)	
Reason for not starting DMTs, n = 58				
Planned but not started yet	17 (27.9)	1 (14.3)	16 (29.6)	
Parents'/patients' refusal	6 (9.8)	–	6 (11.1)	
Low MRI lesion load	2 (3.3)	–	2 (3.7)	
Unknown	36 (59.0)	6 (85.7)	30 (55.6)	
Number of clinical attacks where treatment was started, n = 550				
1	312 (56.7)	35 (44.9)	277 (58.7)	
2	204 (37.1)	34 (43.6)	170 (36.0)	
3	27 (4.9)	7 (9.0)	20 (4.2)	
≥4	6 (1.1)	2 (2.6)	4 (0.8)	
Increase in MRI activity	1 (0.2)	–	1 (0.2)	
Time from the first attack to start of treatment, months, n = 550	6.07 ± 11.0, 2 (0–84)	10.9 ± 17.3, 4.5 (0–84)	5.27 ± 9.36, 2 (0–58)	**<0.001**
Duration of treatments with DMTs, months				
1st DMT, n = 549	18.0 ± 16.3, 12 (1–84)	18.0 ± 19.0, 10 (1–78)	18.0 ± 15.8, 12 (1–84)	0.993
2nd DMT, n = 158	15.4 ± 13.7, 12 (1–66)	17.6 ± 14.5, 11 (1–48)	15.1 ± 13.6, 12 (1–66)	0.477
3rd DMT, n = 32	14.6 ± 13.0, 12 (1–66)	16.3 ± 14.4, 12 (1–36)	14.2 ± 13.0, 11.5 (3–66)	0.743
4th DMT, n = 6	22.0 ± 7.77, 22.5 (12–30)	–	22.0 ± 7.77, 22.5 (12–30)	
Effectiveness* of DMTs				
1st DMT, n = 369				
Effective	161 (43.6)	13 (27.1)	148 (46.1)	**0.013**
Non-effective	208 (56.4)	35 (72.9)	173 (53.9)	
Relapses	189 (51.2)	32 (66.7)	157 (48.9)	
Increased/active MRI lesions	10 (2.7)	2 (4.2)	8 (2.5)	
Adverse events	6 (1.6)	1 (2.1)	5 (1.6)	
Nonadherence/patients' choice	3 (0.8)	–	3 (0.9)	
2nd DMT, n = 81	58 (71.6)	4 (40.0)	54 (76.1)	**0.018**
3rd DMT, n = 17	13 (76.5)	4 (100)	9 (69.2)	0.519
4th DMT, n = 6	3 (50.0)	–	3 (50.0)	

* Effectiveness: defined as the absence of any clinical relapse during the treatment period in patients on medication for at least 12 months. An intent-to-treat analysis was employed, and patients who discontinued DMTs for any reason (ineffectiveness, non-compliance, or adverse effects) were counted as non-responders.
Data are number (%) or mean ± SD, median (minimum-maximum), unless otherwise specified.
S.D: Standard deviation; MRI: magnetic resonance imaging; yrs: years; DMT: Disease-Modifying Treatment.
"n" on the first column is the number of subjects who have data for the specific parameter on that line.

presentation may be attributed to better exclusion of MOG IgG-associated disorders in the current series [6,9,10,40].

The first presentation was polysymptomatic in 53% of our current and 55% of our previous cohorts, and reported between 37 and 67% in other series [6,9,10,21,22,41,42]. Pre-pubertal children tend to present with polysymptomatic involvement including motor, brainstem, sphincter and cognitive functions, and milder residual neurologic sequelae after the first episode whereas post-pubertal children are more likely to present with optic neuritis and sensorial symptoms [20,21]. Except sensorial symptoms, the manifestations of younger-onset MS did not differ significantly between age groups in our study.

The clinical course in 95–100% of pediatric MS patients is relapsing remitting, compared to 85–90% in adults [1,2,6,7,10,43,44]. The finding that none of the children in the current cohort showed a primary progressive course questions whether such presentation exists in children at all. Alternative conditions should be searched in children with suspected primary progressive MS, and this diagnosis should be considered only after comprehensive evaluation for other disorders such as leukodystrophies or interferonopathies [2,45].

General knowledge describes more complete recovery from individual relapses and slower accumulation of long-term disability, but more active inflammation, more frequent relapses, and disability at earlier ages in pediatric MS patients compared adult-onset disease [2,7,19,46]. This may be due to more efficient recovery after a relapse associated with a higher ability for myelin repair and greater plasticity of the developing brain [47]. Indeed physical disability levels are usually low in pediatric MS and EDSS scores ≤2 correspond to minimal motor disability [19]. Our study confirms these data as the mean EDSS scores were less than one with the majority were still zero at the end of four years' follow-up. However, disability can accumulate with continued relapses, and the initial inflammatory phase may progress to neurodegeneration [24].

Table 5
Change in EDSS during follow-up.

	Baseline n = 541	Follow-up				p Value
		First year n = 376	Second year n = 223	Third year n = 112	Fourth year n = 64	
All patients	0.51 ± 0.76, 0 (0–4)	0.46 ± 0.75, 0 (0–4)	0.42 ± 0.76, 0 (0–6)	0.43 ± 0.70, 0 (0–3)	0.52 ± 0.83, 0 (0–4)	0.195
Onset <12 year	0.49 ± 0.75, 0 (0–4)	0.47 ± 0.74, 0 (0–4)	0.57 ± 0.58, 1 (0–2)	0.66 ± 0.68, 1 (0–2)	0.83 ± 1.03, 1 (0–4)	0.255
Onset 12–18 years	0.51 ± 0.76, 0 (0–4)	0.46 ± 0.75, 0 (0–4)	0.39 ± 0.79, 0 (0–6)	0.37 ± 0.69, 0 (0–3)	0.40 ± 0.71, 0 (0–2.5)	0.072

Data are mean ± SD (minimum-maximum).
EDSS: Expanded Disability Status Scale; S.D: Standard deviation.

Early and frequent relapses can affect brain development and reduce brain volume, resulting in lower cognitive performance compared to adults as reported in up to a third of pediatric patients even at earliest stages of the disease [48]. We were unable to confirm such early cognitive decline: 95% of children with MS had adequate academic performance at a median follow-up of 24 months in our series. However, due to its retrospective and multicenter design, our study did not include formal cognitive assessment. We therefore state that there is no cognitive impairment noticeable by patient, family or school in the early years of the disease; but routine testing should be part of the follow-up of pediatric MS in order to detect any subclinical and potentially progressive changes.

The activity of the disease assessed by clinical, imaging and immunologic features were not different between children with MS onset <11 years and ≥11 years in a recent study [49]. Likewise, these findings did not differ significantly between our earlier and later-onset groups who had at least 12 months of follow-up: 1) number of attacks per month and percentage of patients without a new attack, 2) percentage of patients with an interval shorter than 12 months between the first two attacks, 3) total number of T2 and Gd-enhancing lesions, and 4) mean EDSS at follow-up. Moreover, the interval between first two attacks was longer in earlier-onset group, similar to our previous cohort [6]. Thus, we can conclude that pediatric MS with onset <12 years and between 12 and 18 years old are alike, at least after a mean follow-up of 28 months. This conclusion was supported by a large study with a mean follow-up of 17 years as well as a recent study that carefully excluded patients with antibody-related demyelinating syndromes; both reported no significant clinical, radiological, and immunological differences between children with MS < 11 and >11 years of age [7,49].

4.5. MOG-IgG, AQP4-IgG associated diseases and ADEM

Inclusion to this study was based on the diagnosis of pediatric MS in routine clinical practice at each participating center. The McDonald criteria do not require antibody testing for the diagnosis of MS; in any case, serum MOG- or AQP4-IgG are rarely, if any, found in adult and pediatric MS [49–55]. Therefore in the current series these antibodies were tested whenever needed for differential diagnosis and probably more frequently than in adult neurology clinics, considering the possible atypical presentations of pediatric MS, high frequency of MOGAD in children, and the negative effect of some DMTs in MOGAD. However, none of the patients in our series tested for MOG or AQP4 antibodies (483 and 437 patients, respectively) were seropositive. The MOG-IgG assay was a fixed-CBA which can miss 10–15% of positive cases detected with live-CBA, the gold standard.[50,56] Therefore our series may still contain a few MOG-IgG-positive cases. However fixed-CBA is used more frequently in routine practice because of commercial availability and acceptable rate of agreement with live CBA [50,56].

When MOG-Ab-associated patients have been completely separated from the MS group, pediatric MS was found to be more similar to adult-onset MS than previously known [49]. Prior to routine testing for MOG-Ab, studies showed 6'-20% of children with MS had initially been diagnosed with ADEM [6,22,42]. They also reported atypical MRI findings such as extensive white matter involvement, increased frequency of longitudinally extensive transverse myelitis, and lower frequency of intrathecal OCBs compared to adults; these are features now known to be typical of MOG-Ab associated disease. This may explain why our current study shows a lower frequency of ADEM-like presentation compared to our previous report. The literature before and after 2015 displays a similar trend [8,41,49,57]. It can also be speculated that other yet undefined antibodies are associated with CNS demyelinating disorders, particularly in young children: our youngest patients, four children with onset at three and four years old whose serum tested three times were negative for MOG and AQP4 antibodies, had MRI lesions atypical for MS and no CSF-restricted OCBs. The description of other autoimmune demyelinating diseases will allow better characterization of pediatric MS and correct choice of treatment [40].

4.6. Paraclinical findings

Compared with adults, children with MS have a greater number of T2 lesions and larger lesion volume on MRI, particularly in the posterior fossa [58]. A study from Germany reported 41.6% of pediatric MS cases fulfilled criteria for highly active disease defined as ⩾1 attack within the previous year and the presence of ≥9 T2 lesions or ≥1 Gd-enhancing lesion while under therapy with INFβ, GA, or dimethylfumarate [59]. Confirming this finding, 45.3% of patients in our series had 10 or more T2-lesions and about 80% of patients had at least one contrast-enhancing lesion on initial MRI, suggesting that more than half had high lesion burden at disease onset. Compared to our previous cohort, the current cohort had more cortical/juxtacortical and less frequently spinal lesions; this can be attributed to exclusion of patients with anti-MOG antibodies frequently associated with spinal cord lesions, more frequent MRI examination of the spine, and improvements in MRI techniques.

Data on MRI findings of children with pre- and post-pubertal onset MS are limited. While a recent study reported some differences such as more confluent and more frequent infratentorial lesions in earlier-onset compared to later-onset patients [10], infratentorial involvement was similar between two groups in our both previous and current series [6]. However, the current cohort had more periventricular and spinal cord lesions in the later-onset group; this was not seen in our previous study. These controversial results call for better designed studies comparing MRI between early and late-onset pediatric MS.

The presence of two or more OCBs was integrated to the latest revision of the McDonald criteria (2017) as a substitute for dissemination in time [11]. While CSF-restricted OCBs are detected in more than 90% of patients with pediatric MS, they are present only in about 10% of patients with MOG-associated disease and AQP4-associated neuromyelitis optica spectrum disorder (NMOSD) patients and therefore represent a sensitive diagnostic tool for MS [24,53,60,61]. Findings on the status of OCBs in pediatric patients tend to change over time: previous studies reported a frequency of about 70% [9,10]; and more recent studies more than 90%, revealing OCBs as even more common in the

Table 6
Characteristics of current series in comparison with the previous (<2015) cohort.

Findings	Current cohort (2015–2021) n = 634 (%)	Previous cohort (<2015)[a] n = 193 (%)	p
Demographics and clinical characteristics			
Onset under 12 years of age	89 (14.0)	45 (23.3)	**0.002**
Sex ratio, F:M	2.56	1.76	**0.030**
Age at the first clinical attack, years	14.1 ± 2.51, 5 (3–17)	13.5 ± 2.88, 14 (4–17)	**0.005**
Interval between the first two attacks, months	10.3 ± 10.9, 7 (1–84)	10.3 ± 10.9, 6 (1–60)	0.967
Family history of MS	48 (8.7)	12 (6.5)	0.345
Infection/vaccination preceding initial episode	23 (3.7)	30 (15.7)	**<0.001**
Breastfeeding ≥6 months	321 (77.5)	56 (70.9)	0.202
Disease course, Relapsing remitting	634 (100)	191 (99.0)	0.054
Initial diagnosis of ADEM	23 (3.6)	21 (11.0)	**<0.001**
Presenting clinical phenotype, monofocal	297 (46.8)	86 (44.6)	0.577
Functional systems involved during initial attack			
Optic neuritis	194 (30.6)	51 (26.4)	0.266
Motor	228 (36.0)	64 (33.2)	0.476
Sensory	342 (53.9)	85 (44.0)	**0.016**
Brainstem	146 (23.0)	71 (39.7)	**<0.001**
Cerebellar	134 (21.1)	57 (29.5)	**0.015**
Myelopathy	33 (5.2)	4 (2.1)	0.065
Sphincter dysfunction	3 (0.5)	8 (4.1)	**0.001**
Seizure	9 (1.4)	10 (5.2)	**0.005**
EDSS			
Baseline, n = 541/105	0.51 ± 0.76, 0 (0–4)	0.38 ± 0.73, 0 (0–4)	0.101
Year 1, n = 376/71	0.46 ± 0.75, 0 (0–4)	0.38 ± 0.88, 0 (0–4.5)	0.454
Year 2, n = 223/36	0.42 ± 0.76, 0 (0–6)	0.65 ± 1.41, 0 (0–6)	0.343
Year 3, n = 112/24	0.43 ± 0.70, 0 (0–3)	1.04 ± 1.76, 0 (0–6)	0.105
MRI lesions at onset			
Cortical/Juxtacortical	549 (87.5)	113 (64.2)	**<0.001**
Periventricular white matter	603 (96.3)	174 (96.1)	0.904
Infratentorial	424 (67.7)	135 (71.8)	0.291
Spinal cord	321 (51.4)	124 (67.0)	**<0.001**
VEP latency abnormalities at the last follow up	236 (56.9)	81 (51.9)	0.289
Cerebrospinal fluid at the last follow up			
OCBs restricted to CSF	478 (82.8)	115 (68.0)	**<0.001**
Elevated IgG index	374 (74.2)	96 (62.3)	**0.004**

Data are number (%) or mean ± SD, median (minimum-maximum), unless otherwise specified.
MS: multiple sclerosis; S.D: Standard deviation; ADEM: acute disseminated encephalomyelitis; VEP: visual evoked potentials; CSF: cerebrospinal fluid, F: female; M: male.
[a] Yılmaz Ü, Anlar B, Gücüyener K; Turkish Pediatric Multiple Sclerosis Study Group. Characteristics of pediatric multiple sclerosis: The Turkish pediatric multiple sclerosis database. Eur J Paediatr Neurol. 2017; 21(6):864-872.

pediatric group than in adults [61,62]. Consistently, OCBs restricted to CSF were more frequent in our current cohort (82.8%) than in previous series (68.0%) [6]. OCB status of younger children with MS has also changed in recent years: a multi-centre study published in 2010 reported younger children were less likely to exhibit OCBs (43% in <11 years, 63% in 11–17 years), another published in 1999 describing 49 MS patients with disease onset <6 years found OCBs in only 17% [8,63]. On the other hand, a study published in 2004 including 136 patients <16 years and 24 patients <10 years at onset observed similar frequency of OCBs in different age groups, and a more recent study reported no significant difference for OCB status between earlier and later onset pediatric MS [60,61]. However, both series had too few early-onset cases. In our cohort, later-onset patients were more likely to have OCBs compared to earlier-onset group (84.9% versus 70.0%, respectively). The subgroup analysis revealed that only 3/9 (33%) children with onset ≤6 years, and 32/43 (74.4%) children with onset from 7 to 10 years of age had OCBs. We also observed that of 17 children whose OCBs were negative at initial lumbar puncture 10 turned positive after median eight months, indicating the ongoing process of intrathecal immune response in some pediatric patients. We may interpret the evidence from previous studies including ours and current cohorts as: 1) the exclusion of patients with MOG-IgG related disease resulting in exclusion of a number of younger patients and subsequent increase in the frequency of patients with OCB; 2) the presence of a subgroup of very young children (age ≤6 at onset) who have neither OCBs nor anti-MOG-IgG, possibly representing other undescribed disorders.

In consistence with our current and previous reports, optic neuritis has been reported to be a presenting symptom in about one fourth to one third of pediatric MS patients [6,19]. VEP is a useful diagnostic tool not only to confirm the diagnosis of optic neuritis but also to detect subclinical optic nerve involvement [64,65]. VEP is already abnormal at the beginning of the disease in approximately one-third of patients without clinical optic neuritis [6,64,65], and a recent study shows the addition of the optic nerve as a fifth region for dissemination in space improved the diagnostic performance by slightly increasing the accuracy and the sensitivity without lowering the specificity [65].

4.7. Treatment

Prompt initiation of a first-line DMT after diagnosis is recommended by the International Pediatric MS Study Group [66]. However, treatment strategies often reflect the experience of the treating physician or the center, and availability of DMTs. Broadly, two approaches to treatment exist: 1) escalation therapy, defined as administration of first-line DMTs and changing to second or third line in case of ongoing disease activity, 2) initial induction therapy to achieve disease stability, followed by maintenance therapies. Current treatment regimens in children generally follow the escalation route, starting with lower efficacy medications with better safety profiles, escalating to higher efficacy medications if children continue to relapse on treatment [66]. However certain recent studies in adult onset MS show more favorable long-term outcomes after early intensive vs. escalation therapy [67,68]. Among more than 15 DMTs approved for adult-onset MS, only fingolimod (both in the US and EU) and teriflunomide (EU only) have been approved for pediatric MS, the remainder being used off-label. These facts and concerns for long-term safety have likely resulted in a cautious treatment strategy using first-line treatment options for long periods before switching to highly active treatments. However, due to high recurrence rate and lesion burden on neuroimaging, pediatric neurologists currently tend to use highly active treatments earlier, particularly because of reports on highly effective treatments possibly preventing long-term physical and cognitive impairment [46,58,69–71]. This change in treatment approach was also somewhat reflected in our study: while no patient was initially received highly active treatment in our previous cohort [6], in the current series 41 (6.5%) patients were initially treated with highly active medications (dimethyl fumarate, fingolimod, ocrelizumab, rituximab, natalizumab).

While there is no general consensus on the definition of treatment response for MS, the International Pediatric MS Study Group proposed a working definition for inadequate treatment response in pediatric MS: continuing clinical and/or MRI activity (increase or no reduction in relapse rate, or new T2 or contrast enhancing lesions on MRI from pre-treatment period, or ≥ two confirmed clinical or MRI relapses within a 12-month period or less) in patients who are fully compliant and receive full dose therapy for an adequate period of time (at least six months) [66]. Since our study was based on retrospective information where no standard imaging protocols were applied, we did not include MRI

findings to assess treatment response, which we defined as the absence of clinical relapse for at least 12 months after the medication has been titrated to the maximum dose and used for sufficient time (generally 3–6 months determined by treating physicians). According to this definition, 43.6% of our patients remained relapse-free after initiation of DMTs, a rate similar to a previous study reporting up to 60% that require escalation to more effective therapy [59,72].

5. Conclusion

Pediatric MS seems to be less common in children younger than 12 years than previously reported, likely due to exclusion of patients with antibody-mediated diseases. Thus, pediatric MS appears to be more homogeneous and more similar to adult MS than previously thought.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare the absence of any potential conflicts of interest.

Acknowledgement

The authors thank all their colleagues for their help in the follow-up of the patients.

Note added in proof: part of the patients in the present cohort were included in the newly published study: Solmaz I, Doran T, Yousefi M, Konuskan B, Oncel I, Vural A, Anlar B. Frequency of myelin oligodendrocyte glycoprotein antibodies in pediatric onset multiple sclerosis. Mult Scler Relat Disord. 2022 Aug 8;68:104097. doi: 10.1016/j.msard.2022.104097. Epub ahead of print. PMID: 35998500.

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