OPEN ACCESS
OPUS AUGSBURG

Universität Augsburg
Universitätsbibliothek

Characterization of children with early onset pediatric multiple sclerosis

Franziska Kauth, Annikki Bertolini, Eva-Maria Wendel, Georgia Koukou, Ines El Naggar, Jena Chung, Matthias Baumann, Christopher Schödl, Christian Lechner, Sandra Bigi, Astrid Blaschek, Jan Georg Hengstler, Mareike Schimmel, Margherita Nosadini, Stefano Sartori, Marco Puthenparampil, Karin Storm van's Gravesande, Anne Drenckhahn, Marc Nikolaus, Birgit Kauffmann, Charlotte Thiels, Martin Georg Häusler, Matthias Eckenweiler, Michael Karenfort, Adela Della Marina, Ayberk Selek, Ibrahim Öncel, Barbara Kornek, Markus Reindl, Kevin Rostásy

Angaben zur Veröffentlichung / Publication details:

Kauth, Franziska, Annikki Bertolini, Eva-Maria Wendel, Georgia Koukou, Ines El Naggar, Jena Chung, Matthias Baumann, et al. 2025. "Characterization of children with early onset pediatric multiple sclerosis." *European Journal of Paediatric Neurology* 54: 113–20. https://doi.org/10.1016/j.ejpn.2025.01.006.

Nutzungsbedingungen / Terms of use: **CC BY-NC-ND 4.0**

Dieses Dokument wird unter folgenden Bedingungen zur Verfügung gestellt: / This document is made available under these conditions:
CC-BY-NC-ND 4.0: Creative Commons: Namensnennung - Nicht kommerziell - Keine Bearbeitung
Weitere Informationen finden Sie unter: / For more information see:
https://creativecommons.org/licenses/by-nc-nd/4.0/deed.de

Characterization of children with early onset pediatric multiple sclerosis

Franziska Kauth [a], Annikki Bertolini [a], Eva-Maria Wendel [b], Georgia Koukou [a], Ines El Naggar [a], Jena Chung [c], Matthias Baumann [d], Christopher Schödl [d], Christian Lechner [d], Sandra Bigi [e,f], Astrid Blaschek [g], Jan Georg Hengstler [h], Mareike Schimmel [i], Margherita Nosadini [j,k], Stefano Sartori [j,k], Marco Puthenparampil [l], Karin Storm van's Gravesande [m], Anne Drenckhahn [n], Marc Nikolaus [n], Birgit Kauffmann [o], Charlotte Thiels [p], Martin Georg Häusler [q], Matthias Eckenweiler [r], Michael Karenfort [s], Adela Della Marina [t], Ayberk Selek [u], Ibrahim Öncel [u], Barbara Kornek [v], Markus Reindl [w], Kevin Rostásy [a,*]

[a] *Department of Pediatric Neurology, Children's Hospital Datteln, Witten/Herdecke University, Datteln, Germany*
[b] *Department of Pediatric Neurology, Klinikum Stuttgart/Olgahospital, Stuttgart, Germany*
[c] *Department of Paediatrics, Kepler University Hospital Linz, Austria*
[d] *Department of Paediatrics, Division of Paediatric Neurology, Medical University of Innsbruck, Austria*
[e] *Division of Pediatric Neurology, Department of Pediatrics, Children's Hospital of Central Switzerland, Lucerne, Switzerland*
[f] *Institute for Social and Preventive Medicine, University of Bern, Bern, Switzerland*
[g] *LMU University Hospital, Department of Pediatrics, Division of Pediatric Neurology, MUC iSPZ Hauner - Munich University Center for Children with Medical and Developmental Complexity, Dr. von Hauner Children's Hospital, Munich, Germany*
[h] *Leibniz Research Centre for Working Environment and Human, Factors (IfADo), University of Dortmund, Dortmund, Germany*
[i] *Department of Pediatrics and Adolescent Medicine, Division of Neuropediatrics, Faculty of Medicine, University of Augsburg, Augsburg, Germany*
[j] *Paediatric Neurology and Neurophysiology Unit, Department of Women's and Children's Health, University Hospital of Padua, Padua, Italy*
[k] *Paediatric Research Institute "Città della Speranza,", Padova, Italy*
[l] *Department of Neuroscience, University Hospital of Padua, Padua, Italy*
[m] *Department for Neuropediatrics and Muscle Disease, Medical Center - University of Freiburg, Faculty of Medicine, Freiburg, Germany and Department of Pediatrics, Child and Adolescent Psychosomatics, Technical University Munich, Munich, Germany*
[n] *Department of Pediatric Neurology and Center for Chronically Sick Children, Charité-Universitätsmedizin Berlin, Corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health (BIH), Germany*
[o] *Eltern-Kind-Zentrum Prof. Hess, Klinikum Bremen Mitte, Department of Pediatrics and Adolescent Medicine, Pediatric Neurology, Bremen, Germany*
[p] *Department of Neuropediatrics and Socialpediatrics, University Hospital of Ruhr University Bochum, Bochum, Germany*
[q] *Division of Neuropediatrics and Social Pediatrics, Department of Pediatrics, RWTH Aachen University Hospital, Aachen, Germany*
[r] *Department of Neuropediatrics and Muscle Disorders, Medical Center-University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany*
[s] *Department of General Pediatrics, Neonatology and Pediatric Cardiology, University Children's Hospital, Heinrich Heine University Duesseldorf, Germany*
[t] *Department of Neuropediatrics, Developmental Neurology and Social Pediatrics, Centre for Neuromuscular Disorders in Children, University Hospital Essen University of Duisburg-Essen, Essen Germany*
[u] *Department of Pediatric Neurology, Hacettepe University Faculty of Medicine, Ankara, Turkey*
[v] *Department of Neurology, Medical University of Vienna, Vienna, Austria*
[w] *Clinical Department of Neurology, Medical University Innsbruck, Innsbruck, Austria*

ARTICLE INFO

Keywords:
Children
Multiple sclerosis
Early onset pediatric MS
Puberty
Pediatric

ABSTRACT

Background: Early onset pediatric multiple sclerosis (EOPMS) provides an early window of opportunity to understand the mechanisms leading to MS.
Objective: To investigate clinical, laboratory and imaging differences between children with early onset pediatric MS (<11 years, EOPMS) and late onset pediatric MS (≥11 years, LOPMS).
Methods: Mostly prospectively collected data of children with MS including clinical presentation, MRI at onset, time to second relapse, relapse rate, treatment history, and CSF markers were eligible.

* Corresponding author. Pediatric Neurology, Witten/Herdecke University, Children's Hospital Datteln, Dr. Friedrich-Steiner Str. 5, Datteln, D-45711, Germany.
E-mail address: kevin.rostasy@uni-wh.de (K. Rostásy).

Results: In total 274 children were included, n = 53 children with EOPMS and n = 221 children with LOPMS. In children with EOPMS both sexes were equally affected, while in LOPMS the female sex was more prevalent ($p < 0.001$). Presence of additional oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF) was comparable in both age groups (92.3 % vs 89.5 %). Children with EOPMS had more relapses in the first 2 years ($p = 0.004$). Children with LOPMS had significantly more spinal lesions ($p = 0.001$). Presence of a prior EBV infection tested in a subset of children with EOPMS (n = 34) was only detected in 27/34 (79 %).
Conclusion: Our findings suggest that both groups share important similarities but also important differences such as an increased relapse rate and a higher amount of infratentorial lesions in EOPMS. Furthermore, our results allude to a prior EBV-infection possibly not being an indispensable requirement for the development of MS in children with EOPMS.

Abbreviations

AAb	autoantibody
Abs	autoantibodies
ADC	Apparent Diffusion Coefficient
ADEM	acute disseminated encephalomyelitis
ADS	acute demyelinating syndrome
ADHD	attention deficit hyperactivity disorder
AE	autoimmune encephalitis
AQP4	aquaporin-4
ASD	autism spectrum disorder
CA	cerebellar ataxia
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
DIS	dissemination in space
DIT	dissemination in time
DMT	disease modifying therapy
DWI	Diffusion Weighted Imaging
EA	early antigen
EBNA	Epstein-Barr virus nuclear antigen
EBV	Epstein-Barr virus
EDSS	Expanded Disability Status Scale
e.g	example given
EOPMS	early onset pediatric multiple sclerosis
FLAIR	Fluid Attenuated Inversion Recovery
Gd	gadolinium
IQR	interquartile range
LOPMS	late onset pediatric multiple sclerosis
MOG	myelin-oligodendrocyte-glycoprotein
MOGAD	myelin-oligodendrocyte-glycoprotein-associated disease
MRI	magnetic resonance imaging
MS	multiple Sclerosis
OCBs	oligoclonal bands
ON	optic neuritis
VCA	viral capsid antigen

1. Introduction

Multiple sclerosis (MS) is the most common cause for neurologic disability in young adults and occurs in approximately 3–5 percent of all cases already in childhood [1–3]. Compared to adults, children with MS are known to have more relapses in the first six years after disease onset [4] but show a better recovery [5]. Especially rare, with an incidence of 0.09/100000, is early onset pediatric MS (EOPMS) defined as MS with disease onset below or equal to the age of ten. In EOPMS the sex ratio is balanced, while in children older than 10 years, the female sex dominates [6]. Moreover, in EOPMS, children are more likely to have a polysymptomatic onset with motor and brainstem involvement, sphincter dysfunction, cognitive impairment but nevertheless a good recovery after the first episode [7–9]. Children older than 10 years often present with a monosymptomatic episode characterized by optic neuritis (ON), unilateral sensory deficits or motor weakness [10] and do have more often additional oligoclonal bands (OCBs) in cerebrospinal fluid (CSF) compared to EOPMS [10–12]. Several studies also showed a high prevalence of a previous Epstein-Barr virus (EBV) infection in LOPMS, similar to adults with MS [12–15]. The presence of a prior EBV infection in a larger cohort of children younger than 11 years of age has not been reported so far [16–19].

The aim of our study was to investigate differences in children with EOPMS compared to children with LOPMS with regards to clinical, laboratory, imaging features and EBV-status.

2. Methods

2.1. Patients

Between 2007 and 2023 more than 1300 children with a suspected acute demyelinating syndrome (ADS) were sent to our attention from 60 different medical centers in Germany, Austria, Italy, Switzerland, Turkey, and Canada and included in an ongoing prospective study (BIOMARKER-study) to assess whether a group of biomarkers in combination with clinical and neuroradiological data can be used to differentiate between MS, ADEM or other neuroimmunological diseases after the first clinical event. For the purpose of this study, 228 children with a final diagnosis of MS according to the McDonald criteria 2017 were selected prospectively from the cohort mentioned above and included if a complete data set was available (see below). In addition, 36 children with pediatric MS from other Pediatric Neurology Departments were referred retrospectively to this multicentered, observational study.

The final cohort was then divided into two age groups: Children younger than 11 years with no evidence of secondary sexual development in terms of recorded Tanner stages less than pubic-hair growth 2, breast development 1, genitalia 1, and no other documented onset of puberty (start of pubic hair growth, breast development, first menarche, enlargement of scrotum/testes) were defined as EOPMS. The second group consisted of children aged between 11 and 17 years defined as peri/post-pubertal MS or LOPMS.

2.2. Demographic, clinical and laboratory features

The following demographic, clinical and laboratory features were obtained: sex, age at first manifestation, date of first event, date of second event, time interval in days between first and second event, number of relapses in the first two years, mono-versus polysymptomatic

onset, in addition to the presence of OCBs. If available, intrathecal IgM synthesis (increased IgM index in the CSF), cell count, protein in CSF, presence of autoantibodies (abs) directed against myelin oligodendrocyte glycoprotein (MOG) or aquaporin-4 (AQP4) in serum and EBV infection status, were collected. Referring physicians were asked to provide an EDSS score at regular intervals and the treatment history. The disease modifying therapy (DMT) was recorded and divided into three treatment groups, according to the German guideline: low efficacy (e.g. interferons, glatiramer acetate, teriflunamide, dimethyl fumarate), medium (fingolimod) or high efficacy (natalizumab, rituximab [RTX]). Also, the switch from a low DMT to a medium and/or high efficacy treatment was recorded with yes/no.

Furthermore, the presence of psychiatric comorbidities (depression, fear, attention deficit hyperactivity disorder [ADHD]), moodiness, autism spectrum disorder [ASD]), eating disorders), decline in school/cognitive performance (difficulties with concentration, worse grades, early school leaving) and fatigue symptoms (feeling tired after very little activity, waking up feeling tired, and heavy limbs), was assessed by asking about the symptoms at the last follow-up appointment and scored with present-yes or absent-no.

2.3. MR-imaging

MRI evaluation was carried out in two steps. First, for all MRIs, the following variables were analyzed: total number of lesions, total number of infratentorial and supratentorial lesions, in addition to the presence of spinal lesions. Furthermore, in all children follow up MRIs were evaluated for new lesions under DMT. For 148 children this was performed by the first author and for all other children (n = 126) the MRI evaluation was performed by the referring physician at the respective clinic.

Second, cerebral MRIs of a subset of children with EOPMS (n = 14) and LOPMS (n = 30) were evaluated in more detail by three reviewers. The following scoring system was used: total number of brain lesions allocated into three groups including [1] no or only small non-specific lesions [2], 1–10 lesions or [3] more than 10 lesions. In addition, the number of supra- and infratentorial lesions, the involvement of corpus callosum, deep grey matter (thalamus and/or basal ganglia), brainstem, cerebellum, and periventricular white matter. Furthermore, lesions were assigned to one of the following qualities [1]: predominantly poorly demarcated lesions involving grey and/or white matter [2], extensive confluent white matter changes [3], predominantly well-demarcated white matter lesions (MS-like), and [4] mixed qualities. The size of lesions was categorized as [1] smaller than 2 cm [2], 2 cm or larger or [3] both sizes mixed (smaller and larger than 2 cm). In addition, the following features were analyzed: occurrence of T1-hypointense lesions, lesions with gadolinium (Gd) enhancement, and lesions of restricted diffusion (high signal on Diffusion Weighted Imaging [DWI] and low signal on Apparent Diffusion Coefficient [ADC]).

2.4. Antibody assay

In a subset of 180 children with MS serum samples were tested for MOG- and AQP4-abs with live cell-based immunofluorescence assays as previously described [20].

2.5. EBV infection

In 136 children a prior or recent EBV infection at first manifestation was assessed by determining the following serological markers: presence of serum EBNA-1 abs in addition to anti VCA IgG/IgM (Viral Capsid Antigen) and anti EBV EA (Early Antigen) abs in the blood by enzyme-linked immunosorbent assay (ELISA) and detection of EBV DNA (PCR). The screening was performed at the respective hospital at onset.

2.6. Statistical analysis

Statistical analysis was performed with SPSS, version 29.0. For the analysis of demographical in relation to clinical data, for categorical variables, the Chi-square test was used. When more than 20 % of cells had expected frequencies <5, the Fisher's exact test was used. The Wilcoxon-Mann Whitney test was used for independent data (two-sided) for continuous variables. The Cox regression (or proportional hazards regression) method was applied to analyze the association between prognostic factors for the risk of reaching irreversible EDSS scores and 2. The statistical significance was defined by $p < 0.01$.

The results were not false discovery rate (fdr) adjusted and should therefore be considered as explorative.

2.7. Standard protocol approvals, registrations and patient consents

This BIOMARKER study was approved by the Ethics committee of Witten/Herdecke University, Germany as well as the Ethics committee of Medical University Innsbruck, Austria. Patients included via the BIOMARKER study gave written consent. Patients contributed by other hospitals who were not part of the BIOMARKER-study were reported in an anonymous fashion according to local guideline.

3. Results

3.1. Demographical data and clinical presentation

A total of 274 patients were included in the study. 53 children (19 %) were classified as EOPMS, and 221 (81 %) patients were classified as LOPMS.

An equal sex distribution was observed in EOPMS and female predominance in children older than 10 years with MS (1:1 vs. 3:1, $p < 0.001$). No difference was found in the frequency of a mono-compared to a polysymptomatic onset in the two age groups ($p = 0.627$). Children with EOPMS had more often 2 or more relapses in the first 2 years (75 % vs. 54 %, $p = 0.004$).

The frequency of positive OCBs in children with EOPMS was high and comparable to children with LOPMS (92.3 % vs 89.5 %, $p = 0.560$). MOG-abs were tested in 37/53 children with EOPMS and 143/221 children with LOPMS. MOG-abs were detectable in one child with EOPMS, and in LOPMS only 4 children were tested MOG-abs positive (4/143). Follow-up samples showed decreasing titers in patients initially tested positive and the children did not fulfill the Banwell criteria for MOGAD. No difference between the age groups was found comparing in the presence of fatigue, decline in school performance and signs of psychiatric comorbidities ($p = 0.651$, $p = 0.196$, $p = 0.346$).

The screening for the specific psychiatric comorbidities, showed the following: in EOPMS, in 12/41 (29.3 %) patients, psychological symptoms were reported (6/12 signs of depression, 1/12 sleeping disorder, 1/12 fear, 3/12 ADHD, 1/12 ASD), compared to 61/230 (26.5 %) patients in LOPMS (45/61 signs of depression, 1/61 sleeping disorder, 5/61 fear, 1/61 ADHD, 3/61 borderline personality disorder, 2/61 hallucinations, 3/61 ASD, 1/61 anorexia nervosa).

In EOPMS 9/53 (18.8 %), children were initially diagnosed with ADEM. All children subsequently had further demyelinating episodes and new lesions on MRI and therefore were assigned the diagnosis MS. They were all MOG-abs negative and 7/9 had positive OCBs at that time. None of the children in the older group were initially diagnosed with another disease. A detailed summary of clinical and demographical features can be found in Tables 1 and 2.

3.2. MRI features in EOPMS and LOPMS

All children included underwent MR-imaging of the brain and in 149 children additionally spinal imaging was performed. In a first step we analyzed the total number of lesions in the first cMRI scan which did not

differ between the two age groups (p = 0.478) nor did the number of supratentorial lesions (p = 0.239). There was also no difference in the presence of infratentorial lesions (72 % vs 64 %, p = 0.300) but in children with EOPMS the total number of infratentorial lesions was higher (20 % vs. 7.6 %, p = 0.029). In addition, children with LOPMS had significantly more often spinal lesions (64.1 % vs. 37.5 %, p < 0.001). Both groups had approximately equal numbers of new lesions in the follow up MRI studies while receiving treatment (26.1 % vs. 37.1 %, p = 0.161). Table 3 lists the main MRI features grouped by age.

In a second step, we compared the MRIs of the brain at initial presentation for a subset of EOPMS (n = 17) and LOPMS (n = 30) in more detail: in EOPMS, 36 % had a corpus callosum lesion, compared to 87 % in LOPMS (p < 0.001). All LOPMS were affected by periventricular white matter lesions and 77 % of them had subcortical lesions, while all children with EOPMS had subcortical lesions and 86 % were affected by periventricular lesions (p = 0.096; p = 0.078). Both age groups did not differ in size (p = 1.000) or quality of lesions (p = 0.294).

In EOPMS, 29 % had brainstem lesions compared to 47 % in LOPMS 47 % (p = 0.256). Furthermore, 57 % of children with EOPMS and 37 % with LOPMS, had lesions involving the cerebellum (p = 0.202). A table with the detailed subset MRI evaluation can be found in the appendix (Table 4).

3.3. Treatment

DMTs were frequently used in both age-groups with several differences. On average, it took 300 days until treatment was initiated in children with EOPMS and 388 days in children with LOPMS (p = 0.084).

In EOPMS, 9/51 (17.6 %) and in LOPMS 22/218 (10.1 %) children did not receive any treatment over the course of the observation period (p = 0.024, mean 48 months (range 24–84). Although a similar percentage of both groups received high efficacy treatment as first DMT (15.7 % vs 13.8 %) children with EOPMS were very rarely given the medium efficacy substance fingolimod 2/51 (3.9 %). Of 237/274 children, precise information on the first prescribed drug was given. Of 41 children with EOPMS, 30/41 received basic treatment and 14/41 received escalation therapy as first DMT (23/41 interferons, 3/41 glatiramer acetate, 2/41 fingolimod, 2/41dimethyl fumarate, 2/41 teriflunamid, 1/41 natalizumab, 5/44 CD-20 depleting agents 3/41 other).

Of 196 children with LOPMS 116/196 received basic therapy, and 77//196 received escalation therapy as first DMT (91/196 interferons, 16/196 glatiramer acetate, 46/196 fingolimod, 4/196dimethyl fumarate, 5/196 teriflunamid, 29/196 natalizumab, 2/196 rituximab, 3/196 other).

3.4. Outcome

Of 259 children a detailed follow-up including EDSS scores was available. Overall, mean follow-up time was 4.3 years (range 2–7 years). All 259 children were followed at least for 2 years. After 7 years in EOPMS 93.5 % still had an EDSS score of <2 (scores at 7 years follow up: 21/31 EDSS 0, 1/31 EDSS 1, 7/31 EDSS 2, 2/31 EDSS 3), and 79.2 % in LOPMS (scores at 7 years follow up: 20/48 EDSS 0, 12/48 EDSS 1, 4/48 EDSS 1.5, 2/48 EDSS 2, 3/48 EDSS 2.5, 4/48 EDSS 3) (p = 0.082). One child of the LOPMS group reached EDSS 4 and two children reached an EDSS of 5.5. In 39 % of children with EOPMS and in 28 % with LOPMS a decline in school performance was reported (p = 0.196).

Univariate Cox Models of Time from MS onset to EDSS 2 showed an increased risk of reaching EDSS 2 in the EOPMS group (n = 53) if they had psychological symptoms (p = 0.034).

In LOPMS (n = 211), fatigue (p = 0.026), and the presence of psychological symptoms (p < 0.001) were significantly associated with a higher risk of reaching EDSS 2 (see Table 5).

3.5. EBV infection

In 34/53 (64.2 %) children with EOPMS, the referring physicians had tested for evidence of a prior or recent EBV-infection. 27/34 children (79.4 %) were reported as being EBNA-1 ab positive. 7/34 (20.6 %) children were EBNA-1 negative. Of those, 3/7 EBNA-1 negative children had a complete EBV serology performed including negative ab testing for EBV VCA IgG, EBV VCA IgM, and EBV EA IgG, showing they neither had a prior nor a current infection at time of their first MS event. Another 2/7 EBNA-1 negative children had a EBV PCR performed that was negative at their first attack. One child was checked for EBV IgM at the first attack, which was found to be negative. In one child only EBNA-1 abs were tested. 1/7 children was MOG-ab positive at time of examination.

As we had the focus on EOPMS we only asked for EBNA-1 abs and not the detailed EBV screening in LOPMS: 83/102 children were EBNA-1 positive. Of these, 1/83 was also MOG-ab positive at time of examination.

4. Discussion

In our study we show that EOPMS and LOPMS share crucial similarities but also differences such as an increased relapse rate and a higher amount of infratentorial lesions at diagnosis in younger children. Additionally, our results imply, that a prior EBV-infection might possibly not be a sine qua non for the development of MS in children with EOPMS, suggesting that other triggers can also lead to the development of pediatric MS.

We could confirm previous results, such as the different sex distribution between the two age groups characterized by a balanced sex distribution in younger children, and female predominance in adolescence. This underlines the important role of physiological changes occurring in puberty [21,22], particularly the different levels of sex hormones, with regards to MS risk and progression of disease in older children and adults [23].

Another focus of our study was to assess potential differences in MR-imaging. Our results show that children with EOPMS had less often spinal lesion. This is particularly interesting, as the presence of spinal lesions is regarded as poor long-term prognostic marker [6,24–26]. Contrary to our expectations, the total number of lesions, as well as the number of supratentorial lesions, did not differ between the two groups. In a subset of children with a more detailed MRI evaluation, we could not find significant differences in lesion characteristic such as size between the two age groups. Nevertheless, we discovered in our cohort that in a high percentage of patients of both age groups, hypointense lesions on T1, commonly known as black holes, are occurring, meaning signs of brain tissue loss in pre-as well as in post pubertal MS.

Both age groups showed a high frequency of OCBs at first manifestation in the present study, which confirms that the presence of OCBs is a powerful diagnostic tool already in children with EOPMS. Our finding is in line with previous study performed by Pohl and colleagues but in contrast to other studies [10,11,27,28]. 1/58 children with EOPMS and 4/228 children with LOPMS had positive MOG-antibodies at time of their first event. All children showed decreasing titers rapidly shortly after. All of them had a typical course of MS with an EDSS score of still 0 after 2 years FU. They also had typical MRIs, and OCBs. One child with LOPMS was treated with fingolimod as first DMT the rest EOPMS and LOPMS with interferons.

One of our main aims was to assess the frequency of a prior EBV infection in EOPMS. Remote EBV infection is associated with an increased risk for MS in adults and children with LOPMS, but there has not been data for children with EOPMS [17,29–31]. In our cohort only 27/34 children with EOPMS harbored EBNA-1 abs. A detailed EBV serology was performed in 3/3 children with EOPMS and absent EBNA-1- antibodies to rule out a prior but also a current EBV infection at time of the first MS event. All three children had a typical course of MS

with positive OCBs, typical MRI lesions and clinical manifestation. Interestingly in our cohort, also only 83/102 children with LOPMS had positive EBNA.1 antibodies. Larger studies are needed to investigate the prevalence of a prior EBV infection and the role of other triggers that might lead to EOPMS and other viral pathogens such as CMV that seem to exert a protective role [29].

A further interesting finding was that EOPMS was very rarely given the medium efficacy substance fingolimod 2/51 (3.9 %) but a similar percentage of both age groups received high efficacy treatment as first DMT (15.7 % vs 13.8 %), so it seems that highly effective substances seem to be already used in younger children, even if they are not yet officially licensed for this group.

Overall, EDSS progression in our cohort was slow: of all 274 patients only 13 children reached an EDSS of 3 and only 5 patients an EDSS of 4. To maintain statistical power, we therefore estimated prognostic factors for reaching an estimated disability risk only for EDSS 2. These were presence of psychiatric comorbidities in EOPMS and fatigue and presence of psychiatric comorbidities in LOPMS.

More recently it has been approved that the presence of fatigue is an indication for escalating treatment. In our cohort fatigue occurred in approximately one third of children in our cohort affecting both groups equally, just as psychiatric comorbidities. The most common psychiatric comorbidity was depressive mood in nearly every fifth child. Even though there was no significant difference between the two groups with regards to decline in school performance, our data is in line with previously conducted studies [32], which showed that early-onset, higher relapse rate and high lesion load have a higher risk of decline in school performance [33,34].

The following limitations need to be addressed: Tanner stages were not assessed for all children due to the retrospective design. Secondly, follow-up time was only around 4 years with a maximum of 7 years in a subgroup of children mainly driven by loss to follow-up after transition to adult neurology. Furthermore, we did not have a complete EBV serology for all prepubertal children and some of the tests had been performed some years ago. As today's test are more accurate and specific, we recommend reproducing our finding in a larger cohort of EOPMS including markers for infection using today's technology.

Lastly, we were only able to assess the MRI features in a small sample size of children with EOPMS, thereby possibly not including the full spectrum of possible findings in this age group.

5. Conclusion

Our data indicate differences in early and late onset pediatric MS. Importantly, a prior EBV-infection does not seem to be a sine qua non for the development of MS at least in children with EOPMS.

Declaration of conflict of interest

Dr. Bertolini receives travel and congress fees from Octapharma and honorary as member of the advisory board from Horizon pharmaceutics. Dr. Wendel receives travel cost compensation by UCB pharma. Dr. Bigi receives funding from pharmaceutical industries (Novartis, Roche, Sanofi-Aventis, Biogen) for research projects regarding the Swiss Pediatric Inflammatory Brain Disease Registry and serves as an international reviewer for the Operetta II study. Dr. Schimmel receives compensation for advisory boards and talks from Roche, Eisai and Takeda. Dr. Puthenparampil reports grants from Almirall, Teva, Sanofi Genzyme, Merck Serono, Biogen Italy and Novartis, is consultancy for Novartis, Biogen Italy and Sanofi Genzyme and is board member at Sanofi Genzyme, Novartis and Biogen Italy. Prof. Kornek receives honoraria for speaking and participation in advisory boards from Biogen, BMS-Celgene, Janssen, Merck, Novartis, Teva, Sanofi and Roche. Prof. Reindl receives research support by Roche Austria (Vascage subproject B.9): Biomarkers of neuroinflammation, by the Austrian Science Funds (FWF) (P32699): Epitope specificity of MOG antibodies and by the Austrian Research Promotion Agency (FFG) (Vascage subproject B.9): Biomarkers of neuroinflammation. Prof. Rostásy is consultant for Operetta II Study/Roche and receives honoraria for talks (UCB, Euroimmun, Horizon. Mrs. Kauth, Dr. Koukou, Dr. El Naggar, Dr. Chung, Dr. Baumann, Mr. Schödl, Dr. Lechner, Dr. Blaschek, Prof. Hengstler, Dr. Nosadini, Prof. Sartori, Dr. Storm van's Gravesande, Dr. Drenckhahn, Dr. Kauffmann, Dr. Thiels, Prof. Häusler, Dr. Eckenweiler, Dr. Karenfort, Dr. Della-Marina, Dr. Selek, and Dr. Öncel have nothing to disclose.

Acknowledgement

We thank the Swiss Pediatric Inflammatory Brain Disease Registry for collaboration. Prof. Sartori's and dr. Nosadini's research activity is supported by the Pediatric Research Institute 'Città della Speranza', Padova, Italy, and the project 'MUSICA'.

Appendix

Table 1
Summary of clinical and demographical features of 274 children with MS grouped by age at onset.

Features	Early onset	Late onset	p-value
Number of patients (n = 274)	53	221	–
Sex			<0.001
Male	27 (50.9 %)	52 (23.5 %)	
Female	26 (49.1 %)	169 (76.5 %)	
Mean Age	7.99 (SD 1.97)	14.33 (SD 1.77)	–
Symptoms			0.627
Monosymptomatic	31 (58.5 %)	120 (54.7 %)	
Polysymptomatic	22 (41.5 %)	99 (45.3 %)	
Number of relapses in the first 2 years			0.004
Only 1	13 (24.5 %)	102 (46.2 %)	
2 and more	40 (75.5 %)	119 (53.8 %)	
Mean time in days between first and second episode	254.53	283.28	0.147
Diagnosis at first event			<0.001
ON	8 (16.7 %)	34 (17.7 %)	
ADEM	9 (18.8 %)	0 (0 %)	
CIS	7 (14.6 %)	34 (17.7 %)	
RIS	3 (6.3 %)	3 (1.6 %)	
MS	21 (43.8 %)	121 (63 %)	

(*continued on next page*)

Table 1 (*continued*)

Features	Early onset	Late onset	p-value
OCB			0.560
Present	48 (92.3 %)	190 (89.5 %)	
Absent	4 (7.7 %)	22 (10.4 %)	
CSF-cell count/µl (Mean)	10.813	13.832	0.096
CSF-protein mg/l (Mean)	86.14	138.19	0.817
IgM			0.061
Positive	5 (25 %)	56 (47.5 %)	
Negative	15 (75 %)	62 (52.5 %)	
Prior EBV infection			0.804
Positive	27 (79.4 %)	83 (81.4 %)	
Negative	7 (20.6 %)	19 (18.6 %)	
Serum MOG Ab			0.583
Positive	1 (2,7 %)	4 (2.8 %)	
Negative	36 (97,3 %)	139 (97.2 %)	
Serum Aquaporine4 Ab			1.000
Positive	0 (0 %)	1 (0.01 %)	
Negative	33 (100 %)	140 (99.3 %)	

Table 2
Clinical Features and Presentation during course of disease.

Features	Early onset	Late onset	p-value
First DMT			0.024
None	9 (17.6 %)	22 (10.1 %)	
Low efficacy	32 (62.7 %)	120 (55.0 %)	
Medium efficacy	2 (3.9 %)	46 (21.1 %)	
High efficacy	8 (15.7 %)	30 (13.8 %)	
Mean time from diagnosis to start DMT (in days)	299.9	387.72	0.084
Escalation Therapy			0.656
yes	24 (51.1 %)	99 (54.7 %)	
No	23 (48.9 %)	82 (45.3 %)	
Reason for escalation			0.137
MRI lesions load	9 (37.5 %)	22 (20.4 %)	
Relapse	5 (20.8 %)	43 (39.8 %)	
Both	5 (20.8 %)	14 (13.0 %)	
Other	5 (20.8 %)	29 (26.9 %)	
Relapses after escalation treatment			0.857
None	21 (70 %)	71 (68.3 %)	
1 and more	9 (30 %)	33 (31.7 %)	
Fatigue			0.651
Yes	14 (37.8 %)	57 (33.9 %)	
No	23 (62.2 %)	111 (66.1 %)	
Psychiatric Symptoms			0.346
Yes	15 (34.1 %)	53 (24 %)	
no	29 (65.9 %)	167 (76 %)	
Decline in school performance			0.196
Yes	15 (38.5 %)	51 (28 %)	
no	24 (61.5 %)	131 (72 %)	
6 years – follow-up			0.082
EDSS 0-2	29 (93.5 %)	38 (79.2 %)	
EDSS 2.5 and higher	2 (6.5 %)	10 (20.8 %)	

Table 3
General Overview: Main MRI Features.

Features MRI	Early onset	Late onset	p-value
McDonald 2017 criteria			0.381
DIS	6 (12.2 %)	23 (10.8 %)	
DIT	1 (2.0 %)	16 (7.5 %)	
DIS + DIT	42 (85.7 %)	174 (81.7 %)	
Optic neuritis			0.254
Yes	4 (8.3 %)	24 (11.5 %)	
No	39 (81.3 %)	172 (82.3 %)	
bilateral	2 (4.2 %)	10 (4.8 %)	
with contrast agent	3 (6.3 %)	3 (1.4 %)	
Infratentorial lesions			0.300
Yes	32 (72.7 %)	137 (64 %)	
No	12 (27.3 %)	77 (36 %)	
Spinal lesions			<0.001

(*continued on next page*)

Table 3 (*continued*)

Features MRI	Early onset	Late onset	p-value
Yes	18 (37.5 %)	132 (64.1 %)	
no	30 (62.5 %)	74 (35.9 %)	
Total number overall lesions			0.478
<10	27 (52.9 %)	101 (47.4 %)	
>10	24 (47.1 %)	112 (52.6 %)	
Number of lesions supratentorial			0.239
0	0 (0 %)	5 (2.4 %)	
1-5	14 (28 %)	81 (38.4 %)	
5-10	16 (32 %)	44 (20.9 %)	
>10	20 (40 %)	81 (38.4 %)	
Number of lesions infratentorial			0.029
0	17 (34 %)	76 (36 %)	
1-5	23 (46 %)	119 (56.4 %)	
>5	10 (20 %)	16 (7.6 %)	
New lesions while receiving treatment			0.161
Yes	12 (26.1 %)	69 (37.1 %)	
no	34 (72.9 %)	117 (62.9 %)	

Table 4
Detailed MRI Evaluation (Subset EOPMS n = 14, LOPMS n = 30).

MRI Feature	EOPMS	LOPMS	p-value
size of lesions			1.000
only < 2 cm	71.4 % (10/14)	70 % (21/30)	
only > 2 cm,	0	3.3 % (1/30)	
both < 2 cm *and* >2 cm *lesions*	28.6 % (4/14)	26.7 % (8/30)	
quality			0.294
predominantly poorly marginated lesions involving grey and/or white matter	15.4 % (2/13)	16.7 % (5/30)	
extensive confluent white matter changes,	7.7 % (1/13)	0 %	
predominantly well-demarcated 'MS-like' white matter lesions	30.8 % (4/13)	53.3 % (16/30)	
mixed lesions	46.2 % (6/13)	26.7 % (8/30)	
tumefactive lesion	0 % (0/13)	3.3 % (1/30)	
T1-hypointense lesions			0.234
no T1-hypotintense lesions	14.8 % (2/14)	3.3 % (1/30)	
T1-hypointense lesions	85.7 % (12/14)	96.7 % (29/30)	
T1 gadolinium-enhancement			0.05
no T1-enhancement lesions	28.6 % (4/14)	50 % (15/30)	
T1-enhancement lesions	42.9 % (6/14)	46.7 % (14/30	
no gadolinium given	28.6 % (4/14)	3.3 % (1/30)	
periventricular white matter lesions			0.096
no periventricular white matter lesions	14.3 % (2/14)	0	
periventricular white matter lesions	85.7 % (12/14)	100 % (30/30)	
corpus callosum involved			<0.001
no corpus callosum lesion	64.3 % (9/14)	13.3 % (4/30)	
corpus callosum lesion	35.8 % (5/14)	86.7 % (26/30)	
subcortical lesions			0.078
no subcortical lesions	0	23.3 % (7/30)	
subcortical lesions	100 % (14/14)	76.7 % (23/30)	
deep grey matter lesions			0.385
no deep grey matter lesions	57.1 % (8/14)	76.6 % (23/30)	
thalamus	28.6 % (4/14)	10 % (3/30)	
basal ganglia	7.1 % (1/14)	6.7 % (2/30)	
both thalamus and basal ganglia	7.1 % (1/14)	6.7 % (2/30)	
brainstem lesions			0.256
no brainstem lesions	71.4 % (10/14)	53.3 % (16/30)	
brainstem lesions	28.6 % (4/14)	46.7 % (14/30)	
cerebellar lesions			0.202
no cerebellar lesions	42.9 % (6/14)	63.3 % (19/30)	
cerebellar lesions	57.1 % (8/14)	36.75 (11/30)	

Table 5
Univariate Cox Models of Time from MS Onset to EDSS 2 in Early and Late Onset Pediatric MS Patients.

	EDSS 2
	HR 95 % CI p
Early-onset	
Presence of psychological symptoms	5.185 1.132–23.757 0.034

(*continued on next page*)

Table 5 (*continued*)

	EDSS 2		
	HR	95 % CI	p
Late-onset			
Fatigue	2.367	1.110–5.047	0.026
Presence of psychological symptoms	3.346	1.639–6.870	< 0.001

References

[1] K. Reinhardt, S. Weiss, J. Rosenbauer, J. Gärtner, R. von Kries, Multiple sclerosis in children and adolescents: incidence and clinical picture - new insights from the nationwide German surveillance (2009-2011), Eur. J. Neurol. 21 (4) (2014) 654–659, https://doi.org/10.1111/ene.12371.

[2] M.P. Gorman, B.C. Healy, M. Polgar-Turcsanyi, T. Chitnis, Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis, Arch. Neurol. 66 (1) (2009) 54–59, https://doi.org/10.1001/archneurol.2008.505.

[3] T. Kalincik, K. Buzzard, V. Jokubaitis, et al., Risk of relapse phenotype recurrence in multiple sclerosis, Mult. Scler. 20 (11) (2014) 1511–1522, https://doi.org/10.1177/1352458514528762.

[4] C. Renoux, S. Vukusic, Y. Mikaeloff, et al., Natural history of multiple sclerosis with childhood onset, N. Engl. J. Med. 356 (25) (2007) 2603–2613, https://doi.org/10.1056/NEJMoa067597.

[5] K.A. McKay, J. Hillert, A. Manouchehrinia, Long-term disability progression of pediatric-onset multiple sclerosis, Neurology 92 (24) (2019) e2764–e2773, https://doi.org/10.1212/WNL.0000000000007647.

[6] M. Ruggieri, A. Polizzi, L. Pavone, L.M. Grimaldi, Multiple sclerosis in children under 6 years of age, Neurology 53 (3) (1999) 478–484, https://doi.org/10.1212/wnl.53.3.478.

[7] D. Chabas, T. Castillo-Trivino, E.M. Mowry, J.B. Strober, O.A. Glenn, E. Waubant, Vanishing MS T2-bright lesions before puberty: a distinct MRI phenotype? Neurology 71 (14) (2008) 1090–1093, https://doi.org/10.1212/01.wnl.0000326896.66714.ae.

[8] B. Huppke, D. Ellenberger, H. Rosewich, T. Friede, J. Gärtner, P. Huppke, Clinical presentation of pediatric multiple sclerosis before puberty, Eur. J. Neurol. 21 (3) (2014) 441–446, https://doi.org/10.1111/ene.12327.

[9] Y. Mikaeloff, G. Caridade, S. Assi, S. Suissa, M. Tardieu, Prognostic factors for early severity in a childhood multiple sclerosis cohort, Pediatrics 118 (3) (2006) 1133–1139, https://doi.org/10.1542/peds.2006-0655.

[10] M. Weygandt, H.M. Hummel, K. Schregel, et al., MRI-based diagnostic biomarkers for early onset pediatric multiple sclerosis, Neuroimage Clin. 7 (2014) 400–408, https://doi.org/10.1016/j.nicl.2014.06.015. Published 2014 Jul 11.

[11] E. Waubant, E.M. Mowry, L. Krupp, et al., Common viruses associated with lower pediatric multiple sclerosis risk, Neurology 76 (23) (2011) 1989–1995, https://doi.org/10.1212/WNL.0b013e31821e552a.

[12] E. De Meo, M. Filippi, M. Trojano, et al., Comparing natural history of early and late onset pediatric multiple sclerosis, Ann. Neurol. 91 (4) (2022) 483–495, https://doi.org/10.1002/ana.26322.

[13] B. Banwell, L. Krupp, J. Kennedy, et al., Clinical features and viral serologies in children with multiple sclerosis: a multinational observational study, Lancet Neurol. 6 (9) (2007) 773–781, https://doi.org/10.1016/S1474-4422(07)70196-5.

[14] S. Alotaibi, J. Kennedy, R. Tellier, D. Stephens, B. Banwell, Epstein-Barr virus in pediatric multiple sclerosis, JAMA 291 (15) (2004) 1875–1879, https://doi.org/10.1001/jama.291.15.1875.

[15] D. Pohl, B. Krone, K. Rostasy, et al., High seroprevalence of Epstein-Barr virus in children with multiple sclerosis, Neurology 67 (11) (2006) 2063–2065, https://doi.org/10.1212/01.wnl.0000247665.94088.8d.

[16] S.S. Soldan, P.M. Lieberman, Epstein-Barr virus and multiple sclerosis, Nat. Rev. Microbiol. 21 (1) (2023) 51–64, https://doi.org/10.1038/s41579-022-00770-5.

[17] K. Bjornevik, M. Cortese, B.C. Healy, et al., Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis, Science 375 (6578) (2022) 296–301, https://doi.org/10.1126/science.abj8222.

[18] A. Ascherio, K.L. Munger, J.D. Lünemann, The initiation and prevention of multiple sclerosis, Nat. Rev. Neurol. 8 (11) (2012) 602–612, https://doi.org/10.1038/nrneurol.2012.198.

[19] J.D. Lünemann, A. Ascherio, Immune responses to EBNA1: biomarkers in MS? Neurology 73 (1) (2009) 13–14, https://doi.org/10.1212/WNL.0b013e3181aa2a5f.

[20] M. Reindl, K. Schanda, M. Woodhall, et al., International multicenter examination of MOG antibody assays [published correction appears in Neurol Neuroimmunol Neuroinflamm. 2020 Mar 20;7(3):], Neurol. Neuroimmuno. Neuroinflamm. 7 (2) (2020) e674, https://doi.org/10.1212/NXI.0000000000000674. Published 2020 Feb 5.

[21] R. Bove, K. Rankin, C. Lin, et al., Effect of assisted reproductive technology on multiple sclerosis relapses: case series and meta-analysis, Mult. Scler. 26 (11) (2020) 1410–1419, https://doi.org/10.1177/1352458519865118.

[22] J. Correale, M.F. Farez, M.C. Ysrraelit, Increase in multiple sclerosis activity after assisted reproduction technology, Ann. Neurol. 72 (5) (2012) 682–694, https://doi.org/10.1002/ana.23745.

[23] C.C. Ucciferri, S.E. Dunn, Effect of puberty on the immune system: relevance to multiple sclerosis, Front. Pediatr. 10 (2022) 1059083, https://doi.org/10.3389/fped.2022.1059083. Published 2022 Dec 2.

[24] M. Lauerer, J. McGinnis, M. Bussas, et al., Prognostic value of spinal cord lesion measures in early relapsing-remitting multiple sclerosis, J. Neurol. Neurosurg. Psychiatry 95 (1) (2023) 37–43, https://doi.org/10.1136/jnnp-2023-331799. Published 2023 Dec 14.

[25] S.S. Yeo, S.H. Jang, S.M. Son, The different maturation of the corticospinal tract and corticoreticular pathway in normal brain development: diffusion tensor imaging study, Front. Hum. Neurosci. 8 (2014) 573, https://doi.org/10.3389/fnhum.2014.00573. Published 2014 Aug 4.

[26] S.S. Geertsen, M. Willerslev-Olsen, J. Lorentzen, J.B. Nielsen, Development and aging of human spinal cord circuitries, J. Neurophysiol. 118 (2) (2017) 1133–1140, https://doi.org/10.1152/jn.00103.2017.

[27] K. Deiva, Pediatric onset multiple sclerosis, Rev. Neurol. (Paris) 176 (1–2) (2020) 30–36, https://doi.org/10.1016/j.neurol.2019.02.002.

[28] D. Pohl, K. Rostasy, H. Reiber, F. Hanefeld, CSF characteristics in early-onset multiple sclerosis, Neurology 63 (10) (2004) 1966–1967, https://doi.org/10.1212/01.wnl.0000144352.67102.bc.

[29] H. Vietzen, S.M. Berger, L.M. Kühner, et al., Ineffective control of Epstein-Barr-virus-induced autoimmunity increases the risk for multiple sclerosis, Cell 186 (26) (2023) 5705–5718.e13, https://doi.org/10.1016/j.cell.2023.11.015.

[30] L.I. Levin, K.L. Munger, M.V. Rubertone, et al., Temporal relationship between elevation of epstein-barr virus antibody titers and initial onset of neurological symptoms in multiple sclerosis, JAMA 293 (20) (2005) 2496–2500, https://doi.org/10.1001/jama.293.20.2496.

[31] T.V. Lanz, R.C. Brewer, P.P. Ho, et al., Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM, Nature 603 (7900) (2022) 321–327, https://doi.org/10.1038/s41586-022-04432-7.

[32] A. de Chalus, M. Taveira, K. Deiva, Pediatric onset multiple sclerosis: future challenge for early diagnosis and treatment, Presse Med. 50 (2) (2021) 104069, https://doi.org/10.1016/j.lpm.2021.104069.

[33] M.P. Amato, B. Goretti, A. Ghezzi, et al., Cognitive and psychosocial features of childhood and juvenile MS, Neurology 70 (20) (2008) 1891–1897, https://doi.org/10.1212/01.wnl.0000312276.23177.fa.

[34] W.S. MacAllister, A.L. Belman, M. Milazzo, et al., Cognitive functioning in children and adolescents with multiple sclerosis, Neurology 64 (8) (2005) 1422–1425, https://doi.org/10.1212/01.WNL.0000158474.24191.BC.