Review

Disease Modifying Treatment Options in Very Early Onset Multiple Sclerosis—What Choice for Onset Under Age 5 Years?

Dana Craiu *, Denisa Alice Dica , Cristina Pomeran , George Pescaru *, Shay Menascu , Mihaela Simu

Posted Date: 22 September 2025

doi: 10.20944/preprints202509.1793.v1

Keywords: very early onset multiple sclerosis; disease modifying treatment; pediatric onset multiple sclerosis (POMS); natalizumab; interferon; immunoglobulins; acute treatment

Review

Disease Modifying Treatment Options in Very Early Onset Multiple Sclerosis—What Choice for Onset Under Age 5 Years?

Dana Craiu [1,2,3,*], Alice Dica [1,2], Cristina Pomeran [1,2], George Pescaru [1,2,3,*], Shay Menascu [4] and Mihaela Simu [5,6]

[1] Carol Davila University of Medicine, Department of Neurosciences, Pediatric Neurology Discipline, Bucharest, Romania
[2] Alexandru Obregia Hospital, Pediatric Neurology Center of Expertise of Rare Pediatric Neurology Disorders, Bucharest, Romania
[3] Romanian Group of Undiagnosed Rare Disorders of the Institute of Research and Development in Genomics, Bucharest, Romania
[4] Neuroimmunology and demyelinating pediatric service, Multiple Sclerosis Center, Sheba Medical Center, Tel-Aviv Scholl of Medicine and Human Science, Tel-Aviv University, Israel
[5] Department of Neuroscience, University of Medicine and Pharmacy "Victor Babes" Timisoara, Romania
[6] Second Neurology Clinic of Timisoara Emergency Clinical County, Hospital "Pius Brinzeu", Timisoara, Romania
* Correspondence: dana.craiu@umfcd.ro (D.C.); george_pescaru24@yahoo.com (G.P.)

Abstract

Background/Objectives: Very early pediatric onset multiple sclerosis (POMS) is rare; clinical studies using disease modifying treatments (DMTs) have not been performed. Clinicians rely on studies performed at older age. This review resulted due to difficulties faced by clinicians and off label use of DMTs at this age. **Methods**: A literature review between 1980 – 2025 of very early POMS with onset before age 5 has been performed searching for outcome without or with DMTs. The curated database of the selected patients was analyzed using computed descriptive and integrated cohort-level estimates. The clinical, paraclinical, treatment and outcome characteristics were analyzed. Statistical analysis used JASP, with GenAI-assisted verification. Treatment outcome of a 16 year old patient with very early POMS starting at 2 years 4 months that consecutively received interferon, immunoglobulins and natalizumab is presented. **Results**: 101 patients with very early POMS presented at onset ataxic syndrome (57.4%), pyramidal syndrome (41.4%), ophthalmoplegia (10.3%) and optic neuritis (6.9%). In evolution 22.7% had seizures. Half of the patients were not treated. Among those treated, acute steroid therapy was administered; 11 received DMTs: interferon, glatiramer acetate, dimethyl fumarate, azathioprine (three) and only two – high-efficacy therapies (natalizumab, rituximab). Our patient had partial remission under interferon, relapses when stopped and replaced by immunoglobulins and 9 years relapse-free interval when natalizumab was introduced. **Conclusions**: Early treatment with high efficiency DMTs should be considered in very early POMS; association with known increased neuroplasticity at this age may improve prognosis, allowing good recovery of acquired disability.

Keywords: very early onset multiple sclerosis; disease modifying treatment; pediatric onset multiple sclerosis (POMS); natalizumab; interferon; immunoglobulins; acute treatment

 doi:10.20944/preprints202509.1793.v1

1. Introduction

Prior literature typically defines POMS as <18 years and considers early-onset cases those <10 years. In this work, we define very early POMS cases with onset before 5 years of age. POMS represents 3% to 5% of all multiple sclerosis cases, with less than 1% starting before age 10 years (early POMS) meaning 0,09/100 000 population [1]. Prevalence and incidence of very early POMS are unknown [2–4]. Due to the very low incidence of MS at this age, there are no powerful studies concerning DMT benefits or adverse effects. Due to its rarity, only isolated case reports or small case-series exist [5,6]. Therefore, clinicians treating these cases need information to manage diagnosis and treatment for very early POMS. DMTs are of off label and in many countries not covered by insurance system, the patients receiving only acute therapy and sometimes intravenous immunoglobulins, with uncertain efficacy and accumulation of disability [6].

Authors of this review faced difficult decisions for treating a patient with very early POMS in a female with onset at age 2 years 4 month. She initially had frequent episodes of neurological involvement treated with acute steroid therapy with complete remission. DMTs used in sequence (Interferon, intravenous immunoglobulins (IVIGs), and Natalizumab) has different effects. The case presentation is available in section 3.3. Clinical vignette.

This case is the reason for the extensive literature review presented in this publication, aiming to offer our pediatric colleagues a summary of the published cases of very early POMS including clinical aspects and treatment choices.

2. Materials and Methods

Literature Search

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

PubMED, Scopus, Cochraine, Elybrary.ru, Arab World Research Source, CINAHL, OpenGrey were searched using following search terms: *((”Multiple Sclerosis”[Mesh] OR ”multiple sclerosis”[tiab] OR ”pediatric multiple sclerosis”[tiab]) AND (”Child, Preschool”[Mesh] OR ”Infant”[Mesh] OR child[tiab] OR children[tiab] OR toddler[tiab] OR preschool[tiab] OR ”younger than 5”[tiab] OR ”under 5”[tiab] OR ”before age 5”[tiab]) AND (”Therapeutics”[Mesh] OR ”Drug Therapy”[Mesh] OR ”Treatment Outcome”[Mesh] OR treatment[tiab] OR therapy[tiab] OR corticosteroids[tiab] OR interferon[tiab] OR ”disease modifying therapy”[tiab] OR DMT[tiab] OR glatiramer[tiab] OR rituximab[tiab] OR cyclophosphamide[tiab] OR ”dimethyl fumarate”[tiab])) OR (”natalizumab”[Mesh] OR natalizumab[tiab])*

Articles found after manual search in the hospital literature database (selected articles on the topic) and in the references of the selected articles were added.

Articles selection was performed independently by two reviewers (P.G. and D.A.). Inclusion and exclusion criteria were applied consistently at the title, abstract, and full-text to ensure transparency and reproducibility.

The inclusion criteria were: 1. Age at onset below 5 years; 2. Publication date after 1982, in order to include the use of paraclinical investigations introduced by the Poser criteria (with subsequent selection of the cases using McDonald 2001 criteria); 3. Design of the study – case reports, series of cases, clinical trials, literature review articles; 4. Publication language: English, Spanish, Arabic, Russian, and Chinese. Google translate was used from any language to English.

Studies that did not fulfill the contemporary diagnostic requirements for multiple sclerosis at the time of publication, studies that failed to provide clinical and paraclinical details of individual patients or cohorts over 5 years of age were excluded.

Generative artificial intelligence (GenAI) has been used to generate the PRISMA flow diagram, Figure 1. (to illustrate the process of study identification, screening, eligibility assessment, and final inclusion).

 doi:10.20944/preprints202509.1793.v1

A relevant case study of multiple sclerosis with very early onset was described as an example of different DMTs used off label for age; evolution is described and compared with literature findings.

Data Analysis

Authors analyzed following information: 1. Demographic and clinical data 2. Paraclinical data 3. Treatment at episode and DMTs and their effect – see Supplementary material S1: Collected data classification; patients and their characteristics are presented in supplementary material S2: Patients characteristics from selected articles (https://drive.google.com/drive/folders/1uB6k06BwdyNwYM78FjFu6Rh__KROJBtM?usp=sharing).

Statistical Analysis

The statistical analyses and figures were produced in JASP (version 095.1). Verification, cross-checks, and iterative re-analysis of the results were assisted by GenAI under author verification; GenAI was only used to support calculations, code expressions, and interpretation and not to generate or alter primary data.

Descriptive results (counts and percentages) were calculated for demographic, clinical, paraclinical and treatment data.

Authors hypothesized a strong association between younger onset age and a higher incidence of ataxia or seizures at onset. Therefore, Pearson and Spearman rank correlations with 95% CIs were run after excluding records with unknown evolution and cohorts without individual-level data. Ataxia – age association was adjusted for cerebellar lesions, and seizures – age association was adjusted for cortical/subcortical lesions using binomial logistic regression analysis. Models were restricted to cases with Magnetic Resonance Immaging (MRI) data.

The hypothesis whether incomplete remission differed by treatment exposure was examined with χ^2 test across three groups (no treatment, steroid therapy only, and steroid therapy + DMT) for complete or incomplete remission followed by binomial logistic regression with incomplete remission as outcome (odd ratio with 95% CIs; p value < 0.05).

3. Results

3.1. Literature Search

A total of 966 records were identified. Duplicates and articles not fulfilling inclusion criteria were excluded; 22 studies remained for analysis [5,7–27]. (Figure 1. and supplementary material S2).

 doi:10.20944/preprints202509.1793.v1

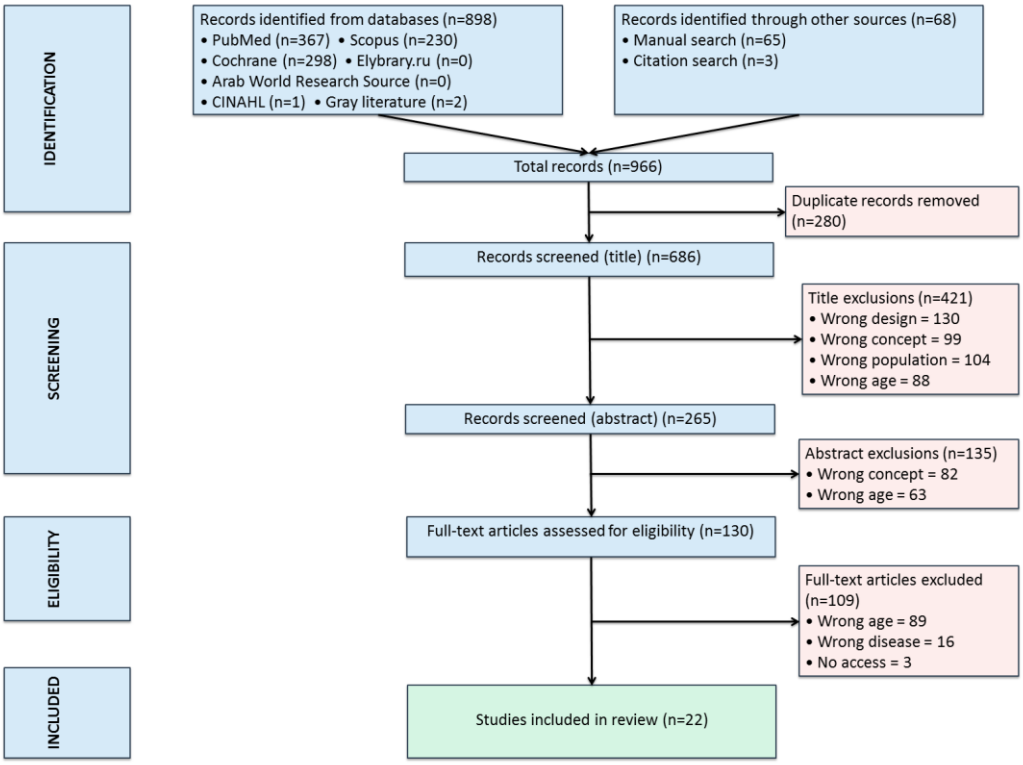

Figure 1. PRISMA flow.

3.2. Data Analysis

3.2.1. Demographic and Clinical Data

A total of 101 patients were identified (Table 1). The female-to-male ratio was 1.4:1. The mean age at onset was 36 months (range: 10 months–5 years). The mean number of relapses was 4.1, with an average of 2.3 relapses within the first two years of life.

Table 1. Demographic features and follow-up.

Features	
Sex	
Male	42
Female	59
F:M ratio	1.47:1
Age at onset (mo.) mean ± SD (range)	36 ± 13.29 (10-60)
Mean total number of attacks	4.1
Mean number of attacks in the first 2 years	2.3
Follow-up time (mo.) mean (range)	26.4 (10-48)

Abbreviations: mo.=months; SD = standard deviation.

Onset signs. The most frequent presenting syndromes were ataxic syndrome (57.4%), pyramidal syndrome (41.4%), fever with or without altered consciousness (17.2%), ophthalmoplegia (10.3%) and optic neuritis (6.9%).

Signs in evolution. Ataxic gait was the most common symptom (42.9%), followed by hemiparesis (35%) and seizures (22.7%) (Table 2).

In the majority of cases, both the initial presentation and early relapses were monosymptomatic (74.3%).

 doi:10.20944/preprints202509.1793.v1

An onset resembling ADEM, with fever, lethargy, impaired consciousness, and vomiting, was reported in 17.8% of cases, all of whom developed classical recurrent remitting multiple sclerosis (RRMS) later on.

Table 2. Clinical Features and Presentation during course of disease.

Features	Onset (%of cases)	Evolution (% of cases)
Symptoms		
Ataxia	57.4%	42.9.%
Pyramidal	41.4%	47.5%
Fever +- Lethargy / Altered Consciousness	17.2%	4.9%
Ophthalmoplegia	10.3%	3.9%
Optic neuritis	6.9%	21.7%
Seizures	4.3%	22.7%
Neurogenic Bladder	3.9%	3.9%
Other Cranial Nerve palsy	3.4%	19.8%

3.2.2. Paraclinical Data

- Imaging. MRI was performed in 98 cases. Supratentorial lesions predominated (57.4%), most commonly periventricular (59.1%); infratentorial lesions were primarily located in the brainstem (32.7% of all cases) (Table 3). Cerebellar lesions were observed in 10 cases (10.2% of all cases) and spinal lesions in 12 cases (10.2% of all cases). Six patients underwent computer tomography (CT) examination (3 had only CT-scan), of which five revealed hypointense lesions. Two of the patients had a normal CT but abnormal IRM at the follow-up. The other one with normal CT had MS characteristic lesions were confirmed by necropsy.
- Cerebrospinal fluid (CSF) analysis performed in 99 cases showed pleocytosis (45 out of 999 cases/45.5%), hyper-proteinorrachia (27 out of 99 cases/27.3%), positive oligoclonal bands (32 out of 99 cases/ 32.3%), elevated IgG index (5 of 9 tested/ 55.5%) and anti-myelin basic protein antibodies (3 out of 3 cases /100%).
- Visual evoked potentials (VEP) were abnormal in 10 out of 30 patients (33,3%) of patients. Autopsy was performed in two deceased patients, revealing multiple small sclerotic lesions, some with cystic components, distributed within the white matter, predominantly supratentorial periventricular.

Table 3. Diagnostic work-up summary.

Features	% of all cases	% of tested cases
MRI		
Supratentorial lesions	**57.4%**	**59.1%**
Periventricular	57.4%	59.1%
Cortical/Subcortical	24.7%	25.5%
Infratentorial lesions	**36.6%**	**37.7%**
Brainstem	31.7%	32.7%
Spinal cord	11.9%	12.2%
Cerebellum	9.9%	10.2%
CSF		
Normal CSF	11.9%	12.1%
Oligoclonal bands (positive)	31.7%	32.3%
Pleocytosis	44.5%	45.5%
Elevated protein	26.7%	27.3%
VEP		
Abnormal VEP	9.9%	33.3%
Normal VEP	19.8%	66.7%

 doi:10.20944/preprints202509.1793.v1

Abbreviations: CSF=cerebrospinal fluid; VEP = visual evoked potentials; MRI=magnetic resonance imaging.

3.2.3. Treatment

- Regarding treatment, 43 of all treated patients (95.6%) received **steroids** for at least one relapse (Table 4). In most cases, high-dose intravenous methylprednisolone was used, with or without subsequent tapering with oral prednisone.
- Three additional patients received **intravenous immunoglobulin (IVIGs)** and steroids.
- **Disease-modifying therapies** were initiated in 11 cases (24.4% of all treated patients), of which 6 received low-efficacy agents (4 interferon, 1 dimethyl fumarate, 1 glatiramer acetate) and 2 received high-efficacy agents (1 natalizumab, 1 rituximab). Azathioprine was administered in 3 cases.

3.2.4. Outcomes

- Complete remission was documented in 88% of cases.
- Poor outcomes were observed in 12 cases, characterized by multiple relapses with incomplete recovery, progressive course, or lack of remission. Two deaths occurred, both in patients from the pre-2001 cohort who had not received treatment. Among patients with incomplete remission, 8 were treated with steroids, and 1 with steroids and dimethyl fumarate.
- Escalation to higher efficacy therapies (rituximab, natalizumab, azathioprine) occurred in 3 cases, with adequate disease control achieved in the first two cases.

Table 4. Treatment overview.

Features	Number	% of all cases	% of treated cases
Steroid therapy	44	43.5%	80%
Methylprednisolone	26	25.7%	47.3%
Prednisone/ Prednisolone	17	16.8%	30.9%
Other steroids	3	2.9%	3.7%
Intravenous immunoglobulin	3	2.9%	3.7%
Disease-modifying therapy	11	10.9%	20.0%
Interferons	4	4.0%	7.3%
Azathioprine	3	2.9%	3.7%
Dimethyl fumarate	1	1.0%	1.8%
Glatiramer acetate	1	1.0%	1.8%
Natalizumab	1	1.0%	1.8%
Rituximab	1	1.0%	1.8%

3.2.5. Statistical Analysis of Treatment Outcomes

No significant associations were detected between age at onset and symptoms at onset: ataxia (Pearson r = 0.364, p = 0.088, 95% CI − 0.057 to 0.675) or seizures (Pearson r = − 0.261, p = 0.229, 95% CI − 0.608 to 0.169). MRI lesions may introduce a bias for epilepsy (the cortical lesions) and ataxia (the cerebellar and spinal lesions). In the adjusted logistic models with MRI lesions as confounder), the statistical associations did not change.

The contingency test assessing remission in treated patients was not statistically significant (χ^2 = 1.26, p = 0.53), although proportion for incomplete remission has a decreasing trend in relation to more complex treatments: 50% incomplete remission in untreated group, 31% for patients treated with steroids only, and 17% for steroids and DMTs. Consistently, logistic regression using steroids and DMTs group as the reference estimated higher odds (but non-significant) for incomplete remission for steroids only group (OR = 2.22, p > 0.05) and no treatment group (OR = 5.00, p > 0.05). Overall, results do not show statistically significant associations, but the statistical model estimates

 doi:10.20944/preprints202509.1793.v1

that adding a DMT on top of corticosteroids likely reduces the chance of incomplete remission, consistent with a clinically favorable effect (Figure 2).

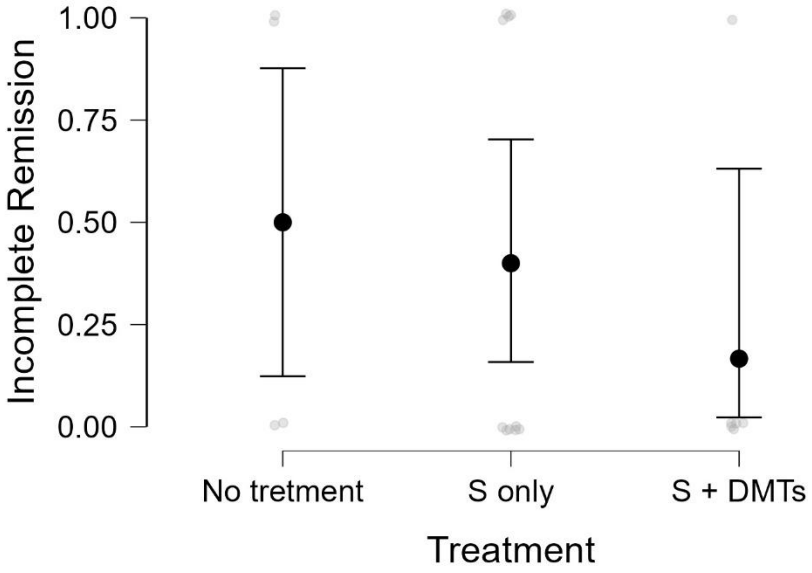

Figure 2. Predicted probability (95% CI) of incomplete remission by treatment group from binomial logistic regression. The plot illustrates a decreasing probability for incomplete remission with increasing treatment intensity. Big black dots represent model-based estimates; bars indicate 95% CIs; light dots show individual remission outcomes tendencies (jitter). S=steroids.

3.3. Clinical Vignette

A 16-year-old female patient is presented. She was born by vaginal delivery after an uncomplicated pregnancy and had normal milestones achievement. Family history was unremarkable for the patients' disease. She had 11 episodes of neurological involvement with stormy onset at 2 years 4 months. As a characteristic, her episodes were long at onset, with complete recovery of short duration (but more than 30 days). After the third episode residual neurological symptoms were noted. The clinical symptoms at onset and subsequent episodes are listed in Table 5. and Figure 3.

 doi:10.20944/preprints202509.1793.v1

Table 5. Detailed description of the episodes and treatment.

Episode	Age	Symptoms	Episode duration	Type of remission	Residual symptoms	Free interval after episode	Treatment in episode	DMT	Observations
I	2y 4m	Severe truncal ataxia Irritability	5 w	Complete	-	30 d	ACTH 0,5 mg/day – 14d Prednisone 0.5mg/kg/day – 7d	-	
II	2y 6m	Severe ataxia (R>L CS) Irritability	5 w	Complete	-	30 d	Dexamethasone 8mg/day – 3d ACTH 1/3 mg/day – 14d	-	
III	2y 8m	Severe ataxia (CS) L>R PS Irritability Saccadic speech (CS)	3 w	Incomplete	L pyramidal Mild ataxia	30 d	Methylprednisolone i.v. 30 mg/kg/day – 6d Tapered with Medrol IVIG 2g/kg (in 6d)	-	Diagnosis = RRMS
IV	2y 10m	Severe ataxia (CS) L>R PS Irritability	1 w	Incomplete	L pyramidal Mild ataxia	30 d	Methylprednisolone i.v. 30 mg/kg/day – 5d Tapered with Medrol	IFN beta-1a*	
V	2y 11m	Severe ataxia (CS) L>R PS Irritability	1 w	Incomplete	L pyramidal Mild ataxia	60 d	Methylprednisolone i.v. 30 mg/kg/day – 5d Tapered with Medrol		
VI	3y 1m	Irritability, mild ataxia	2 d	Incomplete	Mild L pyramidal	60 d	-		
VII	3y 3m	Irritability, mild ataxia	2 d	Incomplete	Mild L pyramidal	10 m	-		
VIII	4y 1m	Slight left intentional tremor (CS) Mild left hemiparesis (PS)	Not known	Incomplete	Mild L pyramidal	13 m	Methylprednisolone i.v. 30 mg/kg/day – 5d Tapered with Medrol	IVIG 2g/kg/administration - monthly	
IX	5y2m	Mild left hemiparesis	1 w	Incomplete	Mild L pyramidal	11 m	Methylprednisolone i.v. 30 mg/kg/day – 5 days Tapered with Medrol		
X	6y1m	Mild left hemiparesis	1 w	Incomplete	Mild L pyramidal	12 m	Methylprednisolone i.v. 30 mg/kg/day – 5d Tapered with Medrol		
XI	7y1m	Mild left hemiparesis	1 w	Incomplete	Mild L pyramidal	9 y – present	Methylprednisolone i.v. 30 mg/kg/day – 5d Tapered with Medrol	Natalizumab 300 mg/dose every 28 d	No relapses since initiation

y=years; m=month; L=left; R=right; DMT = disease modifying treatment; CS= cerebellar syndrome; PS= pyramidal syndrome; d =days; w = weeks; m = months; y – years; *Interferon beta-1a, 6,6µg/dose, every other day, 2 weeks (7 doses), then 8,8µg/dose, every other day, continuously, until now.

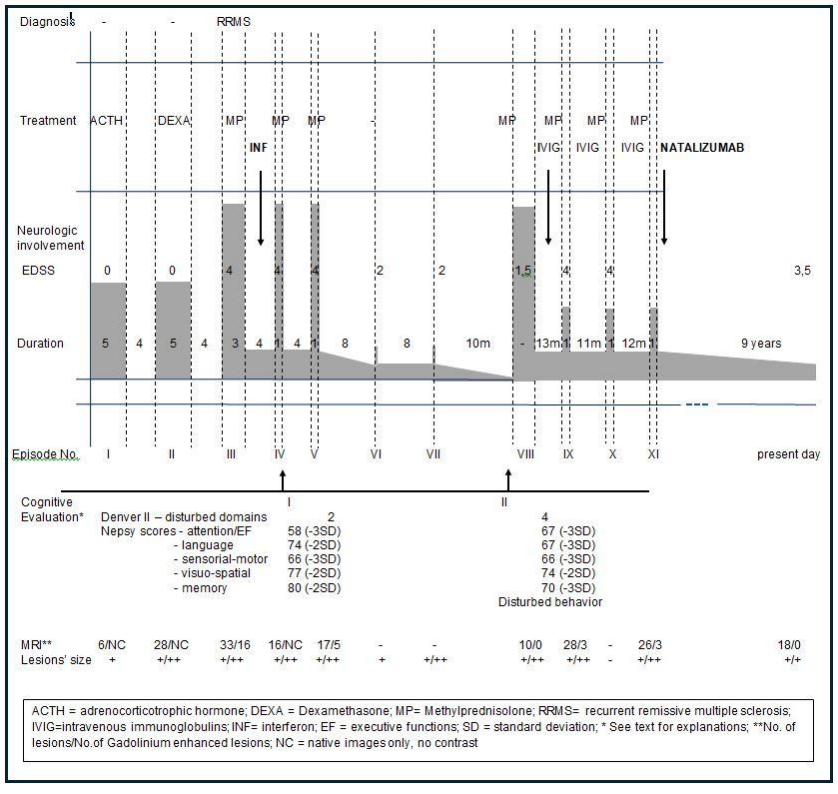

Figure 3. Patient clinical and imaging evolution correlated to treatment.

 doi:10.20944/preprints202509.1793.v1

3.3.1. Workup

The initial symptoms were rapidly progressive gait and equilibrium disturbances and irritability without a prior history of infectious disease. In another hospital a suspicion of ADEM was raised, but clinical and paraclinical data, including imaging, and clinical evolution, with new relapses led to the diagnosis or RRMS after the 3rd episode. Table 6. shows the workup and differential diagnosis.

Table 6. Workup and differential diagnosis [28].

Differential diagnosis	Observations	Investigation
NMO, recurrent	- No optic neuritis - Spinal cord involvement less than 3 spinal segments	AQP4 negative Oligoclonal bands negative
ADEM, recurrent	- No encephalopathy (except behavioral symptoms at first episode) - Remission of the initial symptoms followed by new symptoms after an interval of 1 month (MS more probable) Miller et al. [28]	MRI – DIT, DIS, lesions typical for MS
Infectious diseases including Borreliosis, HIV, HBV, EBV, cysticercosis	- no fever - no other organ involvement	LP - CSF and blood serology negative
Autoimmune disorders	- no other organ involvement	Blood serology negative (ANA, anti-dsDNA antibodies, anti Sm antibodies, serum Complement)
Mitochondrial disorder	- no other organ involvement - clinical evolution typical for MS - treatment - efficacious	Lactic acid negative – blood and CSF; MRI – lesions typical for MS

NMO=neuromyelitis optica; AQP4=serum aquaporin-4 autoantibodies; ADEM=Acute disseminated encephalomyelitis; MS=multiple sclerosis; MRI=magnetic resonance imaging; DIT=dissemination in time; DIS=dissemination in space; HIV=human immunodeficiency virus; HBV=Hepatitis B virus; EBV=Epstein-Barr Virus; LP=lumbar puncture; CSF=cerebrospinal fluid; ANA=Anti-nuclear antibodies; anti dsDNA=anti-double-stranded DNA antibody; anti-Sm=Anti-Smith Antibody.

Infectious and Inflammatory-Immune Disorders Were Ruled Out

The diagnosis of RRMS was established at that time based on Mc Donalds criteria 2010 [29]: she had more than 2 attacks proving dissemination in time (DIT) and objective clinical and MRI evidence of dissemination in space (DIS). On MRI she had lesions in all 4 – periventricular, juxtacortical, infratentorial and spinal cord regions proving DIS; these lesions had different ages proving DIT (Figure 4).

 doi:10.20944/preprints202509.1793.v1

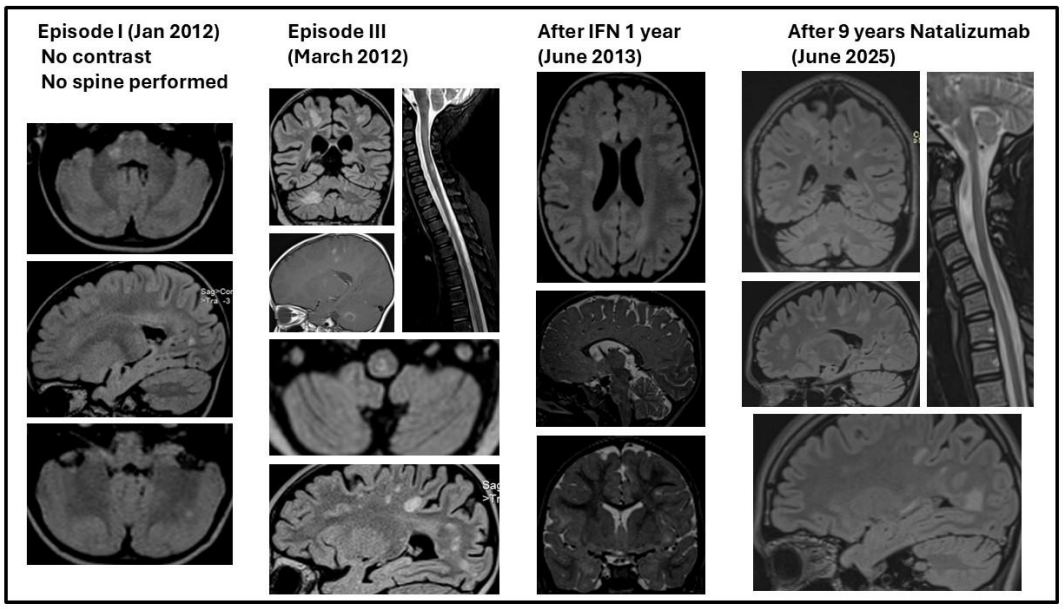

Figure 4. MRI at onset and in evolution.

3.3.2. Evolution Under Treatment

The patient received steroid therapy at every acute event.

Episode I and II: small doses of ACTH (0,33 mg/day for 14 days), followed by Prednisone (0,5 mg/kg), 7 days were administered in the county hospital. She had complete remission 5 weeks after onset.

The second episode started after 30 days (Table 5, Figure 3). No other investigations were carried out by the local physician. Treatment with Dexamethasone 8 mg/day – 3 days and Synachten 0.5 mg/day - 7 days was followed by complete remission within 5 weeks and another 35 days without neurological symptoms. MRI was performed at onset and after remission (Figure 4) of the third episode showing an increased number of MRI lesions.

For the third episode she was admitted in our clinic with cerebellar syndrome (severe ataxia and saccadic speech, pyramidal syndrome (left more than right), irritability. Treatment included acute pulse-therapy with Methylprednisolone 30 mg/kg/day for 6 days; patient was initiated on **DMT (disease modifying treatment)** off label **– Interferone Beta-1a** 22 μg/dose, 3 doses/week; premedication with paracetamol was initiated; no adverse reactions were recorded; periodical follow-up (clinical and biological) showed IFN was well tolerated. She had another two mild and short relapses (1 week each) with 4 weeks intervals between episodes, followed by another 2 relapses of 2 days each with 8 weeks intervals between them (Table A.I., Figure A.1.). With IFN treatment Expanded Disability Status Scale (EDSS) score decreased continuously from 4 to 2 and even 1.5. The sponsor could not support donation of IFN anymore due to legal constraints and it was discontinued. She relapsed dramatically after 10 weeks (episode VIII) and she was initiated on IVIGs (intravenous immunoglobulins) 2 g/kg/cure infused in 3 days, monthly. As a result, she had mild relapses at intervals of 11-13 weeks lasting no more than 1 week each, but EDSS remained 4 also during the "free" intervals between relapses.

Due to international collaboration with colleagues with experience in treating pediatric patients with **Natalizumab**, the patient was initiated at age 7 years on Natalizumab, 300 mg/dose, monthly administrations. Check-up for JCV (John Cunningham virus, Human polyomavirus 2) has been performed before and then monthly and MRI performed for PML (progressive multifocal leukoencephalopathy) at each relapse and yearly for follow-up; both JCV and MRI were done during IFN and Natalizumab therapies. No relapses were recorded after Natalizumab initiation during the next 9 years, until present; EDSS score decreased to 3.5 (persistent disability).

 doi:10.20944/preprints202509.1793.v1

Cognitive involvement. Parents didn't notice changes in patient's cognitive performances. At age 3 years she was evaluated (Romanian validated tests). Denver II showed delayed development in personal-social and gross motor domains with normal functioning for language and fine motor and adaptative behavior domains. Nepsy test showed decreased scores in all domains: attention/executive functions 58, -3SD (standard deviation); language 74, -2SD; sensory-motor 66, -3SD; visuo-spatial 77, -2SD; memory 80, -2SD (Figure...). During testing she collaborated with psychologists, but showed severe inattention, and a mild lack of interest.

She was reevaluated at age 4years 1month by the same psychologists. Denver II showed delayed development in all four domains. Nepsy proved decreased scores for language, visuo-spatial and memory compared with previous examination: attention/executive functions 67, -3SD; language 67, -3SD; sensory-motor 66, -3SD; visuo-spatial 74, -2SD; memory 70, -3SD (Figure 3). The patient showed opposing and provoking behavior, inappropriate verbal and emotional reactions, difficulties in maintaining attention, resulting in lack of collaboration during testing.

She was re-evaluated age 15.5 years, and she has an average normal IQ – 91 with social and adaptative impairment, but she is attending normal high-school (admitted by contest). No complex evaluation was performed.

4. Discussion

Multiple sclerosis is extremely rare before the age of 5 years. Isolated case reports and small case series have been published, and some cases are documented in national registries [20,30].

The case reported in the vignette is an MS patient with an exceptionally early onset (age 2 years 4 month). It is to be speculated an even earlier subclinical onset or unnoticed clinical signs due to the small age of the patient. As described, even earlier onset (10 months old) were previously reported by other groups [20]. It is unknown whether very early onset multiple sclerosis shares the same pathophysiology as in adult patients, or whether distinct underlying biological mechanisms may trigger it. It was hypothesized, but not yet proven, that copy number variation (CNV) may influence genes in large genomic regions involved in disease mechanisms, and contribute to very early onset [31]. Genetic background may play a major role in early onset MS and further studies are expected.

Age-specific incidence: While pediatric-onset multiple sclerosis (POMS) accounts for 3%-5% of all MS cases, with fewer than 1% starting under the age of 10, there is substantial variability in incidence rates based on geographic location and environmental exposures. Regions with higher latitude, such as Scandinavia and Canada, demonstrate significantly higher pediatric MS prevalence due to possible correlations with lower vitamin D levels [2]. These data highlight the importance of understanding regional susceptibility alongside diagnostic patterns, which show that early-onset MS might still be underdiagnosed in populations from lower-income countries.

A marked discrepancy can be observed between the high number of pediatric MS cases with onset before 5 years of age reported during 1980–2000 compared with those, fewer, published between 2001–2025. This phenomenon can largely be attributed to the absence of modern diagnostic criteria before year 2000, limited availability of advanced neuroimaging, and, most importantly, the still undescribed related neuroinflammatory demyelinating disorders such as neuromyelitis optica spectrum disorder (NMOSD), MOG antibody–associated disease (MOGAD), or autoimmune encephalitis [32,33].

In the present review we identified 19 published patients who had been diagnosed with MS but who no longer meet contemporary diagnostic criteria [34–43]. All of these cases were reported between 1981 and 1994. Among them, three patients would now probably classify as MOGAD, two as ADEM, one as NMOSD, and one as autoimmune encephalitis, due to clinical and MRI aspects. For the majority, however, insufficient clinical and paraclinical data were available to fulfill current diagnostic requirements for MS, although the diagnosis cannot be definitively excluded. These articles were excluded from our review.

Symptoms and Early MRI Trends: Ataxia was observed as the most frequent presenting manifestation in our cohort, consistent with prior studies indicating that cerebellar and brainstem

 doi:10.20944/preprints202509.1793.v1

involvement is more pronounced in younger MS patients [20,44,45]. Additionally, patients with seizure onset, although infrequent, displayed a suggestive association with cortical lesions. This aligns with previous reports linking epilepsy to MS regardless of age [46].

Treatment remains a challenge under 5 years of age due to the absence of clinical studies with DMTs. In the analyzed group half of the patients were not treated. Among those treated, acute-phase steroid therapy was administered; DMTs were administered in 11 patients: most received low-efficacy agents such as interferon, glatiramer acetate, or dimethyl fumarate, three were treated with azathioprine [11,20,21] and only two patients received high-efficacy therapies (natalizumab or rituximab) [5,14,24,27]. A patient reported by Sotgiu et al. with disease onset at age 5 years and treated with natalizumab since age 5 years and 5 months had nearly complete remission with significant EDSS score improvement [27]. An Italian observational study using Natalizumab in MS pediatric patients showed good tolerability and good response when administered as early as 4 years of age. [47,48].

A groundbreaking advancement in treating POMS with high-efficacy therapies is highlighted by the study of Menascu et al [49]. The multicenter research focuses on outcomes in pediatric MS treated with natalizumab, revealing significant benefits in reducing relapse rates and stabilizing disease over long-term follow-up. The study demonstrated a significant decrease in EDSS scores and relapse rates in children as young as 5 years of age during natalizumab therapy. Reported adverse events were mild or moderate, and periodic John Cunningham virus (JCV) screening was implemented to mitigate the risk of progressive multifocal leukoencephalopathy (PML). These findings suggest that natalizumab, though off-label for children under 18 years [50], may be a critical tool in cases of highly active POMS, particularly under rigorous monitoring protocols.

After partial response when treated with interferon and no response with IVIGs, our vignette patient similarly benefited from natalizumab, initiated at 7 years of age, experiencing no relapses during a 9-year follow-up period. These results correlate strongly with Menascu et al.'s findings, supporting natalizumab's safety and efficacy for early-onset MS.

Early treatment with high efficiency DMTs may improve prognosis in very early onset pediatric multiple sclerosis cases, especially because association with known increased neuroplasticity at this age, allowing good recovery of acquired disability [51].

Statistical analysis. Overall, our statistical modeling demonstrated trends favoring early introduction of high-efficacy disease-modifying therapies like natalizumab in patients with very early onset multiple sclerosis. Moreover, interventions targeting children under 5 years may provide a critical neurological therapeutic window due to heightened neuroplasticity at these ages**.**

To deepen understanding, future studies should focus on global multicenter efforts to consolidate real-world pediatric data into standardized cohorts**.** This approach would better define the molecular mechanisms, genetic predispositions, and therapeutic responses specific to very early-onset multiple sclerosis. Integrating multicenter approaches, such as that described by Menascu et al., could further optimize strategies for long-term disability prevention and improved quality of life in these pediatric populations.

Supplementary Materials: The following supporting information can be downloaded at: https://drive.google.com/drive/folders/1uB6k06BwdyNwYM78FjFu6Rh__KROJBtM?usp=sharing: Table S1: Collected data classification; Table S2: Patients characteristics from selected articles.

Author Contributions: Conceptualization, D.C. and G.P.; methodology, D.C. and G.P.; formal analysis, G.P.; Investigation, D.C. and G.P.; resources, D.C., A.D., M.S., S.M., C.P., and G.P.; data curation, G.P., D.C.; writing—original draft preparation, G.P., D.C.; writing—review and editing, G.P., D.C., C.P., A.D., M.S., S.M., ; visualization, G.P., D.C.; supervision, D.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

 doi:10.20944/preprints202509.1793.v1

Informed Consent Statement: Written informed consent has been obtained from the patient to publish this paper.

Data Availability Statement: Analyzed data available online – Supplementary materials S1 and S2 (see above).

Acknowledgments: During the preparation of this manuscript, the authors used JASP (version 095.1) for statistical analyses and related figures generation [52]. Generative artificial intelligence (GenAI) has been used for the purposes of generating the PRISMA flow diagram, Figure 1., and verification, cross-checks, and iterative re-analysis of the statistical data results [53] under author verification; GenAI was only used to support calculations, code expressions, and interpretation and not to generate or alter primary data. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors received no financial support for the research, authorship, and/or publication of this article.

Abbreviations

The following abbreviations are used in this manuscript:.

ADEM	Acute disseminated encephalomyelitis
ANA	Anti-nuclear antibodies
anti dsDNA	anti-double-stranded DNA antibody
anti-Sm	Anti-Smith Antibody
AQP4	serum aquaporin-4 autoantibodies
CI	confidence interval
CSF	cerebrospinal fluid
CT	computer tomography
DIS	dissemination in time
DIT	dissemination in space
DMT	Disease Modifying Therapy
EBV	Epstein-Barr Virus
EDSS	Expanded Disability Status Scale
GenAI	Generative artificial intelligence
HBV	Hepatitis B virus
HIV	human immunodeficiency virus
IVIGs	intravenous immunoglobulins
JCV	John Cunningham virus
LP	lumbar puncture
MOG	Myelin Oligodendrocyte Glycoprotein
MOGAD	Myelin Oligodendrocyte Glycoprotein Associated Disease
MRI	Magnetic resonance imaging
MRI	Magnetic Resonance Imaging
MS	Mmultiple sclerosis
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis Optic Spectrum Disorder
OCB	Oligoclonal Bands
POMS	Pediatric Onset Multiple Sclerosis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RRMS	Relapsing remitting multiple sclerosis
S	Steroids
SD	standard deviation
VEP	Visual Evoked Potentials

 doi:10.20944/preprints202509.1793.v1

References

1. Kauth, F.; et al. Characterization of children with early onset pediatric multiple sclerosis. Eur. J. Paediatr. Neurol. 2025, 54, 113–120.
2. Chitnis, T.; Glanz, B.; Jaffin, S.; Healy, B. Demographics of pediatric-onset multiple sclerosis in an MS center population from the Northeastern United States. Mult. Scler. 2009, 15, 627–631.
3. Ness, J.M.; Chabas, D.; Sadovnick, A.D.; Pohl, D.; Banwell, B.; Weinstock-Guttman, B.; International Pediatric MS Study Group. Clinical features of children and adolescents with multiple sclerosis. Neurology 2007, 68(Suppl. 2), S37–S45.
4. Venkateswaran, S.; Banwell, B. Pediatric multiple sclerosis. Neurologist 2010, 16, 92–105.
5. Arkar, U.; Vipotnik Vesnaver, T.; Osredkar, D.; Perković Benedik, M.; Bizjak, N. Multiple sclerosis in a 4-year-old boy: a case report and literature review. Front. Neurol. 2024, 15, 1359938.
6. Mavridi, A.; Bompou, M.E.; Redmond, A.; Archontakis-Barakakis, P.; Vavougios, G.D.; Mitsikostas, D.D.; Mavridis, T. Current and emerging treatment options in pediatric onset multiple sclerosis. Sclerosis 2024, 2, 88–107.
7. Carvalho, I.V.; Dos Santos, C.S.; Amaral, J.; Ribeiro, J.A.; Pereira, C.; Pais, R.P.; Palavra, F. Multiple sclerosis under the age of ten: the challenge of a rare diagnosis in a special population— a case series. Front. Neurosci. 2023, 17, 1297171.
8. Cole, G.F.; Auchterlonie, L.A.; Best, P.V. Very early onset multiple sclerosis. Dev. Med. Child Neurol. 1995, 37, 667–672.
9. Calcii, C.; Aminov, D.; Sprincean, M.; Marga, S.; Anton-Paduraru, D.-T.; Revenco, N.; Groppa, S.; Palii, I.; Pirtu, L.; Hadjiu, S. Very rare incident of pediatric onset multiple sclerosis complicated with status epilepticus: a case report. Austin Neurol. Neurosci. 2023, 6, 1028.
10. Gaccon, L. A case of childhood multiple sclerosis. Br. Ir. Orthopt. J. 2006, 3, 44–46.
11. Gargouri, L.; Safi, F.; Fourati, H.; Kmiha, S.; Turki, F.; Zidi, F.; Mnif, Z.; Mahfoudh, A. Early-onset of multiple sclerosis in a 5-year-old girl. Arch. Pediatr. 2014, 21, 291–295.
12. Guilhoto, L.M.F.F.; et al. Pediatric multiple sclerosis: report of 14 cases. Brain Dev. 1995, 17, 9–12.
13. Hauser, S.L.; et al. Immunoregulatory T-cells and lymphocytotoxic antibodies in active multiple sclerosis: weekly analysis over a six-month period. Ann. Neurol. 1983, 13, 418–425.
14. Hwang, J.S.; Kim, S.J.; Yu, Y.S.; Chung, H. Clinical characteristics of multiple sclerosis and associated optic neuritis in Korean children. J. AAPOS 2007, 11, 559–563.
15. Maeda, Y.; Kitamoto, I.; Kurokawa, T.; Ueda, K.; Hasuo, K.; Fujioka, K. Infantile multiple sclerosis with extensive white matter lesions. Pediatr. Neurol. 1989, 5, 317–319.
16. Mikaeloff, Y.; et al. Prognostic factors for early severity in a childhood multiple sclerosis cohort. Pediatrics 2006, 118, 1133–1139.
17. Pérez-Fernández, V.; Martínez-Salcedo, E.; Climent-Oltra, V.; Domingo-Jiménez, R.; Casas-Fernández, C. Esclerosis múltiple: a propósito de un caso de inicio muy precoz. Rev. Neurol. 1999, 28, 488–491.
18. Rai, B.; Riazat, M.I.; Sharif, F. P652: An unusual case of recurring demyelinating neurological disorder in a 3-year-old. Arch. Dis. Child. 2019, 104, [Abstract P652].
19. Rodríguez Núñez, A.; et al. Esclerosis múltiple en la edad preescolar: aportación diagnóstica de la resonancia magnética. An. Esp. Pediatr. 1992, 37, 405–407.
20. Ruggieri, M.; Polizzi, A.; Pavone, L.; et al. Multiple sclerosis in children under 6 years of age. Neurology 1999, 53, 478–484.
21. Rushdi, R.; Shalaby, N. Pediatric multiple sclerosis: unveiling the trajectory of a toddler-onset case. Neuroimmunol. Rep. 2024, 6, 100222.
22. Saijo, N.; Abe, Y.; Oikawa, Y.; Okubo, Y.; Endo, W.; Numata-Uematsu, Y.; Takahashi, T.; Uematsu, M. Successful treatment with dimethyl fumarate in a child with relapsing–remitting multiple sclerosis. Brain Dev. 2022, 44, 353–356.
23. Sánchez-Calderón, M.; et al. Esclerosis múltiple en la infancia: nuestra experiencia y revisión de la literatura. Rev. Neurol. 1998, 27, 237–241.
24. Sawant, T.A.; et al. A child with early onset multiple sclerosis. BMJ Paediatr. Open 2024, 8(Suppl. 1), A115 (Abstract EPAC.189).

 doi:10.20944/preprints202509.1793.v1

25. Shaw, C.-M.; Alvord, E.C. Multiple sclerosis beginning in infancy. J. Child Neurol. 1987, 2, 252–256.
26. Sivaraman, I.; Moodley, M. Multiple sclerosis in the very young: a case report and review of the literature. Neurodegener. Dis. Manag. 2016, 6, 31–36.
27. Sotgiu, S.; Nieddu, A.; Pruna, D.; et al. On a 5-year-old girl with multiple sclerosis treated with natalizumab. Neurol. Sci. 2023, 44, 2963–2965.
28. Miller, D.H.; Weinshenker, B.G.; Filippi, M.; Banwell, B.L.; Cohen, J.A.; Freedman, M.S.; Galetta, S.L.; Hutchinson, M.; Johnson, R.T.; Kappos, L.; Kira, J.; Lublin, F.D.; McFarland, H.F.; Montalban, X.; Panitch, H.; Richert, J.R.; Reingold, S.C.; Polman, C.H. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult. Scler. 2008, 14, 1157–1174.
29. Polman, C.H.; Reingold, S.C.; Banwell, B.; Clanet, M.; Cohen, J.A.; Filippi, M.; Fujihara, K.; Havrdova, E.; Hutchinson, M.; Kappos, L.; Lublin, F.D.; Montalban, X.; O'Connor, P.; Sandberg-Wollheim, M.; Thompson, A.J.; Waubant, E.; Weinshenker, B.; Wolinsky, J.S. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann. Neurol. 2011, 69, 292–302.
30. Huppke, P.; Huppke, B.; Ellenberger, D.; Rostasy, K.; Hummel, H.; Stark, W.; Brück, W.; Gärtner, J. Therapy of highly active pediatric multiple sclerosis. Mult. Scler. 2019, 25, 72–80.
31. McElroy, J.P.; Krupp, L.B.; Johnson, B.A.; McCauley, J.L.; Qi, Z.; Caillier, S.J.; Gourraud, P.A.; Yu, J.; Nathanson, L.; Belman, A.L.; Hauser, S.L.; Waubant, E.; Hedges, D.J.; Oksenberg, J.R. Copy number variation in pediatric multiple sclerosis. Mult. Scler. 2013, 19, 1014–1021.
32. Chou, I.J.; Wang, H.S.; Whitehouse, W.P.; Constantinescu, C.S. Paediatric multiple sclerosis: update on diagnostic criteria, imaging, histopathology and treatment choices. Curr. Neurol. Neurosci. Rep. 2016, 16, 68.
33. Fadda, G.; Waters, P.; Woodhall, M.; Brown, R.A.; O'Mahony, J.; Castro, D.A.; Longoni, G.; Yeh, E.A.; Marrie, R.A.; Arnold, D.L.; Banwell, B.; Bar-Or, A. Serum MOG-IgG in children meeting multiple sclerosis diagnostic criteria. Mult. Scler. 2022, 28, 1697–1709.
34. Vergani, M.I.; Reimão, R.; Silva, A.M.; Muskat, M.; Espósito, S.; Diament, A. Multiple sclerosis with early childhood onset. A case report. Arq. Neuropsiquiatr. 1988, 46, 195–197.
35. Asai, K.; Inagaki, M.; Maegaki, Y.; Yamamoto, T.; Suzaki, I.; Ohta, S. An early-onset case of multiple sclerosis with thalamic lesions on MRI. Acta Paediatr. Jpn. 1994, 36, 431–434.
36. Murakami, Y.; Matsuishi, T.; Shimizu, T.; Yamashita, Y.; Nagamitsu, S.; Kojima, K.; Kato, H.; Tabira, T. Baló's concentric sclerosis in a 4-year-old Japanese infant. Brain Dev. 1998, 20, 250–252.
37. Bejar, J.M.; Ziegler, D.K. Onset of multiple sclerosis in a 24-month-old child. Arch. Neurol. 1984, 41, 881–882. ([JAMA Network][4])
38. Brandt, S.; Gyldensted, C.; Offner, H.; Melchior, J.C. Multiple sclerosis with onset in a two-year old boy. Neuropediatrics 1981, 12, 75–82.
39. Hanefeld, F.; Bauer, H.J.; Christen, H.J.; Kruse, B.; Bruhn, H.; Frahm, J. Multiple sclerosis in childhood: report of 15 cases. Brain Dev. 1991, 13, 410–416.
40. Bauer, H.J.; Hanefeld, F.; Christen, H.J. Multiple sclerosis in early childhood. Lancet 1990, 336, 1190.
41. Boutin, B.; Esquivel, E.; Mayer, M.; Chaumet, S.; Ponsot, G.; Arthuis, M. Multiple sclerosis in children: report of clinical and paraclinical features of 19 cases. Neuropediatrics 1988, 19, 118–123.
42. Bye, A.M.E.; Kendall, B.; Wilson, J. Multiple sclerosis in childhood: a new look. Dev. Med. Child Neurol. 1985, 27, 215–222.
43. Haas, G.; Schroth, G.; Krägeloh-Mann, I.; Buchwald-Saal, M. Magnetic resonance imaging of the brain of children with multiple sclerosis. Dev. Med. Child Neurol. 1987, 29, 586–591.
44. Dică, A.D.; Craiu, D.; Linca, F.I.; Budișteanu, M.; Iliescu, C.; Sandu, C.; Pomeran, C.; Bârcă, D.; Butoianu, N.; Burloiu, C.; et al. Age-onset-related particularities of pediatric MS—understanding the spectrum: a tertiary center experience. Diseases 2025, 13, 193.
45. Renoux, C.; et al. Natural history of multiple sclerosis with childhood onset. N. Engl. J. Med. 2007, 356, 2603–2613.
46. Neuß, F.; et al. Epileptic seizures in multiple sclerosis: prevalence, competing causes and diagnostic accuracy. J. Neurol. 2021, 268, 1721–1727.

 doi:10.20944/preprints202509.1793.v1

47. Baroncini, D.; Simone, M.; Iaffaldano, P.; Brescia Morra, V.; Lanzillo, R.; Filippi, M.; Romeo, M.; Patti, F.; Chisari, C.G.; Cocco, E.; Fenu, G.; Salemi, G.; Ragonese, P.; Inglese, M.; Cellerino, M.; Margari, L.; Comi, G.; Zaffaroni, M.; Ghezzi, A.; Italian MS Registry. Risk of persistent disability in patients with pediatric-onset multiple sclerosis. JAMA Neurol. 2021, 78, 726–735.
48. Baroncini, D.; Ghezzi, A.; Guaschino, C.; et al. Long-term follow-up (up to 11 years) of an Italian pediatric MS cohort treated with natalizumab: a multicenter, observational study. Neurol. Sci. 2022, 43, 6415–6423.
49. Menascu, S.; Fattal-Valevski, A.; Vaknin-Dembinsky, A.; Milo, R.; Geva, K.; Magalashvili, D.; Dolev, M.; Flecther, S.; Kalron, A.; Miron, S.; Hoffmann, C.; Aloni, R.; Gurevich, M.; Achiron, A. Effect of natalizumab treatment on the rate of No Evidence of Disease Activity in young adults with multiple sclerosis in relation to pubertal stage. J. Neurol. Sci. 2022, 432, 120074.
50. Tysabri, INN: natalizumab. ANNEX I, SUMMARY OF PRODUCT CHARACTERISTICS. Available online: https://ec.europa.eu/health/documents/community-register/2016/20160425134515/anx_134515_en.pdf (accessed on 16. September.2025).
51. Simone IL, Carrara D, Tortorella C, Liguori M, Lepore V, Pellegrini F, Bellacosa A, Ceccarelli A, Pavone I, Livrea P. Course and prognosis in early-onset MS: comparison with adult-onset forms. Neurology. 2002 Dec 24;59(12):1922-8.
52. JASP (version 095.1). Available online: https://jasp-stats.org/download (accessed on 4. September.2025).
53. Generative artificial intelligence (GenAI). Available online: https://chat.chatbot.app/gpt5?utm_source=GoogleAds&utm_medium=cpc&utm_campaign={campaign}&utm_id=22665487438&utm_term=182338911722&utm_content=757447283652&gad_source=1&gad_campaignid=22665487438&gbraid=0AAAAA_a6ETsikdcm2etAVUS29TfmeuBPM&gclid=CjwKCAjw2brFBhBOEiwAVJX5GJ2EQ0nD506CWe1T2v9U%20R1wOyA211E_GT__p4-lcIctgJfiOpggp8xoCW9wQAvD_BwE (accessed on 4. September.2025).