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ORIGINAL ARTICLE

Acquired demyelinating diseases of the central nervous system in children: a single centre experience

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ABSTRACT

Aim To investigate the frequency and clinical, immunological, and radiological characteristics of acquired demyelinating diseases (ADDs) in paediatric patients at the Paediatric Clinic, Clinical Centre of the University of Sarajevo.

Methods This retrospective observational study conducted between 2017 and 2024 included patients <18 years of age with ADD. The diagnosis was established through clinical evaluation, MRI findings, immunological markers, and the exclusion of alternative conditions that mimic ADD, following the IPMSSG (International Pediatric Multiple Sclerosis Study Group) 2010 criteria. Patients were classified into two groups based on the disease course: monophasic and multiphasic group which is further subdivided into multiple sclerosis (MS) and non-MS multiphasic group.

Results Forty-one patients with ADD were included in the study. Seventeen (41.46%) patients remained monophasic, whereas 24 (58.54%) exhibited a multiphasic course. Within the multiphasic group, 22 (91.67%) patients were diagnosed with multiple sclerosis (MS), and two (8.33%) had a non-MS multiphasic disease course. The MS predominantly presented as a relapsing-remitting phenotype, while primary progressive MS was identified in a small subset of cases, highlighting the variability in disease presentation.

Conclusion Recognizing distinct clinical patterns is crucial for enhancing early diagnostic accuracy and optimizing management strategies in this patient population. Ultimately, our study supports the need for a prospective, multicentric investigation to further consolidate data and refine our understanding of ADD epidemiology in Bosnia and Herzegovina.

Keywords: hyperintense lesions, monophasic, multiple sclerosis, non-MS multiphasic

INTRODUCTION

Acquired demyelinating diseases (ADDs) of the central nervous system (CNS) constitute a heterogeneous group disorder of autoimmune origin and cause significant physical and cognitive disabilities (1, 2). It can be defined based on the course of the disease as monophasic events: clinically isolated syndrome (CIS) characterized by monofocal or polyfocal deficits without encephalopathy, or acute disseminated encephalomyelitis (ADEM) characterized by polyfocal deficits and encephalopathy (1). Multiphasic events include both paediatric onset multiple sclerosis (POMS) and non-MS conditions consist of neuromyelitis optica spectrum disorders (NMOSD) associated with aquaporin-4 (AQP4) antibodies, as well as myelin oligodendrocyte glycoprotein (MOG)-associated demyelination (1, 3).

The reported annual incidence of paediatric ADEM varies from 0.07 to 0.9 per 100,000 children (4). Paediatric-onset multiple sclerosis (POMS) constitutes a rare subset of MS, representing about 3-5% of all cases (5). Multiple sclerosis (MS) is a major cause of neurological disability in young people, having a significant social and economic impact. POMS patients generally experience a more aggressive disease onset with disabling clinical symptoms, a polyfocal presentation at disease onset, and a higher relapse rate early in the disease course (6).

Globally, research on acquired demyelinating disorders (ADDs) is advancing, with studies focusing on biomarkers, genetic predisposition, and environmental triggers. While MS in adults has been extensively studied, paediatric MS and other ADDs remain less understood, particularly in terms of their pathophysiology, risk factors, and long-term outcomes. Research has shown that paediatric MS has distinct characteristics, such as a higher relapse rate and different MRI patterns compared to adult MS (7). In Bosnia and Herzegovina (B&H), research on acquired demyelinating disorders (ADDs) in children remains scarce, with limited systematic studies and a lack of comprehensive epidemiological and clinical data. This study will contribute to the advancement of diagnostics and treatment for paediatric ADDs, with a particular focus on differentiating monophasic and multiphasic disease courses, which

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remains a significant challenge in clinical practice. These findings could significantly impact clinical decision-making and patient management.

Given the complexity and variability of these conditions, further research is essential to improve early diagnosis, better understanding of the disease progression, and refine treatment approach.

The aim of this study is to present the frequency and the clinical, immunological, and radiological characteristics of ADDs in paediatric patients at the Paediatric Clinic, Clinical Centre of the University of Sarajevo.

PATIENTS AND METHODS

Patients and study design

This retrospective observational study was conducted at the Department for Paediatric Neurology, Paediatric Clinic, Clinical Centre University of Sarajevo, in the period 2017-2020. Additionally, we compared our results with preliminary findings from an ongoing study conducted in the period 2021–2024, allowing us to assess trends in the frequency of acquired demyelinating diseases among paediatric patients in relation to previous data. Patients were retrospectively identified through a systematic retrospective review of hospital records from the Paediatric Clinic over the study period based on the discharge diagnosis. This method ensured that all consecutive cases that met the inclusion criteria were comprehensively captured for the analysis.

Inclusion criteria were all children younger than 18 years of age who presented with clinical, radiological, and immunological features of acquired demyelinating disorders. The patients were classified according to the clinical presentation of acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), clinically isolated syndrome (CIS), transverse myelitis (TM), or optic neuritis (ON).

Exclusion criteria were patients with secondary demyelinating disease of CNS (proven CNS infections, vasculitis, autoimmune diseases, lupus, radiation/chemotherapy associated with white matter damage or metabolic diseases).

The patients were classified into two groups based on the disease course: monophasic and multiphasic group which was further subdivided into MS and non-MS multiphasic group.

The study was performed in accordance with the ethical principles specified in the declaration of Helsinki. Written informed consent was obtained from all patients.

Methods

After enrolment in the study all relevant data were collected using predesigned form. The form included: detailed patient history, complete physical and neurological examination and laboratory investigations-routine blood (complete blood count - CBC, liver and renal function test), cerebrospinal fluid (CSF) analysis, serum and CSF antibodies for oligoclonal bands (OCB), MOG (myelin oligodendrocyte antibodies) and AQP-4 (aquaporin-4 antibodies) and MRI (brain/spine) scan.

Serum AQP4-ab and MOG-ab were analysed using cell-based assays (CBA) in a central laboratory.

The diagnosis of acquired demyelinating syndrome (ADS) was based on the onset of neurological symptoms, supported by brain/spinal MRI findings (multiple hyperintense lesions on T2-weighted images), CSF analysis (presence of oligoclonal bands), and the exclusion of alternative conditions mimicking ADDs (3), in line with the IPMSSG (International Pediatric Multiple Sclerosis Study Group) 2010 criteria, and revised recommendations of the Neuromyelitis Optica Study Group (NEMOS) (Table 1, 2) (8, 9).

Table 1. Summary of the International Pediatric Multiple Sclerosis Study Group (IPMSSG), 2012 (3, 8)

Acquired demyelinating disease	Criteria
Paediatric clinically isolated syndrome (CIS)	A clinical CNS event with presumed inflammatory demyelinating cause Absence of clinical history of CNS demyelinating disease No encephalopathy Does not meet criteria for MS
Paediatric acute disseminated encephalomyelitis (ADEM)	A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause An encephalopathy that cannot be explained by fever No new clinical or MRI findings 3 months or more after onset Brain MRI: diffuse, poorly demarcated large lesions involving predominantly the cerebral white matter
Paediatric MS	Two or more CIS separated by more than 30 days involving more than one area of brain, optic nerves or spinal cord One CIS associated with MRI findings consistent with 2010 McDonald criteria MRI dissemination in space and in which a follow up MRI shows at least one new lesion consistent with dissemination in time One clinical event (CIS) whose MRI findings are consistent with criteria for DIS and DIT. One ADEM attack followed by one CIS, 3 or more months after symptom onset that is associated with new MRI findings consistent with criteria for DIS

ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; DIS, dissemination in space; DIT, dissemination in time;

Table 2. Neuromyelitis optica spectrum disorder (NMOSD) 2015, diagnostic criteria (9)

NMOSD	Criteria
NMOSD with AqP4 - IgG	One core clinical characteristic Positive AQP4 – IgG testing Exclusion of alternative diagnosis
NMOSD without AQP4-IgG or with unknown status	≥2 Core clinical characteristics: At least one must be optic neuritis; longitudinal extensive transverse myelitis or area postrema syndrome DIS Fulfilment of additional MRI requirements Exclusion of alternative diagnoses
MOGAD	Monophasic recurrent ON, myelitis, brainstem encephalitis or combination of these syndromes MRI, VEP compatible with an inflammatory demyelinating CNS disease Detection of MOG-IgG antibodies in serum

NMOSD, neuromyelitis optica spectrum disorder; AQP4, aquaporin antibodies, MOG, myelin oligodendrocyte glycoprotein antibody; DIS, dissemination in space ; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease

Pharmacological treatment for acquired demyelinating diseases focuses on immunomodulation, symptom control, and neuroprotection. Corticosteroids, such as methylprednisolone, were used for acute exacerbation of multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM), providing anti-inflammatory effects. Plasmapheresis and intravenous immunoglobulins (IVIg) were utilized for severe cases, including neuromyelitis optica spectrum disorder (NMOSD).

The treatment protocol for paediatric-onset multiple sclerosis (POMS) focuses on disease-modifying therapies (DMTs) to reduce relapse rates, delay disability progression, and minimize inflammatory activity in the central nervous system.

The treatment included interferon-beta (INF-β), dimethyl fumarate (DMF), and fingolimod. INF-β was administered as a first-line therapy in patients with mild to moderate disease, aiming to modulate the immune response and reduce inflammatory activity in the central nervous system (8). DMF was used in patients with a more active disease, leveraging its immunomodulatory effects via the Nrf2 pathway to minimize oxidative stress and neuroinflammation. Fingolimod, a sphingosine-1-phosphate (S1P) receptor modulator, was prescribed for patients with high disease activity, with regular monitoring of cardiac function and immunological status to ensure safety (8,9). All ADD patients were closely monitored through scheduled clinical evaluations, laboratory testing, and serial MRI scans to assess disease progression, treatment response, and safety profiles.

Statistical analysis

The data collected were analysed using descriptive statistical methods with the Microsoft Excel program. The data are presented in tables and charts. Qualitative variables are shown as absolute numbers and percentages, while quantitative variables are presented as mean ± SD, minimum, and maximum values.

RESULTS

During the period from January 2017 to November 2024, a total of 47 patients were diagnosed with demyelinating disease. Of these, 41 met the criteria for acquired demyelinating disease and were included in the study (Figure 1).

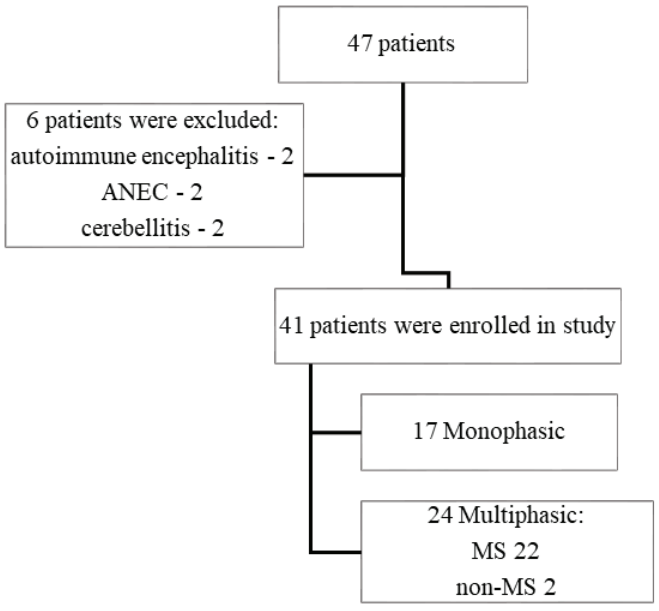

Figure 1. Overview of patients included and excluded from the study

The mean age of disease onset was 14.4 (between 5–18) years. The ratio between females and males was 1.3:1 and did not differ significantly between the presenting phenotypes. A positive family anamnesis, presence of MS, was found in four (9.7%) patients. At the onset of the disease, the patients exhibited several distinct clinical phenotypes: optic neuritis (ON) in 13 (32.5%) patients, of which 11 (84.6%) with unilateral ON, clinically isolated syndrome (CIS) in 16 (39.02%), radiologically isolated syndrome (RIS) in one (2.5%), acute disseminated encephalomyelitis (ADEM) in 10 (25%), and transverse myelitis (TM) in one (2.5%) patient.

Disease onset in winter was the most prevalent, 13 (32%). Vitamin D levels were significantly low (<15 IU) in 22 (53.65%) patients, most of whom were patients with MS. Seventeen (41.46%) patients remained monophasic, including ADEM (N=8), ON (N=5), TM (N =2), CIS (N =1), and RIS (N =1). In one patient, ADEM and TM were developed following measles. So far, the disease has remained monophasic. The first demyelinating attack in another patient (CIS) occurred after a human herpesvirus 6 (HHV6) infection.

Within the multiphasic group, 22 (out of 24; 91.67%) patients were diagnosed with MS, with the majority exhibiting a relapsing–remitting course; two patients were identified as having primary progressive multiple sclerosis (PPMS), and two patients had an ADEM as the first presentation. The mean age of MS diagnosis was 15.97 years.

A non-MS multiphasic disease course was observed in two (out of 24; 8.33%) patients, only two with NMOSD (AQPO4 seronegative and MOG positive, one patient each) (Table 3). Patients with non-MS multiphasic disease were presented with unilateral (NMOSD – MOG ab positive) and bilateral optic neuritis (NMOSD – AqPO4 seronegative).

Table 3. Clinical features of a different disease course

Diagnosis	No (%) patients in the group				
	ADEM (N=8)	ON (N=5)	TM (N=2)	MS (N=22)	NMOSD (N=2)
General symptoms					
Fever	3 (37.5)	0	1 (50.0)	0	0
Headache	5 (62.5)	3(60.0)	0	10 (45.4)	1 (50.0)
Vomiting	4 (8.50)	0	0	0	0
Neurological symptoms					
ON (unilateral: bilateral)	0:1	4:2	0	8:0	1:1
Pyramidal symptoms	8 (100)	0	2 (100)	18 (81.8)	0
Cerebellar symptoms	2 (25.0)	0	0	5 (22.7)	0
Brainstem symptoms	5 (62.5)	0	1 (50.0)	8 (36.0)	0

ADEM, acute disseminated encephalomyelitis; ON, optic neuritis; TM, transverse myelitis; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder; N, No of patients

Oligoclonal bands were present in 23 (out of 41; 57.5%) patients. Type 2 (intrathecal synthesis) oligoclonal bands were most frequently positive. In two patients, type 4 oligoclonal bands were present.

Visual evoked potentials (VEP) were performed in 31 patients. They were pathological in 23 (67.74%) patients, and borderline in 5 (16.12%) patients. VEP was pathological in 16 patients with multiple sclerosis (MS) and all patients (n-5) with optic neuritis (ON). Additionally, it was pathological in one patient with NMOSD (AQPO4 seronegative). Another patient,

who had MOG antibody positive, did not undergo VEP due to lack of cooperation from the parents.

MR brain scans were performed on all children. Most patients had multifocal T2-hyperintense (white matter) WM lesions (Figure 2), located supratentorial or both supra- and infratentorial. Radiologically, the most common sites affected in ADEM and MS were subcortical and periventricular white matter. Thirteen patients (31.7%) also had lesions on the spinal cord, predominantly in the cervical region.

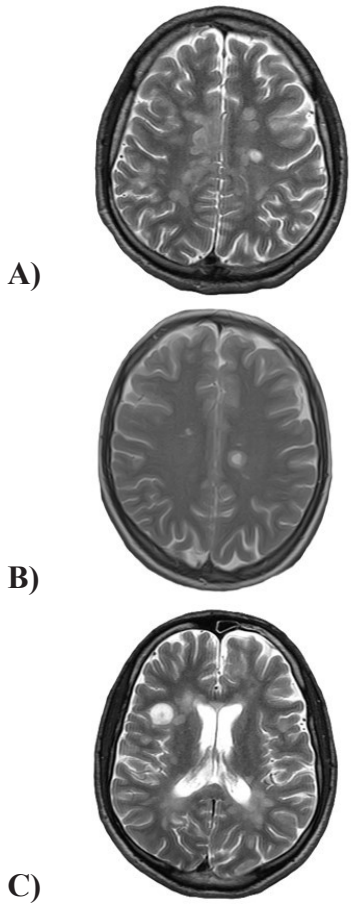

Figure 2. Brain MRI: A) axial FLAIR; B) T2-weighted sequences of paediatric patient with multiple sclerosis demonstrating multifocal hyperintense white matter lesions predominantly located in the periventricular and juxtacortical regions; C) Axial – T2 weighted sequences of paediatric patient with primary progressive multiple sclerosis demonstrating multifocal hyperintense white matter lesions predominantly located in the deep, juxtacortical, and periventricular regions

Thirty-eight (92.68%) patients received pulse methylprednisolone therapy followed by tapering oral steroids over 6 weeks during acute events. Three patients did not receive pulse therapy because their parents either did not consent to it or sought treatment at a foreign centre. One NMOSD (AqPO4 seronegative) patient received, in addition to methylprednisolone, IVIG (immunoglobulins) and subsequently rituximab with an excellent clinical response. Fifteen patients (out of 22; 68.18%) with MS are currently on Disease-modifying therapies (DMTs), four patients are receiving interferon therapy. One of them, due to a relapse, has been switched to fingolimod. Currently, three patients are receiving treatment with dimethyl fumarate, while eight patients are on fingolimod therapy. All patients, except one, have remained stable since starting DMTs. For one patient with a severe clinical state, there is uncertainty about their adherence to the therapy.

Eighteen patients experienced a relapse within one year of follow-up, along with evidence of dissemination in space and progression on MRI brain scans. Among these, thirteen patients were diagnosed with MS.

We performed a temporal cross-sectional analysis and divided the study period into two intervals to asses temporal trends. Between 2017 and 2020, a total of 17 (out of 41; 41.46%) patients were diagnosed with ADD, and between 2021 to 2024, this number slightly increased to 24 (out of 41; 58.53%) patients.

DISCUSSION

Our findings reveal a diverse spectrum of initial clinical presentations. This variety underscores the heterogeneous nature of ADD and emphasizes the need for a comprehensive diagnostic approach that integrates clinical assessments with advanced imaging and immunological testing.

The gender ratio of ADD was 1.3:1 (female: male), consistent with existing literature that suggests a higher prevalence of demyelinating diseases in females, whereas ADEM (Acute Disseminated Encephalomyelitis) is more common in boys (9). However, in our study, there were more affected girls with ADEM.

Differentiating MS from ADEM at the initial episode remains challenging. Multiple sclerosis on the initial episode may be indistinguishable from ADEM, but the majority of ADEM patients would not be subsequently affected with multiple sclerosis because of the risk of 0–28% (10). In our study two patients initially diagnosed with ADEM subsequently developed MS, which resonates with reported relapse risks in the literature (11). Identifying prognostic factors (both clinical and based on MRI criteria) is essential for early differentiation between monophasic and relapsing forms, which has significant implications for long-term management (14,15).

In childhood (6), MS predominantly presents as a relapsing-remitting phenotype (RRMS), with nearly all cases following this pattern. This form is characterized by alternating episodes of neurological dysfunction (relapses) and recovery (remissions). However, in our study, two cases of PPMS were identified, indicating that it can occasionally appear in younger individuals (16).

Long-term disability and disease progression in paediatric ADDs appear to be influenced by critical lesion locations on brain and spine MRI (such as in the spinal cord, infratentorial regions, and grey matter) and by the level of inflammatory activity early in the disease course (12). Canadian prospective cohort study reported that approximately 21% of children with a first episode of CNS demyelination developed MS over a median follow-up of 3.1 years (13).

Infectious etiologies continue to be relevant, particularly in regions with low vaccination coverage. Historically, conditions such as measles, rubella, or varicella have triggered ADEM (14). In our study, we observed a case of ADEM following measles infection, highlighting the need for improved immunization strategies in Bosnia and Herzegovina.

Additionally, we identified a case of radiologically isolated syndrome (RIS) with demyelinating changes detected on brain/spinal MRI affecting the anterior portion of the corpus callosum and cervical spine, accompanied by one oligoclonal band in the CSF. Although this patient has remained clinically stable over a two-year follow-up period, such findings emphasize the importance of careful monitoring in individuals with incidental demyelinating lesions (15).

In the management of paediatric-onset MS (POMS), acute treatment typically involves high-dose steroids. Given the high relapse rate and the relatively favourable recovery following relapses in POMS, early initiation of disease-modifying therapies (DMTs) is strongly recommended (16). Prognostically, POMS exhibits a more inflammatory disease course compared to adult-onset MS (AOMS), with higher relapse rates and earlier milestones of disability (17). This trajectory has prompted a growing emphasis on initiating highly efficacious disease-modifying therapies (DMTs) at an early stage to ensure swift immunomodulatory disease control and to mitigate long-term impacts. These treatment strategies reflect an evolving approach to managing POMS and highlight the importance of tailored interventions for younger patients (20). A multicentre study in the United States has demonstrated that initial treatment of POMS (in cases presenting as CIS/MS) with newer DMTs leads to better disease activity control compared to traditional injectable therapies, supporting their greater effectiveness (17). In our study, four patients were maintained on injectable therapy, one patient was switched to newer DMTs, and 11 patients received fingolimod or dimethyl-fumarate as their initial therapeutic regimen. This shift represents a growing emphasis on aggressive early immunomodulatory approaches to mitigate long-term disability. A patient diagnosed with NMOSD, seronegative for AqPO4 demonstrated excellent clinical recovery following treatment with methylprednisolone, intravenous immunoglobulin (IVIG), and rituximab. This therapeutic approach aligns with existing evidence supporting IVIG and rituximab in managing severe NMOSD cases (18). Furthermore, the low prevalence of relapsing MOG-Ab-associated disease in our study is likely attributed to the recent availability of MOG-Ab testing, which became clinically accessible in 2021.

Transitioning from paediatric to adult care poses unique challenges for adolescents with chronic neuroinflammatory conditions, often accompanied by anxiety. To address this, we have established meetings with adult neurologists prior to patients turning 18, ensuring a smoother transition. These sessions provide detailed case discussions and introduce a new physician who will oversee future care.

The main limitations of this study include the relatively small sample size and the retrospective design. Additionally, the lack of long-term follow-up restricts conclusions about disease progression. As a single-centre study, the results may not be fully representative of broader geographic or demographic populations. Despite these limitations, the study provides valuable insights into acquired demyelinating diseases in children and their clinical characteristics, contributing to better diagnostic and therapeutic approaches.

In conclusion, this study highlights the importance of early diagnosis, targeted immunomodulatory therapies in improving long-term outcomes and clinical care for paediatric patients with acquired demyelinating disorders. The emphasis on early initiation of highly efficacious disease-modifying therapies (DMTs) reflects an evolving standard in clinical management, aiming to control inflammatory activity and prevent long-term disability in POMS. Furthermore, the study underscores the critical role of comprehensive diagnostic evaluations, including neuroimaging, CSF analysis, and bloodwork, in ruling out disease mimics and optimizing patient outcomes. Ultimately, our study supports the need for a prospective, multicentric investigation to further consolidate data and refine our understanding of ADD epidemiology in Bosnia and Herzegovina.

CONTRIBUTIONS

Writing – original draft: E.V.S.; Conceptualization: E.V.S.; Investigation: E.V.S.; Methodology: E.V.S.; Supervision: S.U.; Data curation: E.V.S.; Formal analysis: E.V.S. and Z.H.; Writing – review & editing: E.V.S., S.U., and Z.H. All authors have read and agreed to the published version of the manuscript.

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TRANSPARENCY DECLARATION

Conflict of Interests: None to declare.

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