ORIGINAL ARTICLE

Pediatric-Onset Neuromyelitis Optica Spectrum Disorder in Isfahan: Insights from a Cross-Sectional Study

Masoud Etemadifar, MD[1]; Mehri Salari, MD[2]; Mahdi Norouzi, MD[1,3]

[1]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Functional Neurosurgery Research Center, Shohada Tajrish Neurosurgical Center of Excellence, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Student Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran

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ABSTRACT

Objectives: Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune demyelinating disease of the central nervous system. While NMOSD predominantly affects adults, pediatric-onset NMOSD (PONMOSD) cases are increasingly recognized, necessitating a better understanding of the disease in this population. This study aims to provide a comprehensive insight into the manifestations and management of PONMOSD.
Material & Methods: This study was conducted at the Isfahan MS Clinic, Iran, recruiting 182 NMOSD patients between March 2021 and March 2022. Board-certified neurologists performed diagnosis and examination, applying the 2015 NMOSD diagnostic criteria. Clinical data were collected and analyzed, including demographic information, onset symptoms, family history, treatment, and MRI findings.
Results: Eighteen patients with PONMOSD (9.9% of the total) were identified. The study cohort had a female-to-male ratio 2.6:1, with the most common onset symptoms being optic neuritis (ON) and transverse myelitis (TM). AQP4-Ab was positive in 66.7% of the patients, with longitudinally extensive transverse myelitis (LETM) being the most common MRI finding. Azathioprine and Rituximab were the most commonly used treatments in patients, respectively. Treatment response was generally favorable, with most patients responding to therapy.
Conclusion: The present study provides valuable insights into the clinical characteristics and management of pediatric-onset NMOSD. Despite challenges in diagnosis and treatment, early recognition and appropriate management strategies can lead to improved outcomes in this population. Further research is needed to optimize diagnostic criteria and therapeutic approaches for pediatric NMOSD.

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune demyelinating disease of the central nervous system (CNS), characterized by optic nerve and spinal cord inflammation (1). Previously classified as a subtype of multiple sclerosis (MS), the discovery of aquaporin-4 antibodies (AQP4-Ab) in 2004 reshaped our understanding of the condition. Subsequent investigations and the emergence of atypical forms of the disease led to the adoption of the term NMOSD to describe a spectrum of disorders with similar clinical manifestations (2).

The first case of NMOSD in a patient under 18 years old was documented in 1927, despite the mean age of onset typically being around 40 (3,4). The prevalence of pediatric-onset NMOSD (PONMOSD) has been estimated to be between 5% and 10% (5). Studies suggest that individuals of non-white races tend to experience an earlier onset of the disease (3). Pediatric diagnostic criteria for NMOSD were initially aligned with those for adults; however, the 2015 NMOSD criteria panel recognized specific red flags for pediatric

Corresponding Author:
Mahdi Norouzi. MD
Email: mdnrz1379@gmail.com

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NMOSD (5). Unlike in adults, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is more prevalent in children (6), and longitudinally extensive transverse myelitis (LETM) has less diagnostic specificity in this population (1).

Approximately 20% of NMOSD patients test negative for AQP4 antibodies, with a significant proportion exhibiting antibodies against MOG (7,8). Several studies have reported lower AQP4 antibody seropositivity in pediatric NMOSD patients. For instance, a cohort of 20 pediatric patients with NMOSD showed that 60% of patients are AQP4-Ab positive (7).

In a study on 86 Dutch children with a first demyelinating event, 3.7% were diagnosed with NMO (9). Most pediatric NMOSD patients' onset manifestations are optic neuritis (50-75%) and transverse myelitis (30-50%) (5). However, studies on disease progression and prognosis remain inconsistent.

This study aims to identify the main clinical features and treatment responses and present a study of early-onset NMOSD patients.

Materials & Methods

This study was conducted at the Isfahan MS Clinic, Iran, recruiting 182 NMOSD patients between March 2021 and March 2022, with ethical approval obtained (IR.MUI.MED.REC.1400.198). One hundred eighty-two NMOSD patients referred to the Isfahan MS clinic, Iran, were assessed, with 18 patients under 18. A board-certified neurologist diagnosed and examined all patients, applying the 2015 NMOSD diagnostic criteria (1).

The study's inclusion criteria were as follows:

1. Diagnosis of NMOSD based on the 2015 criteria, 2. Age under 18, 3. Complete documented clinical data, and 4. Consent to participate in the study. Data were collected using a predefined checklist containing demographic information, as well as features and symptoms of NMOSD, including age, gender, onset symptoms, family history, relapses, disease duration, birth trauma, treatment, Expanded Disability Status Scale (EDSS) scores, and MRI findings.

Quantitative data were described using mean and standard deviation, while qualitative data were described using frequency distribution and percentage.

Results

The baseline characteristics of the patients are summarized in Table 1. 182 (141 female and 41 male) patients with NMOSD were analyzed. A total of 18 participants with pediatric-onset NMOSD were examined, with a female-to-male ratio of 2.6:1. The average disease duration was 10.5 years for females and 14 years for males. The average interval between the first and second attacks was 10.7 months for female and 7.6 months for male patients. None of the patients had a history of MS, but 15.38% (two) of female patients had a first-degree family history of NMOSD, and the same percentage had a second-degree family history. Additionally, 40% (two) of male patients had exposure to cigarette smoke, and an equal percentage had a history of Vitamin D deficiency.

AQP4-Ab was positive in 12 patients, while MOG-Ab was positive in one patient. The mean overall EDSS score was 2.44 ± 2.49 over a mean disease duration of 11.5 years. Long-extended transverse myelitis (LETM) was identified in 14 patients, with additional lesions observed in the cervical cord and medulla in two patients each, and singular lesions in the subcortical, frontal, thoracic cord, area postrema, and optic radiation in one patient each. Ocular manifestations were the most common onset symptom, with bilateral blurry vision reported in five patients, right eye blurry vision in three patients, and diplopia in two. Limb paresthesia was observed in five patients, while left and right upper limb weakness were reported in two and one patient, respectively. Proper treatment response was observed in 92.3% (12) females and 80% (4) males.

Table 1. Baseline characteristics

Variable	Total	Female	Male
Number of Patients	18 (100)	13 (72.2)	5 (27.8)
Age of NMOSD onset	13.56 ± 3.61	13.69 ± 3.75	13.20 ± 3.63
BMI (kg/m^2 ± SD)	21.31 ± 1.80	20.94 ± 1.54	22.26 ± 2.26
Family history of MS	0 (0)	0 (0)	0 (0)
Family history of NMOSD	4 (22.22)	4 (30.76)	0 (0)

Discussion

The current study analyses patients with PONMOSD, shedding light on various aspects of the disease in this population. The prevalence of NMOSD among children in this study (9.9%) aligns with previous studies. Studies reporting the prevalence of pediatric NMOSD are relatively rare. A study in Cuba found that up to 3.4% of all NMOSD cases are in patients under 20, but this was before the discovery of AQP4-Ab, possibly leading to underestimation (10). The extensive Mayo Clinic study on AQP4-Ab seropositive patients found that 5% were under 18 (11).

A study by Baghbanian et al. (12) reported a prevalence of 8.8% of pediatric-onset NMOSD among 114 Iranian NMOSD patients, which was in line with the present study. The female-to-male ratio varied among studies, with a ratio of 2.6:1 in the current cohort, compared to 7:1 in the Mayo Clinic study and 4:1 in another study from Iran (11,12).

Table 2. Disease-related characteristics of pediatric NMOSD

Variable	Number (%)
Antibody (Ab) assays	
AQP4-Ab positive	12 (66.70)
MOG-Ab positive	1 (5.60)
Medications	
Azathioprine	12 (66.67)
Tocilizumab	2 (11.10)
Rituximab	9 (50.00)*
Intravenous immunoglobin (IVIG)	2 (11.10)
MRI lesions	
LETM	14 (77.80)
STM (Cervical Cord)	2 (11.10)
Medulla	2 (11.10)
Subcortical	1 (5.60)
Frontal	1 (5.60)
STM (Thoracic Cord)	1 (5.60)
Area postrema	1 (5.60)
Optic radiation	1 (5.60)
Number of disease attacks (mean)	2
The first symptom of NMOSD	
Bilateral ON	5 (27.80)
Right ON	3 (16.70)
Diplopia	2 (11.10)
Lower limb paresthesia	5 (27.80)
Left upper limb weakness	2 (11.10)
Right upper limb weakness	1 (5.60)
Current EDSS† (Mean ± SD)	2.44 ± 2.49

** Some patients latterly switched to Rituximab treatment.*

Studies reported the ON and TM as the first clinical manifestation in most patients (50-75% and 30-50%, respectively). Chitnis et al. (13) reported constitutional, vision, and motor symptoms as the most frequent features of the first attack, respectively, with vomiting observed in 38% of patients, suggesting area postrema involvement. In this study, only one patient revealed area postrema lesions. LETM lesions were predominant in our patients, consistent with findings from other studies. In a study by Absoud et al. (7), 95% of the patients revealed LETM through their follow-up. Chitnis et al. (13) reported LETM in 71% of patients through their first MRIs. LETM can cause motor and sensory symptoms, pain, and bladder dysfunction. Upper cervical lesions can cause nausea, vomiting, and hiccups by involving the medulla. Another reported manifestation is the ADEM-like phenotype, which can affect approximately 10% of patients, making the diagnosis more challenging (8). Brain MRI lesions appear more frequently in children with NMOSD than in adults, often near regions with high AQP4-Ab expression, including diencephalic and brainstem proventricular regions, supra- and infra-tentorial white matter, midbrain, and cerebellum (5).

Accurate diagnosis of NMOSD necessitates the exclusion of other potential diagnoses. It includes demyelinating disorders, systemic inflammatory diseases, and active infections (8). Additionally, higher EDSS, severe attacks, and lower recovery from attacks in AQP4-Ab NMOSD patients compared to MS or MOGAD underscore the importance of proper differentiation. While LETM has lower specificity in diagnosing pediatric NMOSD, area postrema, hypothalamus, and diencephalic involvement indicate high specificity (8). Oligoclonal bands (OCB) may be positive in 25% of the patients (1). Comparing NMOSD and MS regarding brain lesions, the latter tends to have perpendicular to the lateral ventricles surface lesions, juxtacortical lesions engaging the cortical or U fibers, and spinal cord short or peripheral lesions (14). ADEM tends to occur earlier than MS and NMOSD, with male predominance (13). Additionally, identifying AQP4-Ab limits the differential diagnosis. However, AQP4-Ab tends to be less positive (60% in this study) in pediatric-onset NMOSD. Camera et al.

(15) found that 52.3% of NMOSD patients relapsed within one year after the first attack, with Children at younger ages having a higher chance of earlier relapse. Over 79 months of follow-up, permanent visual disability, EDSS score more than 4, and cognitive impairment were observed in 34.3%, 20.7%, and 25.8% of patients, respectively.

The treatment focuses on managing acute attacks and preventing exacerbations. Acute attacks could be managed by intravenous methylprednisolone (IVMP) followed by plasma exchange or IVIG as the second line. Regarding preventive therapy, Azathioprine has shown promising results in some studies. Rituximab (RTX) and Mycophenolate mofetil (MMF) could be administered in case of poor response. Combination therapy, including immunosuppressants and plasma exchange, may be necessary in case of poor response. New drugs (e.g., Tocilizumab, Eculizumab, Aquaporumab, and the like) have shown promising results and could be considered in case of poor response to conventional therapies (5). However, the efficiency and safety of drugs in treating pediatric-onset NMOSD require further studies.

In Conclusion

The present study provides valuable insights into the clinical characteristics and management of pediatric-onset NMOSD. Continued investigative efforts are necessary to shed light on the basic mechanisms that influence disease pathogenesis and to improve diagnostic and treatment strategies for enhanced results in this vulnerable group of patients.

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Ethical Code

IR.MUI.MED.REC.1400.198

Author's Contribution

All authors fulfill the ICMJE criteria for authorship. Masoud Etemadifar contributed to the study design, supervision, datagathering, and review and editing of the manuscript. Mehri Salari contributed supervision and reviewing the manuscript. Mahdi Norouzi contributed to drafting the initial manuscript and the review and editing process. All authors have read and approved the manuscript.

Conflicts of Interest

The authors wish to declare that there are no conflicts of interest.

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