



# Relative frequency of primary headaches in patients with neuromyelitis optica spectrum disorder: A cross-sectional study

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## Keywords

Neuromyelitis Optica; Autoimmunity; Inflammation; Optic Neuritis; Transverse Myelitis; Headache; Migraine Disorders; Tension-Type Headache; Disability

## Abstract

**Background:** Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune inflammatory disease predominantly affecting the central nervous system (CNS). Headaches, although common in patients with multiple sclerosis (MS), have been less studied in NMOSD. This study aimed to investigate the prevalence, characteristics, and associated symptoms of headaches in patients with NMOSD.

**Methods:** This cross-sectional study included 120 patients with NMOSD recruited from MS clinics in Isfahan City, Iran, between 2023 and 2024. Patients were assessed for headache prevalence and characteristics. An expert neurologist conducted

examinations to exclude secondary causes of headaches and classified headache types according to the International Classification of Headache Disorders (ICHD-3).

**Results:** Eighteen patients (15%) reported headaches, all of whom were women. The average age of these patients was  $41.27 \pm 11.33$  years, and the average onset age of NMOSD was  $34.60 \pm 12.12$  years. Of the 18 patients, 14 were diagnosed with migraine and 4 with tension headaches. Patients with migraine reported more severe pain (severity score:  $6.00 \pm 1.42$ ) than those with tension headaches ( $4.20 \pm 1.35$ ). Headache onset was equally likely to occur before or after an NMOSD diagnosis.

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Significant associated symptoms included photophobia, phonophobia, and nausea in patients with migraine, with a substantial impact on occupational disability reported by 57% of migraine sufferers and 50% of tension headache sufferers.

**Conclusion:** Headaches, particularly migraines, are prevalent in patients with NMOSD and significantly impact their quality of life (QOL) and occupational functioning. These findings emphasize the need for clinicians to recognize headache patterns in NMOSD for accurate diagnosis and effective management. Further longitudinal studies are warranted to explore causal mechanisms and develop targeted interventions.

## Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune inflammatory disease characterized by central nervous system (CNS) inflammation.<sup>1</sup> The prevalence of neuromyelitis optica (NMO) ranges from 1 to 5 per 100000 individuals and varies across different populations.<sup>2</sup> The latest NMOSD criteria published in 2015 by the International Panel for NMO Diagnosis (IPND) suggest that the diagnosis of NMOSD is based on at least one of six core clinical characteristics plus anti-aquaporin-4 immunoglobulin G (anti-AQP4 IgG) detection. These clinical characteristics are related to the involvement of the spinal cord, optic nerve, cerebrum, area postrema, and brainstem.<sup>3</sup> Optic neuritis (ON) and transverse myelitis (TM) are the most common presentations.<sup>3</sup> Other manifestations include area postrema syndrome (APS), characterized by hiccups, nausea, and/or vomiting.<sup>4</sup> Acute brainstem symptoms include vomiting, hiccups, oculomotor dysfunction, and pruritus,<sup>5</sup> while symptoms of diencephalic involvement include narcolepsy, hypotension, and amenorrhea.<sup>6</sup>

Headache is common in patients with multiple sclerosis (MS). About 58% of patients with MS have been reported to have headaches. The most common type was tension headache, followed by migraine, with prevalence rates of 31.9% and 25%, respectively. Additionally, there was a significant correlation between relapsing-remitting MS (RRMS) and migraine.<sup>7</sup> However, studies on headaches in NMOSD are limited. A Japanese study on the association between MS and headache, which also included some aquaporin-4 antibody (AQP4-Ab) patients, reported a higher prevalence of migraine in AQP4-Ab seropositive patients compared to others.<sup>8</sup> The relationship between NMO and headache may be related to

other underlying conditions, especially autoimmune disorders. For example, systemic lupus erythematosus (SLE) could be a factor linking these two conditions.<sup>9</sup> A study discovered that approximately 2% to 5% of patients meeting NMOSD criteria also received a diagnosis of SLE.<sup>10</sup> Thus, in this study, we aimed to investigate the patterns, prevalence, characteristics, and associated symptoms of headaches in patients with NMO.

## Materials and Methods

This cross-sectional study aimed to investigate the characteristics and impact of headaches on patients with NMO. A total of 120 patients with NMO were recruited from MS clinics in Isfahan City, Iran, between 2023 and 2024. Patients were eligible for inclusion if they had a confirmed diagnosis of NMO and were able to provide informed consent. The study employed a checklist to gather patient history, detailing headache characteristics, including location, quality, intensity, duration, frequency, triggers, and associated symptoms. Additionally, the impact of headaches on daily activities was assessed. Patients were interviewed and completed a questionnaire rating their pain severity on a visual pain scale from 1 to 10. An expert neurologist conducted examinations to exclude secondary causes of headaches, and headache patterns and types were classified according to the International Classification of Headache Disorders (ICHD-3). For the descriptive analysis of quantitative data, we used mean and standard deviation (SD), and statistical analysis was performed using SPSS software (version 24, IBM Corporation, Armonk, NY, USA). Efforts were made to minimize bias by using a standardized checklist and questionnaire and by having an expert neurologist conduct examinations to exclude secondary causes of headaches. The study is approved by the ethics committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1401.358) and all methods were performed in accordance with the regulations.

## Results

This study investigated 120 patients with NMO (93 women and 27 men). Table 1 presents the clinical characteristics of patients with headaches. Eighteen patients (15%) reported having headaches, all of whom were women. Among these 18 participants, 12 were positive for anti-AQP4-Ab. The average age of patients with

headaches was  $41.27 \pm 11.33$  years.

**Table 1.** Baseline characteristics

| Variable                 | Total (n = 18) [n (%)] |
|--------------------------|------------------------|
| Diabetes mellitus        | 10 (55.56)             |
| Hypertension             | 3 (16.67)              |
| Hypothyroidism           | 1 (5.56)               |
| Cardiovascular disorders | 0 (0)                  |
| Dyslipidaemia            | 6 (33.33)              |

The average onset age of NMO in patients with headaches was  $34.60 \pm 12.12$  years. Of the 18 patients, 14 were diagnosed with migraine and 4 with tension headaches. Table 2 compares characteristics of headaches in patients with migraine and tension headaches. Patients with migraine reported more severe pain compared to those with tension headaches. Nearly half of the patients in each group reported headache onset after an NMO diagnosis. The location and clinical features associated with headaches in each group were consistent with the characteristic symptoms of each headache type. Disability associated with headaches was reported by 57% and 50% of

patients in the migraine and tension headache groups, respectively.

## Discussion

This study provides important insights into the prevalence, characteristics, and associated symptoms of headaches in patients with NMOSD. Our findings highlight that headaches, particularly migraine and tension-type headaches, are a significant concern among patients with NMOSD, with a prevalence of 15%. All patients reporting headaches were women, consistent with the known higher prevalence of NMOSD among women.

Our study aligns with previous findings in patients with MS, where migraine and tension headaches are prevalent (25.2% in previous studies and 15% in the present one).<sup>11,12</sup> Masters-Israilov and Robbins categorized various headache symptoms in patients with NMO, including trigeminal neuralgia, neuropathic pruritus, posterior reversible encephalopathy syndrome (PRES), preeclampsia, and cervicogenic headache, among other headache types.<sup>9</sup>

**Table 2.** Characteristics of headache

|                                           | Migraine          | Tension           |
|-------------------------------------------|-------------------|-------------------|
| Number of cases                           | 14                | 4                 |
| Headache onset age (year) (mean $\pm$ SD) | $31.00 \pm 11.61$ | $29.00 \pm 12.21$ |
| Headache severity score (mean $\pm$ SD)   | $6.00 \pm 1.42$   | $4.20 \pm 1.35$   |
| Headache occurrence (%)                   |                   |                   |
| Before NMO onset                          | 57                | 50                |
| After NMO onset                           | 43                | 50                |
| Headache location (%)                     |                   |                   |
| Frontal                                   | 71                | 50                |
| Occipital                                 | 12                | 25                |
| Generalized                               | 7                 | 25                |
| Characteristic features (%)               |                   |                   |
| Pulsatile                                 | 100               | -                 |
| Unilateral                                | 78                | -                 |
| Bilateral                                 | 12                | 100               |
| Pressing or tightening                    | -                 | 100               |
| Band-like                                 | -                 | 100               |
| Associated symptoms (%)                   |                   |                   |
| Photophobia                               | 85                | -                 |
| Phonophobia                               | 92                | 25                |
| Physical activity aggravation             | 71                | -                 |
| Nausea                                    | 71                | 25                |
| Vomiting                                  | 42                | -                 |
| Hyperhidrosis                             | 35                | 25                |
| Ocular pain                               | 78                | 50                |
| Conjunctivitis                            | 42                | 25                |
| Epiphora                                  | 35                | 25                |
| Occupational disability                   | 57                | 50                |

SD: Standard deviation; NMO: Neuromyelitis optica

Comorbidities such as Sjogren's syndrome and SLE may influence headache expressions in NMO. In a study, it was discovered that 2% to 33% of patients with NMOSD, depending on the specific population being studied, were also diagnosed with Sjogren's syndrome.<sup>10</sup> It is important to note that Sjogren's syndrome can manifest with CNS involvement, leading to symptoms such as headaches and other manifestations related to NMO.<sup>13</sup>

The pathophysiology of headaches in NMO is complex and not fully understood. Potential mechanisms include CNS lesions affecting pain signaling pathways, hypothalamic and upper midbrain involvement, astrocyte dysfunction leading to neurotransmitter imbalances, and disruptions in chemicals like glutamate and gamma-aminobutyric acid (GABA).<sup>9</sup> Wang et al.'s study suggested that lesions in the medulla oblongata were associated with a higher incidence of headaches in patients with NMOSD.<sup>14</sup> Lesions in the peri-aqueductal gray matter and spinal cord, particularly extensive lesions affecting the dorsal gray matter, can interrupt important pain signaling pathways in the spinal cord, including both the pathways that transmit pain signals to the brain and those that inhibit pain. In NMO, the loss of astrocytes, which play a crucial role in balancing excitation and inhibition, is likely to further disturb these pain pathways. In early NMO lesions, pain is linked to high levels of glutamate, while in more established lesions, it is associated with a disruption in the balance between excitatory and inhibitory systems.<sup>9,15</sup> Pentraxin-3 (PTX3) and interleukin 6 (IL-6) are two proposed biomarkers related to headaches. The former has been identified in both patients with MS/NMO and patients with migraine, which might increase in both conditions, especially during relapses.<sup>16,17</sup> IL-6, which has also been suggested as the NMO activity biomarker, has been observed to be elevated in individuals experiencing migraine attacks.<sup>18</sup> This finding might indicate an underlying potential pro-inflammatory mechanism in both diseases.<sup>9</sup> Cavallini et al. stated that headaches could adversely affect a patient's quality of life (QOL) both during the attack phases and in the intervals between them.<sup>19</sup> We found that 72% of patients with headaches reported occupational disability, with a higher incidence among those with migraine headaches. Understanding the link between headaches and NMO may contribute to better disease

management and enhance earlier diagnosis, potentially preventing misdiagnosis. Several case reports have noted that NMO has been misdiagnosed in patients presenting with headaches.<sup>20-22</sup> Therefore, recognizing headache patterns in NMO is crucial for accurate diagnosis and effective treatment.

**Limitations:** The cross-sectional design of our study inherently restricts the capacity to draw causal conclusions. Furthermore, the sample size utilized may not be sufficiently representative of the entire spectrum of patients with NMOSD, thereby potentially constraining the generalizability of our results. Due to this small sample size, we were unable to explore the potential relationship between the degree of disability and the occurrence of headache in patients with NMO. Future studies with larger cohorts may provide more robust data to assess whether such associations exist and how they might impact patient management. Additionally, the elevated baseline prevalence of headaches within the study population poses a challenge to our hypothesis, a phenomenon that can be attributed to the base rate fallacy. It is also conceivable that reporting bias may influence the dependability of our findings, given the possibility that patients may exhibit an increased propensity to report headaches post-diagnosis of their condition. While our study did not collect sufficient data to examine potential differences in the presentation, serostatus, or prevalence of headache among NMO patients, this remains an important area for further research. Future studies should aim to investigate whether these factors influence the headache characteristics among patients with NMO.

## Conclusion

The present investigation sought to elucidate the epidemiological profile, characteristic features, and ramifications of headaches experienced by individuals afflicted with NMOSD. It is imperative that future research, particularly longitudinal studies, be undertaken to fortify the conclusions drawn within this domain. A comprehensive grasp of the headache patterns in NMOSD has the potential to facilitate enhanced disease management strategies and ultimately contribute to the amelioration of patient outcomes.

## Conflict of Interests

The authors declare no conflict of interest in this study.

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