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Pediatric Onset Multiple Sclerosis and Primary Headache: Is There a Link?

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Abstract: *Background*: Pediatric-onset Multiple Sclerosis (POMS) is a rare but often more aggressive form of multiple sclerosis, associated with early cognitive impairment and significant impact on quality of life. While the relationship between multiple sclerosis and primary headaches, especially migraine, is well-established in adults, data on pediatric populations remain limited. *Methods*: this retrospective study analyzed 64 POMS patients, divided into groups with and without headaches, to explore potential associations between headache presence, age at POMS onset, and MRI lesion burden. *Results*: headaches were reported by 78% of patients, predominantly migraines (68%), with a significantly higher prevalence in females (74%). No significant differences were found in age at MS onset or lesion load on brain MRI between patients with and without headaches. Among those with headaches, migraineurs experienced a higher frequency of attacks and a greater need for prophylactic treatment compared to other headache types. Headache characteristics, including pain location and associated symptoms, showed no correlation with age at MS onset or lesion burden. *Conclusions*: these findings indicate that while headaches are common in POMS and more frequent in females, their presence and features do not appear to directly influence the clinical or neuroradiological course of the disease. Further research with larger cohorts and longitudinal follow-up is warranted to better understand the underlying mechanisms and long-term impact of headaches in pediatric MS.

Keywords: pediatric multiple sclerosis; headaches; migraine; childhood; POMS

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS), marked by demyelinating lesions in the brain, spinal cord, and optic nerves. Pediatric-onset MS (POMS), diagnosed in individuals under the age of 18, is relatively uncommon compared to adult-onset MS and poses unique challenges in terms of diagnosis, treatment, and long-term management. In children, the disease may follow a more aggressive course, with faster progression and more severe symptoms, often resulting in early cognitive impairment and a significant impact on quality of life—particularly in areas such as social development and academic performance. Numerous studies have shown that comorbid conditions, including stroke, epilepsy, and headache, can further exacerbate disease burden in MS patients [1,2].

A meta-analysis published in 2021 reported a pooled migraine prevalence of 30% among MS patients—more than twice the rate observed in the general population [3]. The potential causal

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relationship between migraine and MS has been debated for decades. Some researchers suggest that migraine may be a risk factor for the development of MS [4,5], while others propose that MS may either co-occur with or trigger migraine [6]. The two conditions share several risk factors, including female sex, European ancestry, smoking, obesity, vitamin D deficiency [7,8], and adverse childhood experiences [9,10]. Recent evidence also points to some degree of genetic overlap [11].

From a pathophysiological perspective, the mechanisms underlying MS may also contribute to migraine symptoms. Both conditions involve neuroinflammatory processes, and demyelinating lesions—particularly those affecting regions such as the brainstem or periaqueductal gray matter—have been associated with increased headache activity [12]. Moreover, disease-modifying therapies used in MS, including interferon-beta and fingolimod, have been linked to an increased risk of headache as a side effect. Additional factors common in MS, such as fatigue, stress, and depression, may also contribute to higher migraine prevalence [13,14].

Although both MS and migraine can occur in childhood and adolescence—and both can impose a considerable burden—there is a lack of studies exploring their relationship in pediatric populations. To address this gap, we conducted a retrospective study to assess the impact of primary headaches on the clinical, neuroradiological, and therapeutic course of patients with POMS. Particularly, in this study we investigated whether the presence of headache in the clinical history could be associated with a younger age at onset of POMS and a higher number of lesions on brain MRI. Furthermore, we examined the characteristics of headache in POMS patients who reported this symptom, aiming to understand whether these features were related to age at onset and number of brain MRI lesions.

2. Materials and Methods

We included in our study all patients followed by our center who had received a diagnosis of POMS. All patients were contacted by telephone for a questionnaire investigating their history of headaches. Patients who reported having headaches were invited for a screening visit to further investigate the characteristics of their headaches. The data related to POMS were collected retrospectively from our center's databases. Headaches-related data, on the other hand, were collected during these visits from January 2024 to April 2024.

The diagnosis of POMS was based on the McDonald criteria valid at the time of clinical onset (2005–2017) [15]. These criteria combine clinical signs with MRI evidence of dissemination in space and time of CNS lesions. For patients under 18 years old, differential diagnosis excluded other demyelinating syndromes such as MOG antibody disease, neuromyelitis optica spectrum disorder, and acute disseminated encephalomyelitis. Typical MS lesion patterns and cerebrospinal fluid analysis, including oligoclonal bands, were also considered. Clinical data, cerebrospinal fluid and blood biochemical tests, as well as neuroradiological and neurophysiological data, were available for all patients and were consistent with POMS.

The definition and classification of primary headaches were based on the diagnostic criteria outlined in the International Classification of Headache Disorders, Third Edition (ICHD-3) [16]. According to the (ICHD-3), primary headaches are those not attributed to another medical condition and include migraine (with or without aura), tension-type headache, and trigeminal autonomic cephalalgias (TACs). Each diagnosis was established based on detailed clinical criteria such as attack frequency, pain characteristics (e.g., quality, intensity, and location), associated symptoms (e.g., photophobia, phonophobia, nausea), and duration of episodes. Secondary causes of headache were systematically excluded through clinical assessment and diagnostic workup, ensuring that only headaches fulfilling ICHD-3 criteria for primary forms were included in the analysis.

We divided our population into two groups: the first group consisted of POMS patients with headache, and the second group consisted of POMS patients without headache.

The collected POMS data included: demographic (gender, age), clinical (age at onset of MS and headache and age at the time of the screening visit) and neuroradiological variables (lesions' count), and disease modifying therapy (DMT). The lesion's count was considered low when there were fewer than 10 lesions typical of MS, and high when there were more than 10 lesions typical of MS. On MRI, MS typical lesions appear as bright, round or oval spots of demyelination on T2-weighted images, and as hypointense on T1-weighted images. Lesions are found throughout the central nervous system, including the brain (periventricular, subcortical, cortical), spinal cord, and optic nerve [17].

For each patient with headache, we analyzed the following variables: diagnosis of headache (migraine with or without aura, tension type headache or trigeminal autonomic cephalalgias (TACs); side and location of pain, pain quality (throbbing or stabbing or constrictive pain), presence of other symptoms (photophobia, phonophobia, nausea, vomiting), and monthly headache days (MHD). According to MHD the subjects with headache were classified as follows: low frequent episodic (LFE) headache (< 8 MHD), high frequent episodic (HFE) headache (8-14 MHD), and chronic (≥15 MHD). We also evaluated headache treatment-related variables, including the response to painkillers and prophylactic therapy.

Clinical and demographic measures were reported as absolute values and frequencies (%), means and standard deviation score (SDS) for normally distributed data, or medians and interquartile ranges (IQR) for non-normally distributed data.

The chi-square test was used to analyze categorical variables, and ANOVA test was used for continuous variables.

Univariate analysis was performed to analyze separately the correlation between the presence or absence of headache and MRI lesions' count load and age of onset of POMS.

The hypothesis we aimed to verify was that the presence of headache could be a negative predictor associated with a higher lesions' count at MRI and a younger age of onset of POMS.

Multivariate analysis was used to evaluate, in subjects with POMS and headache, the possible correlation between sex, headache diagnosis, headache features (attack frequency, photophobia, phonophobia, and nausea/vomiting), and MRI lesions' count and age on onset of POMS.

Multivariate analysis was performed using a generalized linear model (GLM) with cumulative link and proportional odds assumption.

Significance was determined based on the p-value, with values less than 0.05 considered significant. Bonferroni correction was applied for multiple variables.

3. Results

3.1. All POMS Patients

Our POMS population is made up of 64 patients. Of these, 43 were females and 21 were males, resulting in a female/male ratio of 2:1. At the time of the screening visit for headache, the mean age was 17.77 years (minimum 8.71, maximum 25.39; SDS ± 3.38). The age at POMS onset was 13.6 years (minimum 5.4, maximum 17.8; SDS ± 2.6). The demographics of our POMS population are similar to those reported in the literature, making our population suited to be regarded as an ideal POMS population [18]. On MRI, 23 patients (35.9%) showed a low lesions' count, while 41 patients (64%) had a high lesion count. Regarding therapies with DMT, natalizumab (28%), fingolimod (23%), and ocrelizumab (22%) were the most frequently used ongoing therapies, while cladribine (1.6%), interferon beta (5%), and dimethyl fumarate (5%) were the least used. More details are shown in Table 1.

3.2. POMS Patients with Headaches

Fifty patients (78%) reported suffering from headaches. The age at onset of headaches was 14.6 years (minimum 7.3, maximum 21.5; SDS ± 2.3).

POMS patients with headache more frequently have parents with primary headache than POMS without headache ($p < 0.05$). The 68% of patients reported bilateral pain, while 32% reported unilateral pain, of which 10% described as unilateral with fixed side. Location of pain was most frequently the temporal areas (74%). Throbbing pain was described by the majority of patients (62%), followed by constrictive pain (34%), and a small portion described stabbing pain (4%).

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About half of the interviewees with headache reported photophobia (56%) and phonophobia (44%), and 32% reported nausea or vomiting. According to the ICHD-3 classification, 68% of POMS patients with headaches suffered from migraine, 18% from tension-type headache, and 14% from a primary headache not elsewhere classified. Headache attacks had a mean duration of 519 ± 80 minutes (about 8 hours). There are no significant differences between HFE (32%) and LFE (54%) and14% of patients were chronic.

Regarding treatment, non-steroidal anti-inflammatory drugs (NSAIDs) were the most common molecules used to treat headache attacks, followed by acetaminophen

Just 3 patients were treated with amitriptyline as prophylactic therapy, and all reported an improvement in headache attacks, with a reduction of 50% in the number of attacks per month after three months of therapy. More details are shown in Table 2

From the analysis of the data, no significant correlations were detected between the two groups (POMS with and without headache). In fact, we did not find a significant difference in the age at onset of POMS between those with headaches (13.7 years) and those without headaches (13.4 years), nor was there a significant correlation between lesions' count at MRI and the presence of headache (high count in 64% of POMS with headache and in 64.3% of POMS without headache; $p > 0.05$).

Instead, when analyzing POMS with headache group, the only significant correlation we found in multivariate analysis regards sex. Particularly, female POMS with headache are more frequent than male POMS patients (female POMS: 37/50 - 74%; male POMS: 13/50 - 26%; $p < 0.05$). That is consistent with data reported in the general (no-POMS) population with headache (reference).

We categorized patients by headache diagnosis (migraine, tension-type headache, and headache not elsewhere classified) and found no significant differences in MRI lesions' count. Anyways, patients with migraine most frequently experienced a high frequency of attacks compared to those with tension headaches ($p < 0.05$) and they required prophylactic therapies more frequently ($p < 0.05$). Similarly, there were no correlations between the age at onset of POMS or the count of lesions at MRI and type, side and location of pain, pain quality, presence of other symptoms, frequency of the attacks, or response to painkillers and prophylactic drugs.

Table 1. Demographic and Clinical Characteristics of POMS Patients with and without Headaches.

Variable	POMS with headache	POMS without headache	Sig.
Sex (female,male %)	74%; 26%	42.9 %, 26%	*
Age at onset of POMS (mean± SDS)	13.7 ± 2.6	13.4 ± 2.6	-
Lesions' count at MRI (low, high)	36%, 64%	35.7%, 64.3%	-
Familiarity with headaches	72%	42.9%	*
DMT (%)			
INFb sc	0%	7.1%	
INFb im	2%	7.1%	
DMF	4%	7.1%	
NTZ	24%	42.9%	-
RTX	16%	14.3%	
FNG	28%	7.1%	
OCZ	24%	14.3%	
CLD	2%	1.6%	

CLD: cladribine; DMF: dimethyl fumarate; DMT: disease modifying therapy; FNG: fingolimod; INFb: interferon beta; im: intramuscolar; NTZ: Natalizumab; OCZ: ocrelizumab; RTX: rituximab; sc: subcutaneous; SDS: Standard Deviation Score; Sig: significance; *: $p < 0.05$; - : $p > 0.05$.

Table 2. Clinical profile and treatment approaches for Headaches in POMS.

Feature of headache	Frequency and percentage (total 50 subjects)
Female:Male	37, 74%: 13, 26%
Mean age at onset of headache	14.6 years , SD ± 2.3).
Diagnosis	Migraine without aura 34, 68% Tension type headache 9, 18% Primary headache not elsewhere classified 7, 14%
Frequency of MHD	LFE: 27, 54% HFE: 16, 32% Chronic: 7, 14%
Quality of pain	Throbbing: 31, 62% Constrictive: 17, 34% Stabbing: 2, 4%
Pain side	Unilateral with side preference: 5, 10% Unilateral with no side preference: 11, 22% Bilateral: 34, 68%
Location of pain	Frontal 9, 18% Temporal 37, 74% Widespread 4, 8%
Associated symptoms	Photophobia: 28, 56% Phonophobia: 22, 44% Nausea or Vomiting: 12, 32%
Drugs for the attacks efficacy	Acetaminophen:14, 28% Ibuprofen: 14, 38% Ketoprofen: 9, 18% Nimesulide: 1, 2% Ketoralac: 1, 2%
Prophylactic therapy on chronic subjects	Amitriptyline: 3, 100%

HFE: high frequent episodic (8-14 MHD), and chronic (≥15 MHD); LFE: low frequent episodic (< 8 MHD); MHD: monthly headache days; SDS: Standard Deviation Score.

4. Discussion

Primary headaches and MS are two distinct yet disabling neurological disorders that significantly impact the lives of patients and their caregivers, leading to substantial disability and a decreased quality of life. Over the past few decades, there has been growing interest in identifying potential links between these conditions, driven by several factors. Primary headaches, including migraines, and tension-type headaches are characterized by recurrent episodes of head pain without an underlying medical condition. In contrast, MS is a major cause of neurological disability in young adults, with its pathogenesis influenced by a complex interplay of genetic, environmental, and immunological factors. POMS is relatively rare compared to adult-onset MS. It differs not only in its early age of onset but also in disease severity, lesion burden, early cognitive impairment, and the higher frequency of relapses in the initial stages. The epidemiological and clinical impact of headaches - particularly migraine without aura - on adult-onset MS patients is well-documented, with a large part of adult MS population experiencing headaches. Two extensive meta-analyses estimated that approximately 30% of MS patients suffer from migraines [3,19], with the study population predominantly consisting of Caucasian females diagnosed in early adulthood. Kister et al. (2012) reported a 29% increased risk of MS in females with pre-existing migraines [5]. Based on these findings, some researchers suggest that migraines may contribute as a risk factor for MS. However, it is also debated whether this association results from diagnostic bias, given the overlapping epidemiological characteristics of both diseases (white, young female) or the fact that migraine sufferers frequently undergo brain imaging, which may reveal non-specific white matter abnormalities, potentially leading to an MS diagnosis. Another hypothesis is that migraine-like headaches may serve as an early symptom or part of the MS prodrome [20]. Despite these theories, the prevailing consensus is that since migraines generally precede MS by many years and are rare at disease onset, they are more likely an independent pre-existing condition rather than a direct precursor to MS [21].

Despite the extensive literature on primary headaches and MS in adults, data on pediatric patients remain scarce [3–6]. Mariotti et al. reported the case of a very young girl in whom severe headache was both the presenting symptom and a recurring feature during disease relapses, albeit accompanied by other neurological deficits [22]. A lesion in the brainstem, involving the pain-processing system and associated with brain swelling and a possible meningeal reaction in the periaqueductal gray, was proposed as the pivotal underlying mechanism [23].

Thus, we studied our POMS population to evaluate the possible impact of headaches, their related features, and treatments on disease onset and progression.

Our study did not reveal significant correlations between the presence of headaches and key clinical features of POMS, such as age at onset or demyelinating lesion burden. Specifically, the age at onset of POMS was comparable between patients with headaches and those without and no significant relationship emerged between the extent of demyelinating lesions and headache occurrence. These findings suggest that headaches in POMS are not directly influenced by the overall disease burden or the timing of disease onset.

However, when analyzing the subgroup of POMS patients with headaches, a significant correlation with gender was observed. Female patients experienced headaches more frequently than male patients (74% vs. 26%; $p < 0.05$), a pattern consistent with the well-known epidemiological data from the general population [24,25]. This supports the hypothesis that sex-related biological mechanisms, such as hormonal influences, may contribute to headache susceptibility in POMS as well as in non-POMS individuals [26–29].

Further classification of headache types (migraine, tension-type headache, and headache not elsewhere classified) did not reveal significant differences in their distribution based on disease-modifying therapy (DMT). However, patients with migraines reported a higher frequency of attacks compared to those with tension-type headaches ($p < 0.05$) and were more likely to require prophylactic therapies ($p < 0.05$), indicating a greater burden of disease in this subgroup.

Moreover, no significant correlations were found between the age at onset of POMS and various headache-related characteristics, including pain location, side, features, presence of additional symptoms, frequency, or response to pain management strategies. Similarly, no relationships emerged between demyelinating lesion burden, age, or DMT and any of the analyzed headache variables. These findings suggest that while headaches are a frequent comorbidity in POMS, their occurrence and characteristics are likely influenced by factors independent of MS disease activity and treatment.

Overall, our results highlight the complexity of the relationship between headaches and POMS. The strong female predominance of headaches aligns with known epidemiological trends, while the lack of correlation with lesion burden or disease-modifying treatments suggests that additional mechanisms, possibly related to genetic, hormonal, or environmental factors, may contribute to headache pathophysiology in POMS [30]. Further research with larger cohorts and longitudinal designs is needed to clarify these associations and explore potential underlying mechanisms.

5. Conclusions

Our data indicate that there is no relationship between primary headache and certain parameters related to POMS, such as age of onset, type of treatment, or medications. Therefore, the course of the two diseases appears to be independent. To achieve more robust evidence, a deeper study should be implemented at multiple centers, involving a larger number of patients, conducted prospectively, and with a longer follow-up period. A further study should evaluate the influence of primary headaches on neuropsychological variables (e.g., cognitive, adaptive, executive functions) as well as the impact on the quality of life of patients with POMS and their caregivers, considering the school absences, and highlight any changes in cerebrospinal or humoral inflammatory markers.

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Although a direct causal link has not been confirmed, the co- occurrence of these conditions suggests that patients with MS should be monitored for migraine symptoms, and both conditions should be managed appropriately to improve quality of life.

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Institutional Review Board Statement: This study was conducted according to the guidelines laid down in the Declaration of Helsinki

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author due to ethical restrictions related to patient confidentiality and the protection of sensitive personal health information.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CLD	Cladribine
CNS	Central nervous system
DMF	Dimethyl fumarate
DMT	Disease modifying therapy
FNG	Fingolimod
GLM	Generalized linear model
ICHD-3	The International Classification of Headache Disorders, 3rd edition
IQR	Interquartile range
INFb-im	Intramuscolar interferon beta
INFb-sc	Subcutaneous interferon beta
HFE	High frequent episodic
LFE	Low frequent episodic
MHD	Monthly headache days
MDPI	Multidisciplinary Digital Publishing Institute
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
NSAIDs	non-steroidal anti-inflammatory drugs
NTZ	Natalizumab
OCZ	Ocrelizumab
POMS	Pediatric-onset MS
RTX	Rituximab
SDS	Standard deviation score
TACs	Trigeminal autonomic cephalalgias

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