

Migraine headache in Multiple Sclerosis. Is more frequent among MS patients?

Alia Saberi¹, Mandana Ashkan², Hamidreza Hatamian¹, Ali Ashraf³, Enayatollah Homayirad⁴,
Arash Bakhshi², Kasra Sarlak², Kamal AmirAshjei Asalemi², Nima Broomand Lomer²

¹Department of Neurology, Poursina Hospital, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran

²Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran

³Poursina Clinical Research Development Unit, Guilan University of Medical Sciences, Rasht, Iran

⁴Social Determinants of Health Research Center, Guilan University of Medical Sciences, Rasht, Iran

ABSTRACT

Objectives. Multiple sclerosis (MS) is a chronic disease of the central nervous system that is associated with inflammation, demyelination of neurons and gliosis. There are different reports about the association between migraine and MS. Taking note of headaches experienced by people with MS and providing appropriate treatment can help enhance their quality of life. We aimed to determine the frequency of migraine headache in MS patients.

Materials and methods. This was a descriptive cross-sectional study, conducted in 2020 among 125 MS patients referred to neurology clinic of Poursina Hospital or registered in Guilan MS Registry System and 125 controls with minor head trauma in Rasht. After obtaining written consent, all the subjects were asked to fulfil a checklist about their demographics, MS and headache characteristics by phone call.

Outcomes. In this study 96 RRMS, 19 PPMS and 10 SPMS patients participated among which frequency of mild, moderate and severe disability was 74.4%, 22.4% and 3.2%, respectively. The frequency of migraine in MS patients was significantly higher than the control group [28.8% (n=36) vs. 12.8% (n=16) p=0.002]. After adjusting the confounding factors a significant relationship was found between MS and migraine (OR: 2.76, p = 0.004).

Conclusions. MS patients experience migraine headaches approximately twice the general population.

Keywords: migraine, headache, multiple sclerosis, neurodegeneration, demyelination

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating, neurodegenerative and autoimmune disorder of central nervous system (CNS) leading to gliosis and plaque formation in various areas of brain and spinal cord [1]. The global prevalence of disease in 2020 was estimated 2.8 million people [2]. It occurs three times more in females and predominantly between 20 to 40 years of age [3]. Although, the etiology yet remains to be unknown, but some factors are demonstrated to have some associations including, immune deficiency, genetic and familial susceptibility, geographic factors, viral infections and stress [4]. Multiple sclerosis emerges with various clinical phenotypes ranging from a be-

nign form of disease to a rapid progressive and debilitating one [5,6].

Headache is one of the conditions that physicians are frequently facing with in daily practice [7]. Nearly 90% of people experience headache disorders during their lifetime [8]. Migraine is a neurological disorder characterized by recurrent and severe unilateral headache accompanied by symptoms such as nausea, vomiting, photophobia, and phonophobia. It is believed to be initiated by a series of events in the CNS, making the individual more susceptible to environmental triggers. Furthermore, activation of trigeminal nerve and the release of calcitonin gene-related peptide (CGRP) from the trigeminovascular system have been linked to migraine headaches [9].

Corresponding author:
Nima Broomand Lomer
E-mail: nima.broomand@gmail.com

Article history:
Received: 17 March 2023
Accepted: 28 March 2023

Several mechanisms are suggested to explain higher rates of migraine occurrence in patients with MS. First, postmortem histological analyses have shown that it could be due to the presence of lymphoid follicle-like structures in the gyri and meninges leading to meningeal inflammation [10]. Second, cortical demyelination resulted from inflammation might explain the presence of migraine in MS patients, as it accelerated cortical spreading depression in rodent models in a study [11,12]. Third, the location of lesions might have some associations, as in a retrospective study, patients having MS lesions in midbrain's periaqueductal gray were more likely to develop migraine headaches [13].

MS and migraine share some common demographic and epidemiologic characteristics. Both are more common in females, young adults and Caucasians compared to Asians and Africans [14,15]. MS patients with migraine headaches are more susceptible to experience severe neurologic symptoms, fatigue, depression and stress compared to MS patients without migraine [16]. Several studies have shown headache, especially migraine and tension type headache as a common presentation in patients with MS with a prevalence of more than 50% [17,18]. In a retrospective review, headache was reported in 55.6% of MS patients, comprising migraine in 61.7%, tension type headache in 25.3% and mixed type in 13% of them [19]. Taking into account the divergent reports regarding the frequency of migraine in MS, and the increasing number of MS cases in Guilan, our goal was to determine the prevalence of migraine headaches in MS patients in this region.

METHODS AND MATERIALS

In this descriptive cross-sectional study, conducted in 2020 we recruited a total number of 125 patients with MS and 125 controls. Initially, we provided a list of patients with MS who were referred to neurology clinic of Poursina hospital within the past year using ICD codes, or registered in Guilan MS Registry System. In the next step, we picked a random sample of 125 cases out of the aforementioned list. Parallel randomization method was used for the selection of control group out of a list of patients admitted with minor head trauma within the same period of time. Participants included in the study must have met a definite MS diagnosis according to the revised McDonald 2017 criteria [20]. All the participants entered the study voluntarily. Those without sufficient cooperation and the ones experiencing headaches of other types were excluded. All cases and controls underwent a comprehensive clinical interview through phone call concerning their age, gender, usage of any MS-related drugs, anti-depres-

sive drugs and anti-anxiety drugs, duration of disease, phenotype of MS, disability level (EDSS) and history of migraine headaches. The International Classification of Headache Disorders, 3rd edition (ICHD-3b) diagnostic criteria were used to evaluate migraine headaches in patients [21].

This study was approved by the ethics committee of Guilan university of medical sciences (Registry Code: IR.GUMS.REC.1400.499). Written and informed consent was provided by all participants. Statistical analysis was conducted using SPSS version 28. The Mantel Haenszel method was utilized to adjust for confounding effects, and a logistic regression model was employed for the study analysis. A significance level of 0.05 was set.

OUTCOMES

Result of our study showed that out of 125 patients with MS, majority of patients in MS group were females, diagnosed with RRMS and mild disability. The mean age of patient group was significantly higher than control group ($p < 0.05$). Prevalence of migraine in patients with MS was significantly higher than control group ($p = 0.002$). There was no significant difference among the number of patients using anti-depressive drugs or anti-anxiety drugs compared to controls ($p > 0.05$) (Table 1).

After adjusting for confounding factors (i.e., gender and age), a logistic regression model revealed a significant correlation between MS and the development of Migraine headaches (Odds Ratio = 2.76, $p = 0.004$). This suggests that MS patients are more than twice as likely to develop Migraine headaches than individuals without MS (Table 2).

CONCLUSIONS

In this cross-sectional study, we evaluated the prevalence of migraine headaches among a group of MS patients and a group of controls. The findings of this study revealed a significant difference in the prevalence of migraine headaches between the MS group (28.8%) and control group (16.8%). After controlling for potential confounding variables such as age and gender, a significant association was observed between having MS and developing migraine headaches, so that those with MS were 2.76 times more likely to experience migraine headaches.

Similar results have been reported in previous studies in different countries. Mirmosayyeb et al. in a meta-analysis among 11372 MS patients resulted a pooled migraine prevalence of 31%. Besides, the prevalence of migraine among studies, ranged from 2% to 67% among different nations and also, the pooled prevalence of migraine in different continents were significantly different [22]. In another

TABLE 1. Demographic characteristics of participants

Variables	MS (N=125)	Controls (N=125)	P value
Age	37.54 ± 11.05	32.21 ± 11.45	0.0002
Gender (Female%)	71.2%	50.4%	0.001
Type of MS	RRMS	76.8%	NA
	PPMS	15.2%	
	SPMS	8%	
Disability	Mild (0≤EDSS≤3.5)	74.4%	NA
	Moderate (3.5≤EDSS≤7)	22.4%	
	Severe (7≤EDSS≤10)	3.2%	
MS-Related Drugs Users	96%	NA	NA
Anti-Anxiety Drugs Users	4%	7.2%	> 0.05
Anti-Depressive Drugs Users	16.8%	14.4%	> 0.05
Disease Duration	6.14 ± 4.77 (min=2; max=28)	NA	NA
Migraine Prevalence	28.8%	12.8%	0.002

Abbreviations: NA= not applicable; EDSS= expanded disability status scale; RRMS= relapsing remitting MS; PPMS= primary progressive MS; SPMS= secondary progressive MS

TABLE 2. Logistic regression model after eradication of Confounding factors

	Odds ratio	Standard error	z-score	P> z	95% CI
MS	2.76	0.96	2.89	0.004	1.38-5.49
Age	0.98	0.01	-1.13	0.258	0.95-1.01
Gender	0.59	0.21	-1.46	0.143	0.29-1.19
Constant	0.31	0.17	-2.05	0.04	0.1-0.94

meta-analysis, Wang et al. reported that among a total of 3560 patients with MS, overall prevalence of migraine headache was 27% and also, migraine headache prevalence of included studies ranged from 16.7% to 47% [23]. In a recent nationwide inpatient sample study among 18955 MS patients, the prevalence of migraine headaches was reported 7% [24]. Inconsistencies observed upon prevalence of migraine headaches in different studies could be attributed to unequal mixture of cases in terms of age, gender, ethnicity, weight, concomitant disorders and other factors.

There are various hypotheses concerning the high rates of headache occurrence in patients with MS. Mechanisms comprising decreased levels of serotonin in CSF, hypoactivity of sympathetic system, cytokines levels alterations and presence of B cell follicular structures in meninges and gyri are deemed to

be responsible [10, 25]. Some studies suggest that demyelinating plaques in CNS might have some associations. A few studies reported associations of MS lesions in brainstem, C2 dorsal horn and periaqueductal gray area with severe migraine headaches [13,26-31]. Another hypothesis suggests that headaches arising from MS, especially migraine headache, originate from a common environmental or genetic factor influenced by hormonal alterations. One of the confirmatory observations concerning this hypothesis is lowered levels of MS activity and migraine attack frequency during pregnancy [32]. Besides, Immunologic alterations are also assumed to be a contributory factor, considering decreased levels of T8+ lymphocytes both in MS patients and migraine headaches [19]. These hypotheses are assumed to be the most probable, however, the exact pathophysiology of headaches related to MS has yet to be fully elucidated.

Our study had some limitations. We could not reach any evidence indicating presence of migraine attacks prior to MS occurrence. Our study design was unable to clarify whether migraine attacks are resulted through the course of MS or migraine attacks act as a predisposing factor for MS occurrence. This study was conducted among a small number of participants in one geographic region. We recommend that future studies use larger samples from multiple countries in order to account for additional influential factors, such as ethnicity.

In conclusion, our study demonstrated that patients with MS are more likely to experience migraine headaches approximately more than twice the general population and they can take advantage of prior therapy and avoidance from triggers in early stages of the disease.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

- Brück W, Stadelmann C. Inflammation and degeneration in multiple sclerosis. *Neurol Sci.* 2003 Dec;24 Suppl 5:S265-7. doi: 10.1007/s10072-003-0170-7.
- Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. *Mult Scler.* 2020 Nov;26(14):1816-21. doi: 10.1177/1352458520970841.
- Garg N, Smith TW. An update on immunopathogenesis, diagnosis, and treatment of multiple sclerosis. *Brain Behav.* 2015 Aug;5(9):e00362. doi: 10.1002/brb3.362.
- Shahnazari Z, Marandi SM, Shayegan Nejad V. The Effect of Pilates Exercises and Aquatic Training on Walking Speed in Women with Multiple Sclerosis. *NMJ.* 2013;10(2):10-7. url: nmj.goums.ac.ir/article-1451-en.html.
- Weiner HL. A shift from adaptive to innate immunity: a potential mechanism of disease progression in multiple sclerosis. *J Neurol.* 2008 Mar;255 Suppl 1:3-11. doi: 10.1007/s00415-008-1002-8.
- Yetimalar Y, Seçil Y, Inceoglu AK, Eren S, Başoğlu M. Unusual primary manifestations of multiple sclerosis. *N Z Med J.* 2008;121(1277):47-59. PMID: 18677330.
- Sierpina V, Astin J, Giordano J. Mind-body therapies for headache. *Am Fam Physician.* 2007;76(10):1518-22. PMID: 18052018.
- Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population- a prevalence study. *J Clin Epidemiol.* 1991 Jun;44(11):1147-57. doi: 10.1016/0895-4356(91)90147-2.
- Edvinsson L, Villalón CM, MaassenVanDenBrink A. Basic mechanisms of migraine and its acute treatment. *Pharmacol Ther.* 2012 Dec;136(3):319-33. doi: 10.1016/j.pharmthera.2012.08.011.
- Magliozzi R, Howell OW, Reeves C, Roncaroli F, Nicholas R, Serafini B, et al. A Gradient of neuronal loss and meningeal inflammation in multiple sclerosis. *Ann Neurol.* 2010 Oct;68(4):477-93. doi: 10.1002/ana.22230.
- Merkler D, Klinker F, Jürgens T, Glaser R, Paulus W, Brinkmann BG, et al. Propagation of spreading depression inversely correlates with cortical myelin content. *Ann Neurol.* 2009 Sep;66(3):355-65. doi: 10.1002/ana.21746.
- Pakpoor J, Handel AE, Giovannoni G, Dobson R, Ramagopalan SV. Meta-analysis of the relationship between multiple sclerosis and migraine. *PLoS One.* 2012 Sep;7(9):e45295. doi: 10.1371/journal.pone.0045295.
- Gee JR, Chang J, Dublin AB, Vijayan N. The association of brainstem lesions with migraine-like headache: an imaging study of multiple sclerosis. *Headache.* 2005 Jun;45(6):670-7. doi: 10.1111/j.1526-4610.2005.05136.x.
- Kakalacheva K, Lünemann JD. Environmental triggers of multiple sclerosis. *FEBS Lett.* 2011 Dec;585(23):3724-9. doi: 10.1016/j.febslet.2011.04.006.
- Breslau N, Rasmussen BK. The impact of migraine: Epidemiology, risk factors, and co-morbidities. *Neurology.* 2001 Mar;56(6 Suppl 1):S4-12. doi: 10.1212/wnl.56.suppl_1.s4.
- Minen MT, Schaubhut KB, Morio K. Smartphone based behavioral therapy for pain in multiple sclerosis (MS) patients: A feasibility acceptability randomized controlled study for the treatment of comorbid migraine and ms pain. *Mult Scler Relat Disord.* 2020 Sep;46:102489. doi: 10.1016/j.msard.2020.102489.
- La Mantia L, Prone V. Headache in multiple sclerosis and autoimmune disorders. *Neurol Sci.* 2015 May;36 Suppl 1:75-8. doi: 10.1007/s10072-015-2146-9.
- Putzki N, Katsarava Z. Headache in multiple sclerosis. *Curr Pain Headache Rep.* 2010 Aug;14(4):316-20. doi: 10.1007/s11916-010-0126-6.
- D'Amico D, La Mantia L, Rigamonti A, Usai S, Mascoli N, Milanese C, et al. Prevalence of primary headaches in people with multiple sclerosis. *Cephalalgia.* 2004 Nov;24(11):980-4. doi:10.1111/j.1468-2982.2004.00790.x.
- Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 2018 Feb;17(2):162-73. doi: 10.1016/S1474-4422(17)30470-2.
- The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia.* 2013 Jul;33(9):629-808. doi: 10.1177/0333102413485658.
- Mirmosayyeb O, Barzegar M, Nehzat N, Shaygannejad V, Sahraian MA, Ghajarzadeh M. The prevalence of migraine in multiple sclerosis (MS): A systematic review and meta-analysis. *J Clin Neurosci.* 2020 Aug;79:33-8. doi: 10.1016/j.jocn.2020.06.021.
- Wang L, Zhang J, Deng ZR, Zu MD, Wang Y. The epidemiology of primary headaches in patients with multiple sclerosis. *Brain Behav.* 2021 Jan;11(1):e01830. doi: 10.1002/brb3.1830.
- Koffman B. Migraine Headache associated with Multiple Sclerosis: Results from the Nationwide Inpatient Sample. Translation: *The University of Toledo Journal of Medical Sciences.* 2021 Apr;9(1):1-5. doi: 10.46570/utjms.vol9-2021-269.
- Elliott DG. Migraine in multiple sclerosis. *Int Rev Neurobiol.* 2007 May;79:281-302. doi: 10.1016/S0074-7742(07)79012-8.
- Haas DC, Kent PF, Friedman DI. Headache caused by a single lesion of multiple sclerosis in the periaqueductal gray area. *Headache.* 1993 Sep;33(8):452-5. doi: 10.1111/j.1526-4610.1993.hed3308452.x.
- Fragoso YD, Brooks JB. Two cases of lesions in brainstem in multiple sclerosis and refractory migraine. *Headache.* 2007 Jun;47(6):852-4. doi: 10.1111/j.1526-4610.2007.00823.x.
- Galer BS, Lipton RB, Weinstein S, Bello L, Solomon S. Apoplectic headache and oculomotor nerve palsy: an unusual presentation of multiple sclerosis. *Neurology.* 1990 Sep;40(9):1465-6. doi: 10.1212/wnl.40.9.1465.
- Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain.* 1997 Nov;120 (Pt 11):2059-69. doi: 10.1093/brain/120.11.2059.
- Cooney BS, Grossman RI, Farber RE, Goin JE, Galetta SL. Frequency of magnetic resonance imaging abnormalities in patients with migraine. *Headache.* 1996 Nov;36(10):616-21. doi: 10.1046/j.1526-4610.1996.3610616.x.
- Tortorella P, Rocca MA, Colombo B, Annovazzi P, Comi G, Filippi M. Assessment of MRI abnormalities of the brainstem from patients with migraine and multiple sclerosis. *J Neurol Sci.* 2006 May;244(1-2):137-41. doi: 10.1016/j.jns.2006.01.015.
- Kister I, Caminero AB, Monteith TS, Soliman A, Bacon TE, Bacon JH, et al. Migraine is comorbid with multiple sclerosis and associated with a more symptomatic MS course. *J Headache Pain.* 2010 Oct;11(5):417-25. doi: 10.1007/s10194-010-0237-9.