

Neurology and Neurosurgery

UDC: 616.8:616-06:616.8-004:616.8-009

IMPACT OF COMORBID PRIMARY HEADACHE ON NEUROLOGICAL FUNCTION OF PATIENTS WITH MULTIPLE SCLEROSIS

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Multiple Sclerosis (MS) is a progressive disease affecting the working population. Due to the demyelination process, patients have motor, sensory and cognitive impairments. Often patients with MS complain of headaches. Comorbid primary headache accompanies more than half of patients with MS. The aim of our study was to reveal the relationship between the presence of primary comorbid headache and the progression of MS. For this purpose, the Expanded Disability Status Scale (EDSS), motor testing for 25-Foot Walk Test (25FWT), 9-Hole Peg Test (9HPT) were used. International Classification of Headache - 3 (ICHD-3) scale was used for differential diagnosis of headache types. The obtained data were compared among patients with different types of MS: Relapsing-Remitting (RRMS); primary and secondary progressive, which was combined into Progressive forms of MS (PMS). 130 patients with MS were studied, among whom patients with RRMS prevailed (n=98), primary comorbid headache was found in 56.2% (n=73). Among patients with MS, migraine prevailed (p=0.015), in particular, the most cases were found in patients with RRMS. Among patients with PMS, tension headache prevailed (p<0.05). The 9HPT and 25FWT scores did not differ significantly between the groups with and without primary comorbid headache, however, according to the confidence intervals, the EDSS score exceeded the score in the group of patients with comorbid headache. It was found that patients with comorbid migraine performed the motor test faster than patients with tension type headache. Therefore, it can be concluded that comorbid primary headache may have an impact on motor function indicators among MS patients and requires further investigation to determine the role of comorbid headache in the patterns of initial MS symptoms.

Keywords: *central nervous system, demyelination, migraine, tension type headache, motor function, comorbidity.*



Цитуйте українською: Московко ГС, Андрієвська МІ.
Вплив коморбідного первинного головного болю
на неврологічну функцію пацієнтів з множинним склерозом.
Експериментальна і клінічна медицина. 2023;92(3):63-72.
<https://doi.org/10.35339/ekm.2023.92.3.man> [англійською].

Cite in English: Moskovko GS, Andrievska MI.
Impact of comorbid primary headache on neurological function
of patients with multiple sclerosis.
Experimental and Clinical Medicine. 2023;92(3):63-72.
<https://doi.org/10.35339/ekm.2023.92.3.man>

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Introduction

Multiple sclerosis (MS) is a chronic neuroinflammatory progressive disease with an unknown etiology [1; 2]. At the moment, it is known that a complex interaction of both environmental and genetic factors is being considered [1]. Also, MS includes an autoimmune process in the central nervous system, characterized by loss of myelin protein (demyelination) and simultaneous loss of axons [3]. Symptoms of MS can be diverse in individuals and quite unpredictable [4]. The signs of the disease and its symptoms can also vary greatly during the course of the disease. The most frequent are disturbances of motor function, sensitivity and visual impairment, less common and still important are dysfunction of the urinary tract and intestines, pain sensations, complaints of fatigue, cognitive decline and mood changes [3]. MS affects women more often than men [4]. Disease is disabling and affects young people, the average age of disease manifestation is 40 years old. There is data that the disease begins about five years earlier in women than in men [4]. Over the past ten years, several studies have shown that comorbidities among patients with MS are very common, particularly even at the time of diagnosis or early onset of the main disease, and that their prevalence and manifestations increase with age [5]. Comorbidities affect people with MS and affect the entire course of the disease, from the onset of symptoms to the end of life [6]. On the one hand, individually, comorbidity can be associated with a higher frequency of relapses, more pronounced motor and mental disorders, reduced quality of life, which is related to the state of health, as well as higher mortality. On the other hand, at the level of the healthcare system and society, comorbidity

is associated with increased demand and seeking help in health care facilities, higher costs, and reduced performance at work [6]. Recent studies claim that MS affects the prognosis of comorbidities [6]. Comorbidities are strongly associated with reduced quality of life in MS [7]. In addition, some studies have suggested that comorbidities may partially explain the variability in clinical course among people with MS [7].

Several case-control studies have found higher rates of headache in the MS population compared to healthy individuals [3]. However, the potential association between headache and multiple sclerosis has been known for a long time, and was first reported more than 50 years ago [3]. Several large-scale population-based studies, such as those in Sicily, have reported the prevalence of headache among patients with multiple sclerosis increased twice compared to controls [8]. It was recently shown that patients with MS had a three-fold higher frequency of migraine compared to healthy controls. Although this data is controversial [3].

Another German study did not find a higher prevalence of headache or migraine in 491 MS patients compared to 447 controls [3]. However, this may have been due to the very high prevalence of primary headache in the local population [8]. As for the explanations of such a connection, recent studies of the pathology of MS have shown that the meninges are involved in the pathological process of MS with the presence of "tertiary B-cell follicles" located in the gyri [1]. Because of knowledge that irritation of the meningeal membranes is known to cause headache, this meningeal inflammatory process may be a pathomorphological and important substrate of headache in MS [1].

The International Headache Society distinguishes between primary, secondary and other types of headaches [1]. In our study, we focused on patients with primary headache, including migraine, tension headache, and cluster headache. Migraine is a mostly unilateral throbbing headache lasting from 4 to 72 hours with a prevalence of 10% in the normal population [1]. Etiology and pathogenesis are still being investigated. The prevalence of migraine among patients with MS ranges widely from 43.3% to 71.8% [1].

Tension-type headache is characterized by constant pulling pain in the form of a hoop with a lifetime prevalence of 30–70% [1]. As with migraine, the etiology and pathogenesis are not yet fully understood [1], but central mechanisms are evident. Similar to migraine, TSH in MS patients ranges from 12.2% to 55.2% [1]. The presence of migraine-like headache in different subtypes of MS suggests a common pain modulation pathway in both migraineurs and MS patients. It has been suggested that headaches may be associated with MS, especially among patients with a relapsing-remitting course [1].

Although the literature supports the idea of an association between MS and migraine, the exact mechanism(s) for this association is not well understood [3, 8]. There are few questions to ask about. Firstly, is migraine definitely a comorbid condition of MS? Secondly, could this be a signal of the possible manifestation of MS? Thirdly, do comorbid headaches have an impact on the course of MS [3]? These questions are important for the diagnosis and treatment of MS and need to be addressed in future studies [3].

Several studies have examined migraine frequency in relation to the clinical course of MS and found that migraine frequency is increased in patients with relapsing-remitting (RR) MS, while tension-type headache is more common in patients with progressive forms of MS [3].

This indicates that migraine can be a significant symptom at the early onset of the disease [3]. So, it is unclear whether there is a link between headache and MS, and specifically for migraine and MS. The question of whether comorbid migraine in a patient with MS affects the symptomatology, comorbidity, and course of MS has not been sufficiently studied, and the observed relationship between the presence of migraine and the relapsing course of MS [8] has not been found in all studies. Despite the facts above, there is data that describes the tendency among patients with multiple sclerosis (MS) that a history of migraine may not be associated with worsening disability or neurological function [9].

Purpose of the study – to show the prevalence of primary comorbid headache among patients with multiple sclerosis, to investigate the influence of comorbid primary headache on motor function in patients with different courses of multiple sclerosis.

Materials and Methods

We examined 130 patients with multiple sclerosis in the Department of Neurology in National Pirogov Memorial Medical University, Vinnytsya. Diagnosis multiple sclerosis was confirmed according to the McDonald criteria 2017. The inclusion criteria were the next: confirmed MS, relapsing-remitting type, primary, secondary progressive type with usage of McDonald's criteria, in phase of clinical remission (last clinical relapse at least 3 months ago), any steroids, pulse-therapy or analgesics for last 3 months before the study started, absence of other autoimmune disorder or comorbid disease except primary headache. Type of primary headache was classified according to the International Classification of Headache Disorders - 3 (ICHD-3). Secondary types of headaches were excluded from the study as well as brain tumor or vascular disorders among patients. Firstly, patients were divided into 2 clinical groups according to the type of MS:

with Relapsing-Remitting MS (RRMS) and progressive MS (included Primary Progressive MS (PPMS) and Secondary Progressive MS (SPMS)). Secondly, among these patients two groups were created: patients with MS without primary comorbid headache – MS-NH (n=73); and patients with MS plus comorbid primary headache – MS-H (n=57 patients). According to ICHD-3 we found patients with comorbid migraine, tension type headache and vegetative cephalgias. To achieve the purpose of the study, a clinical method of assessment and some questionnaires were included. To assess the condition of patients with MS we used a neurological examination according to the Expanded Disability Status Scale (EDSS). This tool was useful to compare progression of the disease in case of worsening of disability. To be more precise in analysis of neurological function we added 25-Foot-Walk-Test (25FWT), 9-Hole-Peg-Test (9HPT) to evaluate motor function. The research was carried out into account the principles of the Helsinki Declaration of the World Medical Association "Ethical Principles of Medical Research with the participation of a person as an object of research". Received data was analyzed by usage of the SPSS statistics program, version 26.0.0 (USA), with descriptive statistical methods and determination of bivariate comparisons with Pearson correlation, assessment of reliability according to the Student's criterion). The level of significance was taken to be equal to 0.05.

Results and Discussion

Among 130 patients with MS patients with RRMS accounted for the majority of cases of MS (n=98 or 76%), patients with PMS accounted for 24% of included cases (n=32). PPMS was confirmed in 6% of respondents (n=8), SPMS – 18% (n=24). Gender description was the following: 63.8% of females (n=83) and 36.2% of males (n=27) were observed. This data is comparable to the information

that MS is a female predominant disease with more frequent type of disease course as RRMS with alterations between relapses and remissions [10]. The prevalence of primary headaches is a quite common complaint among patients with MS [11] In our research patients, suffered from primary headache, accounted for 56.2% (Figure 1).

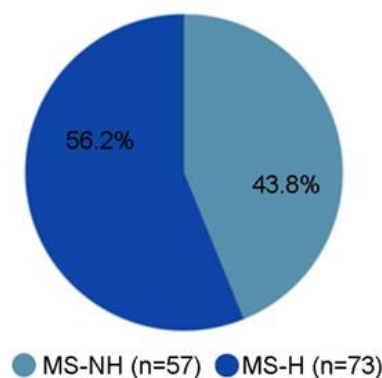


Fig. 1. Prevalence of comorbid primary headache among patients with multiple sclerosis.

Notes: MS-NH – multiple sclerosis without comorbid primary headache;

MS-H – multiple sclerosis without comorbid primary headache.

According to the sample data (Table 1), primary headache occurred frequently among RRMS patients (56 patients with RRMS, 57%), although RRMS is prevalent among the studied MS respondents (p<0.001). Among progressive forms of the course of MS (PPMS and SPMS), comorbid primary headache is expanded among 17 patients of 32 in general (53%) that is still more than a half of respondents.

The mean age in the MS-NH group was (35.28±10.0), in the MS-H group – (36.81±9.99), which confirms that MS is a disease of young people. It should be said that primary headache occurred more frequently in women respondents compared to men (55 females [75.3%] and 18 males [24.7%]).

Table 1. Ratio of the number of patients with different types of multiple sclerosis course and comorbid primary headache.

Course of MS	Presence of primary headache	Absence of primary headache	General quantity of MS patients
	n (%)		
RRMS	56 (77)	42 (74)	98 (76)
PPMS	6 (8)	2 (3)	8 (6)
SPMS	11 (15)	13 (23)	24 (18)
All	73 (100)	57 (100)	130 (100)

Notes: MS – multiple sclerosis; RRMS – relapsing-remitting multiple sclerosis; PPMS – primary progressive multiple sclerosis; SPMS – secondary progressive multiple sclerosis.

The mean age in the MS-NH group was (35.28±10.0), in the MS-H group – (36.81±9.99), which confirms that MS is a disease of young people. It should be said that primary headache occurred more frequently in women respondents compared to men (55 females [75.3%] and 18 males [24.7%]).

According to the obtained data, it was found that among patients with MS, the most common type of primary headache is migraine (p=0.015), which occurs mainly among women (n=38) compared to men (n=2), (p<0.001). The prevalence of tension type headache by gender is equal (16 women and 14 men). Vegetative cephalgias were presented only in three observed patients. Among them were 2 patients with trigeminal neuralgia and 1 patient with cluster headache. Data on the distribution of primary comorbid headache are presented on Figure 2.

Evaluating the types of MS course, the following regularities were found for RRMS:

- migraine occurred most often and accounted for 68% (n=38) among other types of comorbid primary headache (p<0.018);
- the prevalence of tension type headache was lower and accounted for 32% (n=18) as one of the types of comorbid primary headache (p<0.018).

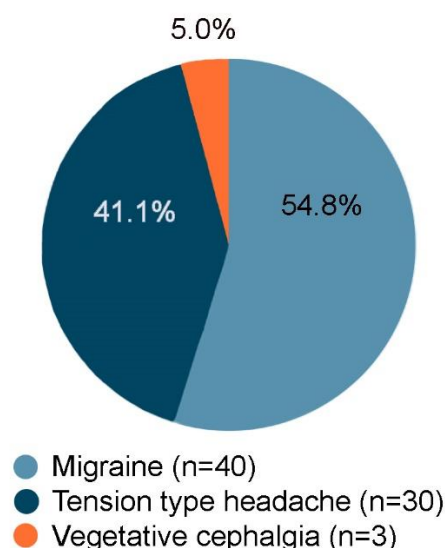


Fig. 2. Distribution of primary comorbid headache among patients with multiple sclerosis.

Among patients with progressive forms of MS (PPMS and SPMS), the percentage of primary tension headache (70%, n=12) exceeded that of migraine (30%, n=5) in this group of respondents, p<0.018.

Average data that assessed motor function between different courses of MS was compared and shown on Table 2. Generally, the duration of motor test performance is longer than is expected in a healthy population. The EDSS score did not differ significantly by gender ([4.05±1.3]

Table 2. Comparison of average data of motor testing between different types of multiple sclerosis course and headache comorbidity

Scale	MS-H	MS-NH	RRMS	PMS	p
9HPT, sec	26.24±11.64	26.24±12.0	22.75±6.92	36.93±17.12	<0.005
25FWT, sec	12.25±32.19	12.05±28.89	5.45±2,49	32.26±53.81	<0.005
EDSS, points	4.02±1.21	4.035±1.27	3.5±0.85	5.56±1.11	<0.005

Notes: MS – multiple sclerosis; RRMS – relapsing-remitting multiple sclerosis; PMS – progressive multiple sclerosis; MS-NH – multiple sclerosis without comorbid primary headache; MS-H – multiple sclerosis without comorbid primary headache; 25FWT25 – 25-Foot-Walk-Test, 9HPT – 9-Hole-Peg-Test.

for males; and [4.02±1.21] for females). When comparing scores among different types of MS course, it becomes noticeable that patients with RRMS perform motor testing much faster than patients with PMS. Particular attention should be paid to the 25FWT test, which assesses walking speed. As is known, the function of the lower extremities is one of the characteristics that is affected and progresses the fastest. In patients with PMS, the speed of this test is much lower compared to patients with RRMS. This is also confirmed by the average value of the EDSS score. Among patients with RRMS, it is (3.5±±0.85) points, which corresponds to a fully ambulatory patient who walks ≥500 m without rest. Among patients with PMS, it is higher – (5.56±1.11) points – and shows that patients walk ≥100 m and less than 200 m without support until the first stop (this characteristic corresponds to a score of 5.5 according to the EDSS scale). Comparing the average indicators between groups of patients with MS without and with comorbid primary headache, no clinically significant difference was found (indicators in the group of patients with comorbid primary headache: 9HPT – [26.24±±11.64] sec; 25FWT – [12.25±32.19] sec).

We analyzed the indicators among patients with comorbid primary headache in Table 3. As can be seen in Table 3, pa-

tients with comorbid migraine and MS had better indicators of motor scales than patients with comorbid tension type headache and MS. This is due to the fact that observed patients with RRMS mostly suffered from comorbid migraine, and patients with PMS – from tension type headache, so the indicators have a similar relationship between themselves, as when comparing the values of RRMS and PMS. When evaluating the EDSS score, it can be seen that patients with comorbid headache have a slightly higher score than the general score of patients with RRMS, but lower than patients with PMS.

A positive correlation was found between comorbid primary headache duration and 25FWT score – (r=0.209, p=0.017), see Figure 3. No statistically significant relationship was found between comorbid primary headache duration and 9HPT.

EDSS score was compared between MS-H and MS-NH groups. Using confidence intervals in assessment of correlation between these variables, it was found that the presence of comorbid primary headache increased the EDSS score in patients with MS (see Table 4).

As it was observed in our study, headache is a quite common comorbid problem among patients with MS. Due to the pathophysiological process it could be explained why the high prevalence of primary co-

Table 3. Comparison of average data of motor testing and duration of disease between types of comorbid primary headache in patients with multiple sclerosis

Scale	Migraine	Tension type headache	p
9HPT, sec	22.85±5.13	31.14±16.02	<0.005
25FWT, sec	5.77±2.49	21.52±49.12	<0.005
EDSS, points	3.7±0.99	4.56±1.22	<0.005
MS duration, years	8.07±6.78	10.3±8.18	<0.005
Headache duration, years	9.86±6.82	7.1±5.55	<0.005

Notes: MS – multiple sclerosis; 25FWT25 – 25-Foot-Walk-Test, 9HPT – 9-Hole-Peg-Test; EDSS – Expanded Disability Status Scale.

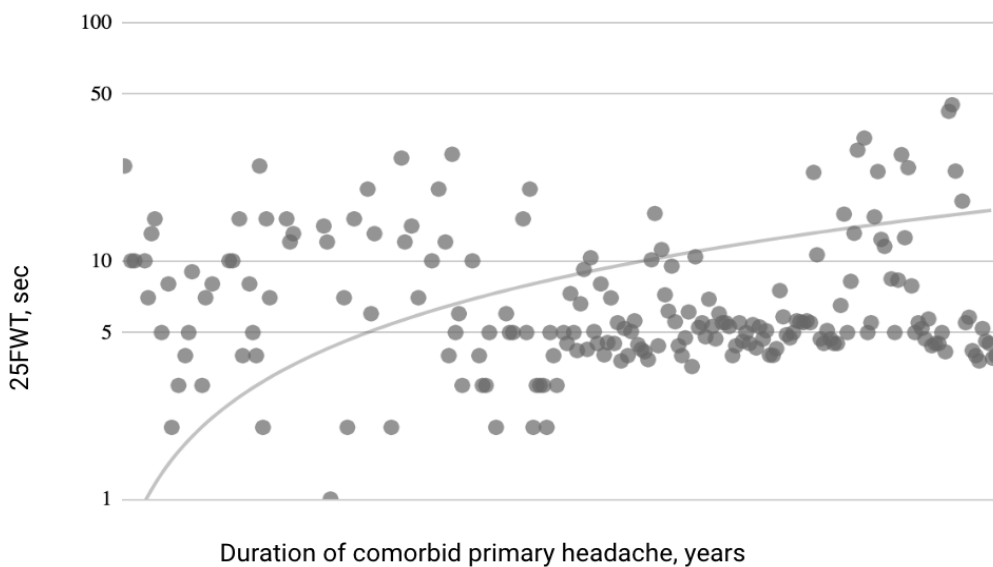


Fig. 3. Correlation between duration of comorbid primary headache (in years) (x) and 25-Foot-Walk-Test (in seconds) (y).

Table 4. The value of confidence intervals (CI) in the assessment of the relationship between the presence of comorbid primary headache among patients with MS and the EDSS score.

	EDSS, points	
	Primary comorbid headache	0.025
Migraine	0.587	0.593
Tension type headache	0.595	0.604

Notes: EDSS – Expanded Disability Status Scale.

morbid headache, especially migrainous type, is observed. Typically, migraine occurs more frequently among females that

is indicated in our study as well. The process of migraine is connected with meningeal inflammation that activates the noci-

ceptive system located in the trigeminal nerve. Because of the active inflammatory process in MS at the onset of the disease it could be considered that headache may in fact be an early symptom of MS as well as other well-known neurological symptoms of MS [11].

Conclusion

To conclude, comorbid primary headache may have a slight impact on the progression of the disease, especially in precise testing of motor function. The evidence was shown that comorbid primary headache, type of headache and its duration may influence the results of such motor scales as 25FWT and 9HPT as well as EDSS score. Females in the majority of observed cases were established in both MS population and MS with primary comorbid headache population. Among different types of primary headaches migraine was registered as the most common type of headache. Higher prevalence of migraine occurred among patients with RRMS

to compare with PMS where tension type headache was in the first place. Determination of primary headaches in MS course is still unresolved and remains controversial.

Prospects of the research

The future research related to headache as a variant of early symptoms of MS would be an unmet need among clinicians. Also, perspective research is needed to see if a headache could be a sign of the relapse among patients with relapsing-remitting MS.

Funding

The work is a part of planned research topic of the Department of Nervous Diseases in National Pirogov Memorial Medical University, Vinnytsya "Clinical epidemiological and pathophysiological peculiarities of the course of multiple sclerosis in patients with comorbid primary headache", planned on the academic council in National Pirogov Memorial Medical University, Vinnytsya, on October 14, 2020.

Conflict of interests is absent.

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ВПЛИВ КОМОРБІДНОГО ПЕРВИННОГО ГОЛОВНОГО БОЛЮ НА НЕВРОЛОГІЧНУ ФУНКЦІЮ ПАЦІЄНТІВ З МНОЖИННИМ СКЛЕРОЗОМ

Множинний (розсіяний) склероз (МС) є прогресуючим захворюванням, що вражає працездатне населення. Через процес демієлінізації пацієнти мають моторні, чутливі та когнітивні порушення. Часто пацієнти з МС скаржаться на головний біль (ГБ). Коморбідний первинний ГБ супроводжує більше половини пацієнтів з МС. Завданням нашого дослідження було виявити зв'язок між присутністю первинного коморбідного ГБ та прогресуванням МС. Для цього було використано Розширену шкалу порушень життєдіяльності Курцке (Expanded Disability Status Scale, EDSS), моторне тестування на проходження 25 фунтів (25-Foot Walk Test, 25FWT) та тест з 9 отворами і кілочками (9-Hole Peg Test, 9HPT). Для диференційної діагностики видів головного болю було використано шкалу Міжнародної класифікації головного болю (International Classification of Headache - 3, ICHD-3). Отримані дані порівнювалися серед пацієнтів з різними типами перебігу МС: рецидивуючо-ремітуючим (РРМС); первинно- та вторинно-прогресивним, що було об'єднано в прогресуючі форми МС (ПМС). Було досліджено 130 пацієнтів з МС, серед яких переважали пацієнти з РРМС (n=98), первинний коморбідний ГБ був знайдений у 56,2 % (n=73). Серед пацієнтів з МС переважала мігрень (p=0,015), зокрема найбільше випадків виявлено у пацієнтів з РРМС. Серед пацієнтів з ПМС переважав головний біль напруги (ГБН) (p<0,05). Показники 9HPT та 25FWT істотно не відрізнялися серед груп з та без первинного коморбідного ГБ, проте згідно довірчих інтервалів показник EDSS перевищував бал у групі пацієнтів з коморбідним ГБ. Було виявлено, що пацієнти з коморбідною мігренню виконували моторне тестування швидше, ніж пацієнти з ГБН. Тому можна підсумувати, що коморбідний первинний ГБ може мати вплив на показники моторної функції серед пацієнтів з МС та потребує подальшого дослідження в плані визначення ролі коморбідного ГБ у паттернах початкових симптомів МС.

Ключові слова: центральна нервова система, демієлінізація, мігрень, головний біль напруги, моторна функція, супутня патологія.

Надійшла до редакції 06.09.2023

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