

ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ

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COMORBID PRIMARY HEADACHE: OCCURANCE AND PREVALENCE IN PATIENTS WITH RELAPSING REMITTING MULTIPLE SCLEROSIS

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Abstract. Multiple sclerosis (MS) is an autoimmune progressive disease of the nervous system based on the demyelization of nerve fibers, belongs to the group of chronic disabling diseases that most often affects young people who are actively able to work. The prognosis of MS depends on the course of disease and presence of comorbidity. One of the most common comorbid conditions in MS is headache. The connection between MS and primary headache has long been known. The comorbidity of headaches and MS is poorly understood. Relapsing remitting multiple sclerosis (RRMS) is a type of MS which is characterized by periods of active clinical symptoms and phases of remission. RRMS is the most frequent variant of the course of MS.

Objective: to describe the prevalence and structure of primary headache comorbidity in patients with RRMS, to show the frequency of different types of primary headache among patients with RRMS, to find gender correlations between presence of headache and MS, to determine the duration, frequency, intensity of headache and presence of chronic headache, to analyze social history.

Material and methods. 46 patients with RRMS were examined. Structure of the primary headache was determined according to the criteria of ICHD-3. The intensity of the headache was measured using the VAS - Visual Analogue Scale. Statistical processing of the obtained results was performed in the SPSS program.

Results. Patients were randomized in two clinical groups depending on the presence of primary headache: 19 patients - with presence of comorbid headache, 27 - without any comorbidity. The average age of respondents with and without comorbid headache was 35.79 and 31.52 years respectively. Gender status was the following: 16 males and 36 females. 22 patients were married, 19 patients were single, and 5 patients were divorced. The prevalence of comorbid headache was higher in females among examined patients. The duration of the RRMS disease from the moment of the first symptom in the examined groups of patients was 7.43 ± 5.218 years. The average duration of headache is 10.05 years. Structure of the primary headache was the next: 13 patients - migraine, 5 patients - migraine with aura, 6 patients - tension type headache. Patients with autonomic cephalgia or cluster headache have not been identified. 12 patients noted the appearance of pain before the diagnosis of RRMS. In 7 patients the headache began after the diagnosis of MS. The average frequency of headache in patients was 8.68 days per month, the intensity of headache according to the VAS was 6.11 points - middle intensity. Chronic headache was observed in 7 patients, 12 patients had episodic headache. 10 patients found that headache impaired daily activity, 7 patients noted that headache provoked excessive fatigue and required additional rest, and 13 patients noted that headache reduced concentration. Along with frequent motor dysfunction in MS, patients experience limited daily activity due to the comorbid headache.

Conclusion. Comorbid headache in RRMS has a significant negative impact on the functioning and quality of life of patients, thus, cannot be ignored. The frequency of headache is about half of patients with RRMS. Migraine predominates in the structure of comorbid headache in RRMS. The majority of patients noted the appearance of headache before the first symptoms of MS. The question of whether headache is a risk factor for MS and one of the symptoms of exacerbation in RRMS remains unresolved.

Keywords: multiple sclerosis, comorbidity, headache, migraine, pain syndromes.

Introduction. Multiple sclerosis (MS) is an autoimmune progressive disease of the nervous system based on demyelization of nerve fibers. MS belongs to the group of chronic disabling diseases that most often affects young people who are actively able to work.[3] The diagnosis is characterized by different clinical types of course, including relapsing-remitting type of multiple sclerosis, which eventually becomes secondary-progressive type of course, as well as primary-progressive course of the disease. The most common is relapsing-remitting type of multiple sclerosis. Relapsing-remitting type of multiple sclerosis is defined as MS in which patients have period of relapses that may include visual disturbances (ex. visual loss in one or

the other eye), loss of motor function (paresis or paralysis, spasticity), sensitivity disorders (numbness, tingling, decreased touch, pain or vibration sense), cerebellar disorders (ataxia, dysmetria, balance problems), headache as nonobligatory symptom, and periods of remission and stability of clinical symptoms between relapses. Relapses mean a new or worsening symptoms of neurological deficit that last more than 48 hours without any other cause (ex. fever or infection).[6] Relapsing-remitting type of multiple sclerosis is the form of MS, where younger patients are more likely to have this form of MS than older patients. However comorbid disorders also have a significant impact on the course of the disease. One of the most

common comorbid conditions is headache. [4] The connection between MS and primary headache has long been known. The comorbidity of headaches and MS is poorly understood.

Background of the research. There are more than 3 million patients with MS in the world, and recently there is a tendency to increase the prevalence of the incidence both in the world and in Ukraine. [6] This draws the increased attention of researchers to a more detailed study of the pathology of MS [7]. The progression of the main disease is connected with the presence of comorbid pathology. [2] Headache has taken one of the first places of comorbidity in patients with MS, especially with relapsing remitting type. [4] There is an absence of precise mechanisms why headache has such a high prevalence among RRMS patients. According to one study [2], more than 50% of people with a confirmed diagnosis of MS reported cephalgia (most often migraine and tension type headache). The clearest correlation existed between the presence of migraine and the relapsing-remitting course of the underlying disease. In another study [4] it was published about the correlation between migraine and MS and was found that migraine was twice as common in people with MS as in the general population. Now in the last studies there was a discussion if headache may be the initial symptom of relapsing-remitting MS or one of the manifestations of exacerbation. [5] So far there is no evidence in the literature that throbbing short-term intense paroxysmal pain may be a predictor of relapse in relapsing-remitting MS. [5] However, exact detection of comorbid headache will have a significant impact and on the course of the disease and on the quality of life of the patient. These results underscore the importance of finding headaches in MS patients in a clinical setting to provide an integrated approach to monitoring both conditions to improve the quality of life of such patients and the quality of care. [6]

The lifetime prevalence of comorbid headache seems to vary widely, with data ranging from 4% to 58%. [2] Evidence data suggests that headaches may vary depending on the form of MS and the location of the lesion, and patients with MS with migraine have a more symptomatic clinical course. [5]

Headache during relapsing-remitting MS is observed in patients in both remission and relapse period. For relapsing-remitting MS, the most common form of comorbid headache is migraine, as the mechanisms of pathogenesis for both diseases are similar. Comorbid headache significantly affects the quality of life of patients, worsens the clinical course of relapsing-remitting MS. [4] In this study RRMS precisely was chosen to be observed to compare with prevalence of headache for this type of MS.

Objective: to describe the prevalence and structure of primary headache comorbidity in patients with RRMS, to show the frequency of different types of primary headache among patients with RRMS, to find gender correlations between presence of headache and MS, to determine the duration, frequency, intensity of headache and presence of chronic headache, to analyze social history.

Materials and methods: 46 patients with relapsing-remitting multiple sclerosis were examined. These patients were on the observation at the Department of Nervous Diseases in Vinnytsia National Pirogov Memorial Medical University. All patients met the MacDonald

criteria 2017 of relapsing-remitting MS according to the results of neurological examination and MRI-scan examination. All patients were in clinical remission and didn't use any steroid or analgesic treatment for at least 3 months. Thus, inclusion criteria for this study were the following: confirmed RRMS according to the MacDonald criteria 2017, phase of clinical remission, absence of clinical relapses during 3 months before the study start, absence of hormonal pulse-therapy for 3 months before the study, absence of other comorbid autoimmune disorders. Patients were randomized in two clinical groups depending on the presence of primary headache: 19 patients were observed with presence of comorbid headache, 27 – without any comorbidity. Furthermore, to achieve the goal of this research, the clinical method, medical history data and questionnaires for patients were used. According to the patient's responses, the demographics of the patients, the duration of the underlying disease, the structure and prevalence of headache among the patients with relapsing-remitting MS, the duration and intensity of headache, the impact on daily activity and quality of life were analyzed. The occurrence of headache before or after the main diagnosis of relapsing-remitting MS, changes in the characteristics of the headache after diagnosis of relapsing-remitting MS was also analyzed. The structure of the primary headache was determined according to the criteria of ICHD-3: The international Classification of Headache Disorders. None of patients have other conditions like brain tumor or vascular pathology that can provoke headache. The intensity of the headache was measured using the VAS - Visual Analogue Scale. Statistical processing of the obtained results was performed in the SPSS statistics 26.0.0 program using descriptive statistics methods and determination of bivariate comparisons that was performed using Pearson correlations.

Results: 46 patients with confirmed relapsing-remitting MS according to the MacDonald 2017 criteria were observed. The mean age of patients with and without comorbid headache was 35.79 and 31.52 years respectively, indicating the presence of headache in older patients.

Gender features were the next: among the 46 examined patients there were 16 males and 36 females, which confirm the higher prevalence of the MS among female.

Social indicators such as employment and marital status were identified. Among the study group, 22 patients were married, 19 patients were single, and 5 patients were divorced. Employment of patients was the following: 24 patients were employed, 22 patients weren't employed.

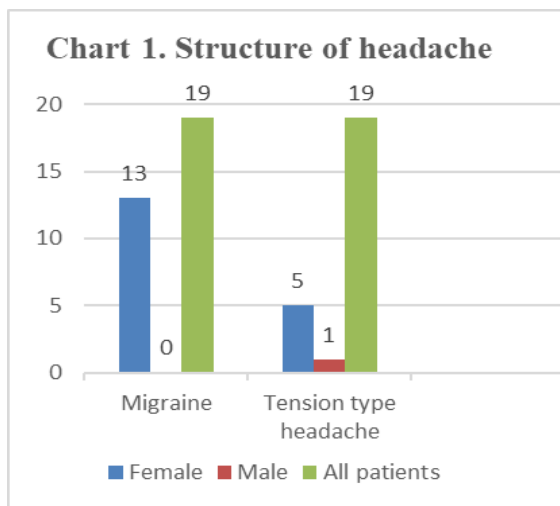
The prevalence of headache among patients with relapsing-remitting MS was analyzed (see Table 1). The prevalence of comorbid headache was higher in females among examined patients as well.

The duration of the relapsing-remitting MS disease from the moment of the first symptom in the examined group of patients is from 1 to 19 years (mean value - 7.43 ± 5.218). In the group of patients without headache and with comorbid headache, the average duration of the disease is 6.63 and 8.58 years respectively and is not significantly different. The mean duration of headache in this study is 10.05 years. In this case the presence and start of headache is more frequent in younger patients.

Table 1

Gender prevalence of headache			
Gender	Presence of comorbid headache	Absence of comorbid headache	All respondents
Male	1	15	16
Female	18	12	30
All respondents	19	27	46

Structure of headache was analyzed (see Chart 1).



Among the patients with relapsing-remitting MS and comorbid headache, 13 patients had migraine, among them 5 patients had migraine with aura, 6 patients suffered from tension type headache. Patients with autonomic cephalgia or cluster headache have not been identified.

Migraine took the first place in the occurrence of primary headaches in patients with MS. The attacks of migraine were described by patients as headache with unilateral location, with pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia that met the ICHD-3 criteria. To compare with the headache structure in relapsing-remitting MS in male and female, the prevalence of tension headache is slightly higher in men.

The relationship between the onset of relapsing-remitting multiple sclerosis and the onset of headache was analyzed (see Table 2).

12 patients noted the appearance of pain before the diagnosis of relapsing-remitting MS, and in half of these patients the worsening of the headache occurred after the diagnosis of MS, in the other half respondents the characteristics of the headache did not change. In 7 patients, the headache began after the diagnosis of MS.

The average frequency of headache in patients was 8.68 days per month, the intensity of headache according to the VAS was 6.11 points – middle intensity.

Table 2

Appearance of headache and its structure before or after relapsing-remitting MS diagnosis				
Start of headache		Before relapsing-remitting MS diagnosis	After relapsing-remitting MS diagnosis	All
Type of headache	Migraine	9	4	13
	Tension type headache	3	3	6
All respondents		12	7	19

Chronic headache was observed in 7 patients, 12 patients had episodic headache. Middle direct proportional correlation was observed between the duration of relapsing-remitting MS diagnosis and chronic headache ($r=0.310$). It estimated that long duration of relapsing-

remitting MS with presence of comorbid headache could be a factor of headache chronic course.

The social inadaptation impact on the appearance of headache accounted. However, this study found a weak inverse proportional correlation between the presence of headache and marital status ($r = -0.120$) (See Table 3).

Table 3

Marital status and presence of headache			
Marital status	Absence of comorbid headache	Presence of comorbid headache	All respondents
Single	12	7	19
Married	13	9	22
Divorced	2	3	5
All respondents	27	19	46

There were not found a correlation between the presence of headache and employment of the patient with relapsing-remitting MS ($r=-0.096$).

The effect of headache on patient's daily activity was analyzed. Among 19 patients with comorbid

headache, 10 patients found that headache impaired daily activity, 7 patients noted that headache provoked excessive fatigue and required additional rest, and 13 patients noted that headache reduced concentration. According to these results comorbid headache can decrease the quality of life

of patients with relapsing-remitting MS. Along with frequent motor dysfunction in MS, patients experience limited daily activity due to comorbid headache.

Discussion. Headache comorbidity is definitely common among patients with RRMS. In spite of the small number of responders the percentage of occurrence of primary headache is higher than in the general population. Young-aged patients are more affected with headache comorbidity, which can be a cause of lower quality of life and earlier disability. Nevertheless, the collected data showed only quarter of respondents with only relapsing-remitting course and did not collect data about others courses of MS.

Prevalence of both multiple sclerosis and primary comorbid headache showed that female patients suffer more than males. There are few reasons to explain this fact. Firstly, it can be caused by the role of hormones such as testosterone and estrogen because its relationship in pathophysiology of the disease is estimated. Secondly, frequent obesity among women plays its own role in the MS inflammation process. According to the study results only 1 male have noticed headache during relapsing-remitting MS, and in structure of headache it was tension-type variant. The presence of a headache in male may indicate a more severe course of the disease. The reason behind this observation is unclear. Further research is needed to determine whether gender differences affect the course of headache and the severity of the disease.

Headache can occur both in the beginning of the main disease and during the course of the main disease. Migraine without aura and tension type headache is the most common primary headaches in patients with RRMS. The localization of demyelinating lesions may be of great importance in these cases of prevalence. For instance, presence of lesions of demyelization in the red nucleus, brainstem, and cortical lesions may lead to the cephalgia syndromes. Immune system-induced inflammation of the meninges of the brain is also involved in the pathogenesis of MS, and it can be a pathophysiological explanation of the high prevalence of headache, especially migraine.

The ratio of prevalence of primary headache indicates the possibility of comorbid headache being a risk factor for multiple sclerosis or being a symptom of multiple sclerosis. However, so far in the literature this is only an assumption and requires more research.

Presence of headache comorbidity showed worsening of disability, depression and other psychological issues in patients with relapsing-remitting MS and comorbid headache. Correlations between depression, anxiety and headache in MS patients were not analyzed in this study and will be the next step in observation in patients with comorbid headache.

Conclusions. It can be concluded that comorbid headaches in relapsing-remitting MS have a significant negative impact on the functioning and quality of life of patients, thus, cannot be ignored. Despite the variability of headache prevalence data, the association between MS progression and headache structure is obvious and therefore requires a study of headache in all MS patients. According to the results of the study, the following conclusions can be listed:

1. The prevalence and structure of comorbid headache in relapsing-remitting MS were established: the

frequency of headache is about half of patients. Migraine predominates in the structure of comorbid headache in relapsing-remitting MS.

2. Gender features of the course of MS and comorbid headache were determined: both MS and comorbid headache are more common in female. Migraine is more typical for female, and tension type headache is slightly more common for male.

3. The role of MS in the course of pain syndromes was established: in the majority of patients the headache appeared before the first symptoms of MS, half of them showed worsening of comorbid headache symptoms after the diagnosis of MS.

4. The role of social inadaptation was analyzed: a weak inverse proportional correlation between the presence of headache and marital status was established, no significant correlation between the presence of headache and employment of the patient with relapsing-remitting MS were found.

5. Analyses of responses showed that the presence of comorbid headache in relapsing-remitting MS significantly reduces the quality of life of patients, affects daily activity and concentration, increases fatigue and requires additional rest.

6. The question of whether headache is a risk factor for MS and one of the symptoms of exacerbation in RRMS remains unresolved. Nevertheless, determining the prevalence and structure of headache will help in selecting adequate treatment for pain in MS, reducing the frequency and intensity of pain attacks, improving the quality of life of patients, ability to work and socialization.

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КОМОРБІДНИЙ ПЕРВИННИЙ ГОЛОВНИЙ БІЛЬ: ПОШИРЕНІСТЬ СЕРЕД ПАЦІЄНТІВ З РЕЦИДИВУЮЧО-РЕМІТУЮЧИМ МНОЖИННИМ (РОЗСІЯНИМ) СКЛЕРОЗОМ

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Резюме. Множинний (розсіяний) склероз (МС) – це хронічне аутоімунне захворювання центральної нервової системи (ЦНС), яке призводить з часом до інвалідизації молодого працюючого населення. Прогноз захворювання залежить від перебігу та коморбідності основної хвороби. Найчастішою коморбідністю при МС є головний біль (ГБ). Найбільш часто зустрічається рецидивуючо-ремітуючий тип МС (РРМС). Зв'язок коморбідного первинного ГБ із МС і досі чітко не з'ясовано.

Мета. Описати поширеність та структуру коморбідного первинного ГБ у пацієнтів з РРМС,

визначити зв'язок та поширеність ГБ у чоловіків та жінок із МС, визначити тривалість, частоту, інтенсивність нападів, появу хронічного головного болю, проаналізувати соціальний анамнез.

Матеріали і методи. Було обстежено 46 пацієнтів з РРМС. Критерії МС визначено згідно з критеріями Мак-Дональда, 2017. Первинний ГБ оцінено згідно з Міжнародною класифікацією головного болю ICHD-3. Інтенсивність нападів ГБ визначено за шкалою ВАШ – Візуальна Аналогова Шкала. Статистична обробка здійснювалася у програмі SPSS.

Результати. У 19 пацієнтів із МС було виявлено коморбідний первинний ГБ. Серед структури переважала мігрень, здебільшого у жінок. Середній вік респондентів з коморбідним ГБ та без нього – 35.79 і 31.52 років, відповідно. Тривалість МС з появи першого епізоду – 7.43±5.218 років. Середня тривалість головного болю – 10.05 років. У 12 пацієнтів ГБ з'явився до моменту підтвердження МС, у 7 пацієнтів – після підтвердження основного захворювання. Середня частота нападів у пацієнтів – 8,68 днів на місяць, інтенсивність нападу – 6.11 балів за ВАШ.

Висновки. Коморбідний ГБ поширений у близько половини пацієнтів із РРМС, здебільшого жіночої статі. Серед структури ГБ переважає мігрень. Присутність такої коморбідності сприяє погіршенню якості життя пацієнтів з МС.

Ключові слова: множинний (розсіяний) склероз, коморбідність, головний біль, мігрень, больовий синдром.

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