Acta Biomed 2023; Vol. 94, N. 6: e2023229 DOI: 10.23750/abm.v94i6.14609

Predictors of neuropathic dysesthetic pain occurrence and chronification in multiple sclerosis (2-year prospective study)

Mykhaylo Delva, Kateryna Skoryk, Iryna Delva
Neurological Department, Poltava State Medical University, Poltava, Ukraine

Abstract. *Background:* Patients with multiple sclerosis (MS) are a high-risk group for neuropathic dysesthetic pain (NDP) with various negative consequences. *Objective*: to investigate predictors of NDP occurrence and chronification in patients with MS during a 2-year observation period. *Methods:* After the exclusion criteria application and signing of informed consent, we recruited in the study 241 patients among which 23 patients prematurely stopped participating in the study. During the 2-year observation period, new NDP was diagnosed on the PainDETECT questionnaire (>18). Patients with newly diagnosed NDP were examined at baseline, in 1, 3, and 6 months depending on pain duration. The socio-demographic, neuropsychological, cognitive, sleep quality and clinical characteristics of patients were evaluated at the beginning of the study and updated at baseline examination in cases of newly diagnosed NDP. *Results:* Over a 2-year observation period, NDP occurred in 34 patients (15.6%). Out of 34 cases of newly diagnosed NDP, in 20 cases (58.9%) pain became chronic (lasting longer than 3 months). In the Cox proportional hazards multifactorial model, progressive types of MS were an independent predictor of NDP occurrence (hazard ratio 2.60; 95% confidence interval, 1.30-5.18; p=0.01). In the multifactorial logistic regression analysis, subclinical depressive disorders (according to Hospital Anxiety and Depression Scale) were identified as an independent predictor of NDP chronification (odds ratio 7.14; 95% confidence interval, 1.12-45.59; p=0.04). *Conclusions:* Patients with progressive MS types are a high-risk group for developing NDP, and patients with newly diagnosed NDP who have depressive disorders are a high-risk group for NDP chronification. (www.actabiomedica.it)

Key words: multiple sclerosis, neuropathic dysesthetic pain, occurrence, chronification, predictors

Introduction

In the recent decade, clinical neurologists and neuroscientists paid close attention to dysfunctions beyond physical disability (e. g. fatigue, cognitive impairment, neuropsychiatric symptoms, pain, etc.) in various neurological diseases (1-3).

Patients with multiple sclerosis (MS) make up a high-risk group for neuropathic pain (NP) of central origin. According to the meta-analysis by Foley PL. et al., the prevalence of NP in the MS population has been estimated to reach 29% (4). Based on the reports of MS patients, NP is represented by dysesthetic pain, Lhermitte's phenomenon, and trigeminal neuralgia (5).

In patients with MS, neuropathic dysesthetic pain (NDP) is the most commonly reported type of NP, having a prevalence of 12–28% (6,7). NDP is thought to be a type of deafferentation pain secondary to lesions in the spino-thalamo-cortical pathways (8).

In MS patients NP is associated with many negative outcomes. Even in patients with newly diagnosed clinically isolated syndrome or relapsing-remitting MS, NP was strongly linked to fatigue, depression, and disability; moreover, these links were even stronger

after 4 years than at baseline (9). In other studies, it was also found that MS patients with NP had significantly higher depression (10,11), fatigue (10,12), disability according to the Extended Disability Status Scale (EDSS) (13), and significantly lower mental flexibility (14). Moreover, it has been demonstrated that NP in MS is associated with a significantly worse quality of life. (10,12).

To date, all studies about risk factors for NP in MS patients had a cross-sectional design that did not enable the identification of risk factors for NP occurrence. In a few prospective studies about pain in MS, only a limited number of comorbid and biopsychosocial conditions were evidenced as risk factors for pain occurrence and pain worsening (9,15).

However, identifying risk factors for NP occurrence and risk factors for NP chronification in MS patients could serve as a theoretical basis for improving NP management in MS. Particularly, identifying modifiable risk factors for NP is thought to provide an essential contribution to the development of preventative measures.

Objective

To investigate predictors of NDP occurrence and predictors of chronification of the newly diagnosed NDP in patients with MS during a 2-year observation period.

Material and methods

This study was conducted at the Poltava Regional Center for MS patients over three years (2020-2023 years). This study was approved by the Ethics Committee of Poltava State Medical University, in accordance with the Declaration of Helsinki (protocol №189/2020). Written informed consent was obtained for all patients before their inclusion in the study.

We examined a total of 321 individuals participating in the study. Inclusion criteria were clinically confirmed diagnosis of MS according to McDonald's 2017 criteria, age over 18 years, and obtained written informed consent for participation in the study. Exclusion criteria were as follows: severe speech and writing disorders, neurological diseases that could be the cause of NP (e. g. traumatic brain and spine injury, strokes, Parkinson's disease, syringomyelia, polyneuropathy, etc.), presence of central and (or) peripheral NP at baseline examination (PainDETECT questionnaire (PDQ) >18 points).

Among 268 eligible individuals (83.5%), 241 people agreed to participate in this 2-year study (follow-up rate 89.9%) and freely and voluntarily signed informed consents.

For the diagnosis of NDP, we used PDQ. It is a self-report questionnaire that does not require clinical examination. PDQ has shown a high sensitivity and specificity of 85% and 80% respectively, in the screening of NP in patients with low back pain (16). Although the original validation study of PDQ was for peripheral NP, it has been validated for use in spinal cord injury with a diagnostic accuracy of 78% in a central NP presentation (17). PDQ has seven weighted sensory descriptor items (never to very strongly) and two items relating to the spatial (radiating) and temporal characteristics of the individual pain pattern. Results are scored from −1 to 38; where −1 to 12 represents non-NP; 13 to 18 possible NP and 19 to 38 indicates definite cases of NP.

Each patient who signed informed consent to participate in the study was given PDQ and was instructed on how to fill it in.

Patients were asked to report any new painful sensations in any convenient way (by phone, e-mail, social networks, visiting the clinic, etc). If a patient did not contact us every 3 months, we call him/her and asked about any new painful sensation, which might appear during the last 3 months period. If a patient reported new pain, he/she was invited to visit the clinic. If a patient with a new pain could not visit the clinic, he/she was asked to fill in PDQ and send it to us. Based on PDQ, NDP was diagnosed at >18 score level. If NDP was diagnosed remotely, patients were invited for baseline assessment. Patients with newly diagnosed NDP were examined in the clinic at baseline, in 1, 3, and 6 months after NDP onset. If NDP was not reported at 1- or 3-month visits, the patients were not invited to the next scheduled visit.

Patients were matched on pain drug use as much as possible. The treatment of NP in MS patients is

challenging, mostly due to the low efficacy and side effects of pharmacological agents (20). Current treatment of NP in MS patients should be based on the general principles for treating NP, taking into account drug-induced adverse effects (18). The recommended first-line drug treatments for NP include tricyclic antidepressants, gabapentin, pregabalin, and serotonin-norepinephrine reuptake inhibitors (duloxetine, and venlafaxine) (19). But, according to the official instructions for use only pregabalin is indicated for the treatment of central NP (duloxetine, venlafaxine, and gabapentin have no indications for the treatment of central NP). Besides, MS patients often suffer a variety of disease-induced symptoms (dizziness, ataxia, bladder/bowel retention, drowsiness, and fatigue) that can all be potentially intensified by the addition of a TCA to their medication regimen.

In cases of newly diagnosed NDP patients were prescribed to take pregabalin 150 mg b.i.d. daily for 5 days; when pregabalin failed to produce an analgesic effect or this effect was insufficient, the daily dose of the medicine was increased to 300 mg. After 1-month patients were re-evaluated. For this purpose, pregabalin was tapered down for 2 days and patients were examined after they had been off drugs for at least a day. In cases of NDP recurrence or intensification after drug discontinuation at the 1-month examination, the patients were recommended to resume pregabalin therapy in former doses for the next 2 months. The same procedure of tapering off drug dosages and examination of patients was performed 3 months after the NDP onset. In the cases of NDP recurrence or intensification following the pregabalin discontinuation at the 3-month visit, the patients were recommended to resume the medication in the previous dosage for the next 3 months with the same procedure of tapering off drug doses and examining at the 6-month visit.

During the 2-year observation period, 23 patients out of 241 individuals declined participation in the study for various reasons (dropout rate 9.5%).

The reasons for the dropout were as follows: unwillingness to cooperate anymore (10 patients, including 1 patient with remotely diagnosed NDP), no answer to calls (9 patients), transportation problems to visit the clinic (2 patients with remotely diagnosed NDP), moving to another place (2 patients). The dropout rate was quite low, so any attrition bias in this study was likely, not substantial.

Each patient who signed informed was examined. We recorded the following socio-demographic data including gender, age, level of education (higher education / no higher education), marital status (married/single), current employment, and place of residence (urban/rural). The patients were also divided into "non-smokers" (those who did not smoke for at least 1 last year) and "smokers" (those who smoked regularly during the last year). Anxiety and depression were diagnosed by using Hospital Anxiety and Depression Scale (HADS): subclinical anxiety and depressive disorders were recorded by values of the anxiety and depression subscales of 8 – 10 points, clinical anxiety/depression by ≥11 points (20). Starkstein apathy scale was used to diagnose apathy disorder (cut-off level >13 points) (21). Fatigue was assessed by using the Fatigue Severity Scale (FSS) with a critical value of ≥4 points (22). Cognitive impairments were diagnosed according to the Montreal Cognitive Assessment (a critical value of <26 points) (23). Sleep quality was assessed using the Pittsburgh Sleep Quality Questionnaire, with a score of ≥5 points considered an indicator of poor sleep quality (24). We also determined the following clinical characteristics of MS: age of MS onset, disease duration, MS type – relapsing-remitting or progressive (primary and secondary), and severity of neurological deficit according to the EDSS. We took into account comorbidities that had a prevalence rate of at least 5% in the sample, including arterial hypertension, abdominal obesity (waist circumference ≥ 102 cm for men and ≥88 cm for women), migraine, and tension-type headache.

In cases of newly diagnosed NDP, to determine the predictors of NDP chronification we updated during the baseline examination actual marital, employment, and smoking status, as well as the scores of HADS, Starkstein apathy scale, FSS, Montreal Cognitive Assessment, the Pittsburgh Sleep Quality Questionnaire, and the EDSS.

Quantitative values were presented as median (Me) and interquartile range (Q1-Q3). Qualitative values were presented as numbers and percentages. Quantitative values were compared using the nonparametric Mann–Whitney U-test. Qualitative variables

were compared using Fisher's exact test. A stepwise multivariate Cox regression with a 95% confidence interval (CI) was used to determine the predictors of NDP occurrence. For hazard ratio (HR) calculation, we included all variables that had p <0.05 in the univariate Cox model into the multiple Cox model. Univariate logistic regression analysis was performed to analyze the odds ratio (OR) with 95% CI of factors associated with the development of NDP chronicity. Variables having a p-value less than 0.05 in the univariate analysis were selected and evaluated by multivariate logistic regression models. Differences at p <0.05 were considered significant.

Results

The observation group consisted of 69 men (28.6%) and 172 women (71.4%). The median age of patients was 39.5 (32.0-47.0) years (ranging from 21 to 60 years). The median duration of MS diagnosis was 12.0 (6.0-18.0) years (ranging from 1 to 29 years). 178 patients had relapsing-remitting (73.9%), 2 patients had primary progressive (0.8%) and 61 patients had secondary progressive MS course (25.3%). The EDSS score was 4.5 (3.5-4.5) points (ranging from 1.5 to 7.5 points).

During a 2-year observation period, NDP developed in 34 patients (15.6%). Out of 34 cases of newly diagnosed NDP, 20 cases (58.9%) became chronic, i.e., persistent or recurrent pain that lasted longer than 3 months (25).

Four patients with newly diagnosed NDP initially refused to take pregabalin. There were two dosage regimens for the patients who started pregabalin therapy: 18 patients took 150 mg per day and 12 patients took 300 mg per day. During the follow-up period, 16 patients changed the drug regimen (14 patients stopped taking pregabalin, and 2 patients changed the dosage without consulting with doctors) because of pain resolution (in 11 cases) or significant reduction in pain (in 2 cases), or pregabalin side effects (in 3 cases – dizziness, nausea, and lack of libido).

As shown in Table 1, there were no significant differences in demographic and social characteristics between the patients who had and who had no newly diagnosed NDP.

According to Table 2, the patients with newly diagnosed NDP did not demonstrate any significant differences in rates of neuropsychological, cognitive, and sleep quality characteristics compared to the patients without NDP.

Table 3 shows that the patients with newly diagnosed NDP compared to patients without NDP demonstrate a significantly higher prevalence of progressive MS and significantly more severe disability by EDSS scores. In univariate Cox regression analysis, progressive types of MS (HR=2.90; 95% CI, 1.47-5.71; p<0.01) and EDSS score per 0.5 points (HR=1.12; 95% CI, 1.01-1.24; p=0.03) were found to be predictors for NDP occurrence. In the Cox proportional hazards multifactorial model, only progressive types of MS remained an independent predictor for NDP occurrence (HR 2.60; 95% CI, 1.30-5.18; p=0.01).

Table 1. Socio-demographic variables of MS patients.

Variables		Newly diagnosed NDP		p
		yes	no	
sex	males	11 (32.4%)	52 (28.3%)	0.68
	females	23 (67.6%)	132 (71.3%)	
age (years), Me (Q1-Q3)		42.0 (34.0-48.3)	39.0 (32.0-47.0)	0.27
higher education		18 (52.9%)	89 (48.4%)	0.71
marital status (married)		19 (55.9%)	113 (61.4%)	0.57
employed		16 (47.1%)	105 (57.1%)	0.35
rural residence		13 (38.2%)	57 (31.0%)	0.43
smoking		5 (14.7%)	21 (11.4%)	0.57

Table 2. Neuropsychological, cognitive, and sleep quality variables of MS patients.

Variables		Newly diagnosed NDP		p
		yes	no	
anxiety symptoms	subclinical	19 (55.9%)	80 (43.5%)	0.19
	clinical	5 (14.7%)	23 (12.5%)	0.78
depression symptoms	subclinical	15 (44.1%)	90 (48.9%)	0.71
	clinical	6 (17.6%)	25 (13.6%)	0.59
apathetic symptoms		7 (20.6%)	28 (15.2%)	0.45
fatigue		13 (38.2%)	64 (34.8%)	0.70
cognitive impairment		6 (17.6%)	48 (26.1%)	0.39
poor sleep quality		10 (29.4%)	70 (38.0%)	0.44

Table 3. Clinical variables of MS patients.

Variables		Newly diagnosed NDP		p
		yes	no	
age of MS onset (years), Me (Q1-Q3)		28.5 (22.8-32.3)	26.0 (22.0-32.0)	0.41
MS duration (years), Me (Q1-Q3)		13.0 (5.0-20.3)	12.0 (6.0-18.0)	0.46
MS type	relapsing	15 (44.1%)	145 (78.8%)	0.01
	progressive	19 (55.9%)	39 (21.2%)	
EDSS (points), Me (Q1-Q3)		5.3 (4.0-6.5)	4.5 (3.5-5.5)	0.02
arterial hypertension		3 (8.8%)	25 (13.6%)	0.58
abdominal obesity		5 (14.7%)	33 (17.9%)	0.81
migraine		6 (17.6%)	22 (12.0%)	0.40
tension-type headache		14 (41.2%)	60 (32.6%)	0.33

The next stage of the study was devoted to the factors contributing to the chronification of the newly diagnosed NDP.**Table 4**. Socio-demographic variables of MS patients with newly diagnosed NDP.

Table 4 shows that MS patients with chronic NDP did not demonstrate any significant differences in demographic and social characteristics.

Table 5 shows that among the MS patients with chronic NDP, there was a significantly higher prevalence of subclinical anxiety and depressive disorders according to the HADS. In the univariate logistic regression analysis, subclinical anxiety disorders (OR 7.50; 95% CI, 1.61-34.95; p=0.01) and subclinical depressive disorders (OR 11.14; 95% CI, 1.92-64.54; p=0.01) were found as predictors for NDP chronification. In the multifactorial logistic regression analysis, only subclinical depressive disorders turned out to be an independent predictor of the NDP chronification (OR 7.14; 95% CI, 1.12-45.59; p=0.04).

As Table 6 shows, there were no significant differences in any clinical characteristics in MS patients with chronic NDP.

Discussion

We did not reveal any association between socio-demographic characteristics and risk of NDP occurrence or risk of NDP chronification in MS patients. At present, there is little evidence of the association between socio-demographic factors and pain in MS patients. The single prospective study about pain in MS that recruited 949 consecutive patients with confirmed MS reported that older age was associated

Table 4. Socio-demographic variables of MS patients with newly diagnosed NDP.

Variables		Newly diagnosed NDP		p
		non-chronic	chronic	
sex	males	3 (21.4%)	8 (40.0%)	0.29
	females	11 (78.6%)	12 (60.0%)	
age (years), Me (Q1-Q3)		45.0 (35.8-48.3)	38.0 (33.3-49.3)	0.47
higher education		7 (50.0%)	11 (55.0%)	1
marital status (married)		9 (64.3%)	10 (50.0%)	0.50
employed		9 (64.2%)	7 (35.0%)	0.16
rural residence		4 (28.5%)	9 (45.0%)	0.48
smoking		1 (7.1%)	4 (20.0%)	0.38

Table 5. Neuropsychological, cognitive, and sleep quality variables of MS patients with newly diagnosed NDP.

Variables		Newly diagnosed NDP		p
		non-chronic	chronic	
anxiety symptoms	subclinical	4 (28.6%)	15 (75.0%)	0,01
	clinical	1 (7.1%)	4 (20.0%)	0,38
depression symptoms	subclinical	2 (14.3%)	13 (65.0%)	0,01
	clinical	2 (14.3%)	4 (20.0%)	1
apathetic symptoms		2 (14.3%)	5 (25.0%)	0.67
fatigue		3 (21.4%)	10 (50.0%)	0.15
cognitive impairment		4 (28.6%)	2 (10.0%)	0.20
poor sleep quality		5 (35.7%)	5 (25.0%)	0.70

Table 6. Clinical variables of MS patients with newly diagnosed NDP.

Variables		Newly diagnosed NDP		p
		non-chronic	chronic	
age of MS onset (years), Me (Q1-Q3)		29.5 (21.8-34.3)	27.0 (23.3-31.8)	0.73
MS duration (years), Me (Q1-Q3)		15.0 (5.5-23.8)	11.5 (5.0-19.5)	0.56
MS type	relapsing	5 (35.7%)	10 (50.0%)	0.50
	progressive	9 (64.3%)	10 (50.0%)	
EDSS (points), Me (Q1-Q3)		3.5 (3.0-5.0)	3.3 (2.5-5.8)	0.80
arterial hypertension		0	3 (15.0%)	0.25
abdominal obesity		2 (14.3%)	3 (15.0%)	1
migraine		1 (7.1%)	5 (25.0%)	0.36
tension-type headache		7 (50.0%)	7 (35.0%)	0.49
patients who refused (or interrupted) pregabalin therapy		6 (42.9%)	14 (70.0%)	0.16

with a greater risk for the incident disruptive pain at any point during 2 years (OR 1.03; 95% CI, 1.01–1.04) (15). In a cross-sectional study of 1249 patients with MS, NP measured by DN4 questionnaire was independently associated with female gender (OR 2.40; 95% CI, 1.59–3.62; p <0.001) and older age (per 1-year increase – OR 1.03; 95% CI, 1.01–1.04; p=0.002) (13).

None of the studied neuropsychological, cognitive, and sleep quality factors (except subclinical depressive disorders) were found to be associated with an increased risk of NDP occurrence.

Although in the cross-sectional studies, it was shown associations between NP and the above-mentioned variables in MS patients. The presence of chronic NP in MS was significantly associated with symptoms of fatigue and with lower scores for measures of mental flexibility (14). In MS population NP (assessed by PDQ), together with cognitive fusion and alexithymia showed significant correlations with anxiety symptoms (26). Patients with NP (assessed by PDQ) had significantly higher fatigue and sleepiness compared to MS participants without pain (10).

At the same time, we revealed that subclinical depressive disorders can be an independent predictor for the NDP chronification. We suggest that clinical depressive disorder could also be associated with the development of NDP chronicity, but we could not prove this hypothesis because of the small number of cases.

Numerous cross-sectional studies highlighted associations between NP and depressive disorders in the MS population. Participants with NP (due to PDQ) had significantly higher depression than those with musculoskeletal pain and those without pain (10). Chronic NP in MS was significantly associated with symptoms of depression (14). MS patients with pain (among whom in 58% of cases were features of NP) had significantly higher levels of depression compared to patients without pain (27). In the MS population increasing in the depression survey (HADS) in every 1-point the likelihood of having NP (evaluated by PDQ) increases 0.66 times (11). From the basic science data, the co-occurrence of pain and depression (along with fatigue, and cognitive impairment) in MS appears to be associated with a common set of underlying etiological factors, namely neuroanatomical changes, pro-inflammatory cytokines, dysregulation of monoaminergic pathways, and a hyperactive hypothalamic-pituitary-adrenal axis (28).

Prospective studies of the general population prove that chronic pain and depressive disorders have a strong reciprocal impact (29). Chronic pain is known to be able to induce depressive disorders, and, in turn, depressive disorders through various mechanisms can increase the risk of pain chronification (30).

Among clinical variables, only progressive types of MS have been found as an independent predictor for NDP occurrence. None of the clinical variables were risk factors for the NDP chronification. The previously mentioned prospective study emphasizes that a progressive course of MS is associated with a greater risk for incident disruptive pain during 2 years (OR 1.60; 95% CI, 1.04–2.48) (15). Till now all studies about NP and the clinical characteristics of MS are cross-sectional. There was no significant difference in the severity of disability and MS duration in patients with chronic NP (14). MS patients without pain had lower EDSS scores compared to those with NP (assessed by PDQ) (10). The presence of NP (assessed by the DN4 questionnaire) was distinctly associated with the EDSS score (OR 1.33; 95% CI, 1.18–1.49) (13). Patients with pain (in 58% of cases pain had neuropathic features) presented greater disability, a longer period of MS, and progressive forms of MS; in a logistic regression analysis, greater disability as measured by EDSS was independently associated with pain (OR 1.7; 1.1-2.7; p=0.014) (27). A progressive course of MS regardless of the patient's age and disability has been shown as the only factor associated with a higher risk of NDP (OR 2.25; 95% CI, 1.2-4.2) (31).

The mechanisms underlying the increased risk of NDP in the progressive MS types have not been fully elucidated; nevertheless, there is a suggestion that progressive cases have a greater axonal loss, which can affect also descending inhibitory nociceptive pathways and be associated with more important deafferentation leading to a higher frequency of prevalence of central NP such as NDP (32).

Thus, over the 2-year observation period, in MS patients the progressive types of MS are an independent predictor for the occurrence of NDP, whereas subclinical depressive disorders according to the HADS are the independent predictor of the development of NDP chronicity.

From a clinical application standpoint, patients with progressive MS types should be considered a group at increased risk for developing NDP. Moreover, MS patients with newly diagnosed DP should be under control for the early detection and correction of

depressive disorders (including subclinical) to prevent NDP chronification.

This study's strengths are its prospective design and the large number of MS patients involved who were under the 2-year observation period. This is the first longitudinal study with the primary aim to identify predictors for NDP occurrence and predictors for the chronification of newly diagnosed NDP in individuals with MS.

The study results should be interpreted taking into account the main limitations. It is a single-center study so results are not necessarily generalizable to the whole population. For the diagnosis of NDP, we used PDQ that was not validated for use specifically in the MS population. In some cases, data from PDQ were obtained by remote patients interviewing which might cause biases in their responses and their further assessment, and, as a consequence, might contribute to the underdiagnosing of NDP. In cases, when patients did not contact us for 3 months and then we called them, we took into account that patients denied any new pain due to their reluctance to visit the clinic and (or) to fill in PDQ. The diagnosis of NDP was made without objective information on lesion location provided by magnetic resonance imaging. Because of cases of non-adherence or partial adherence to pregabalin therapy, patients could not be matched on pain therapy which might lead to subsequent result biases about NDP chronification.

Conclusions

Patients with progressive types of MS make up the group at increased risk for NDP occurrence. For patients with MS, who have newly diagnosed NDP, subclinical depressive disorders according to the HADS are the predictor for NDP chronification.

Funding Statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: MD: conceptualization, methodology, software, validation, formal analysis, investigation, data curation; KS: formal analysis, investigation, data curation. iryna delva: methodology, data curation.

References

1. Kawachi I. Neuropathological features of "non-motor" symptoms in multiple sclerosis and neuromyelitis optica. Clin Exp Neuroimmunol. 2019 Aug;10(3):161-8. doi: 10.1111/cen3.12533.
2. Titova N, Chaudhuri KR. Non-motor Parkinson disease: new concepts and personalised management. Med J Aust. 2018 May 21;208(9):404-9. doi: 10.5694/mja17.00993.
3. Delva I, Lytvynenko N, Delva M. Factors associated with post-stroke fatigue within the first 3 month after stroke. Georgian Med News. 2017 Jun 1(267):38-42. PMID: 28726651.
4. Foley PL, Vesterinen HM, Laird BJ, et al. Prevalence and natural history of pain in adults with multiple sclerosis: systematic review and meta-analysis. Pain. 2013 May 1; 154(5):632-42. doi: 10.1016/j.pain.2012.12.002.
5. O'Connor AB, Schwid SR, Herrmann DN, Markman JD, Dworkin RH. Pain associated with multiple sclerosis: systematic review and proposed classification. Pain. 2008 Jun 30;137(1):96-111. doi: 10.1016/j.pain.2007.08.024.
6. Nurmikko TJ, Gupta S, Maclver K. Multiple sclerosis-related central pain disorders. Current pain and headache reports. 2010 Jun;14:189-95. doi: 10.1007/s11916-010-0108-8.
7. Truini A, Galeotti F, Cruccu G. Treating pain in multiple sclerosis. Expert opinion on pharmacotherapy. 2011 Oct 1; 12(15):2355-68. doi: 10.1517/14656566.2011.607162.
8. Truini A, Barbanti P, Pozzilli C, Cruccu G. A mechanism-based classification of pain in multiple sclerosis. Journal of neurology. 2013 Feb;260:351-67. doi 10.1007/s00415-012-6579-2.
9. Heitmann H, Haller B, Tiemann L, et al. Longitudinal prevalence and determinants of pain in multiple sclerosis: results from the German National Multiple Sclerosis Cohort study. Pain. 2020 Apr 1;161(4):787-96. doi: 10.1097/j.pain.0000000000001767.
10. Kahraman T, Özdoğar AT, Ertekin Ö, Özakbaş S. Frequency, type, distribution of pain and related factors in persons with multiple sclerosis. Mult Scler Relat Disord. 2019 Feb;28:221-225. doi: 10.1016/j.msard.2019.01.002.
11. Karakas H, Kaya E, Abasiyanik Z, Ozdogar AT. Investigation of neuropathic pain distribution and related factors in people with multiple sclerosis. J Mult Scler Res. 2022; 2(2): 46-51. doi: 10.4274/jmsr.galenos.2022.2022-7-2.

12. Kasap Z, Uğurlu H. Pain in patients with multiple sclerosis. Turk J Phys Med Rehabil. 2022 Feb 16;69(1):31-39. doi: 10.5606/tftrd.2022.10524.
13. Solaro C, Cella M, Signori A, et al. Identifying neuropathic pain in patients with multiple sclerosis: a cross-sectional multicenter study using highly specific criteria. J Neurol. 2018 Apr;265:828-35. doi: 10.1007/s00415-018-8758-2.
14. Foley P, Kong Y, Dirvanskiene R, et al. Coupling cognitive and brainstem dysfunction in multiple sclerosis-related chronic neuropathic limb pain. Brain Commun. 2022; 4(3):fcac124. doi: 10.1093/braincomms/fcac124.
15. Fiest KM, Fisk JD, Patten SB, et al. Comorbidity is associated with pain-related activity limitations in multiple sclerosis. Mult Scler Relat Disord. 2015 Sep 1;4(5):470-6. doi: 10.1016/j.msard.2015.07.014.
16. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006 Oct;22(10):1911-20. doi: 10.1185/030079906X132488.
17. Hallström H, Norrbrink C. Screening tools for neuropathic pain: can they be of use in individuals with spinal cord injury? PAIN®. 2011 Apr 1;152(4):772-9. doi: 10.1016/j.pain.2010.11.019.
18. Solaro C, Uccelli MM. Pharmacological management of pain in patients with multiple sclerosis. Drugs. 2010 Jul;70:1245-54. doi: 10.2165/11537930-000000000-00000.
19. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet Neurology. 2015 Feb 1; 14(2):162-73. doi: 10.1016/S1474-4422(14)70251-0.
20. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x.
21. Starkstein SE, Migliorelli R, Manes F, et al. The prevalence and clinical correlates of apathy and irritability in Alzheimer's disease. Eur J Neurol. 1995 Dec;2(6):540-6. doi: 10.1111/j.1468-1331.1995.tb00171.x.
22. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989 Oct 1;46(10):1121-3. doi: 10.1001/archneur.1989.00520460115022.
23. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005 Apr;53(4):695-9. doi: 10.1111/j.1532-5415.2005.53221.x
24. Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989 May 1;28(2):193-213. doi: 10.1016/0165-1781(89)90047-4.
25. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. Pain. 2015 Jun;156(6):1003. doi: 10.1097/j.pain.0000000000000160.
26. Carvalho T, Gomes C, Rodrigues A, da Motta C. Neuropathic pain, cognitive fusion, and alexithymia in patients with multiple sclerosis: cross-sectional evidence for an explanatory model of anxiety symptoms. J Clin Psychol. 2023 May;79(5):1342-1356. doi: 10.1002/jclp.23483.
27. Grau-López L, Sierra S, Martínez-Cáceres E, Ramo-Tello C. Analysis of the pain in multiple sclerosis patients. Neurología (English Edition). 2011 Jan 1;26(4):208-13. doi: 10.1016/S2173-5808(11)70043-8.
28. Chitnis T, Vandercappellen J, King M, Brichetto G. Symptom interconnectivity in multiple sclerosis: a narrative review of potential underlying biological disease processes. Neurol Ther. 2022 Sep;11(3):1043-70. doi: 10.1007/s40120-022-00368-2.
29. Kroenke K, Wu J, Bair MJ, Krebs EE, Damush TM, Tu W. Reciprocal relationship between pain and depression: a 12-month longitudinal analysis in primary care. J Pain. 2011 Sep 1;12(9):964-73. doi: 10.1016/j.jpain.2011.03.003.
30. Surah A, Baranidharan G, Morley S. Chronic pain and depression. Contin Educ Anaesth Crit Care Pain. 2014 Apr 1; 14(2):85-9. doi: 10.1093/bjaceaccp/mkt046.
31. Martinelli Boneschi F, Colombo B, Annovazzi P, et al. Lifetime and actual prevalence of pain and headache in multiple sclerosis. Mult Scler J. 2008 May;14(4):514-21. doi: 10.1177/1352458507085551.
32. Truini A, Galeotti F, La Cesa S, et al. Mechanisms of pain in multiple sclerosis: a combined clinical and neurophysiological study. Pain. 2012 Oct 1;153(10):2048-54. doi: 10.1016/j.pain.2012.05.024.

Correspondence:
Received: 19 April 2023
Accepted: 3 July 2023
Mykhaylo Delva, MD
Neurological department, Poltava State Medical University
Poltava, 36024 Ukraine
E-mail: mdelwa@gmail.com