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Стаття надійшла 29.07.2022 р.

DOI 10 26724/2079-8334-2023-3-85-56-60
UDC 616.832-004.2-071

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OCCURRENCE AND CLINICAL EVOLUTION OF NEUROPATHIC DYSESTHETIC PAIN IN MULTIPLE SCLEROSIS (2-YEAR PROSPECTIVE STUDY)

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The occurrence and evolution of neuropathic dysesthetic pain in patients with multiple sclerosis during a 2-year observation period was studied. 241 patients were included in the study. Dysesthetic pain was diagnosed using the PainDETECT questionnaire. Patients with newly detected (recurrent) dysesthetic pain were examined at the beginning of the study, after 1, 3 and 6 months depending on the duration of the pain. Over a 2-year period, the cumulative risk of dysesthetic pain was 15.6 % (11.4 %–21.0 %), and the cumulative risk of recurrence was 8.8 % (3.0 %–23.0 %). The first detected (recurrent) dysesthesia lasted more than 3 months in two-thirds of cases. The first detected (recurrent) dysesthesia was mainly localized in the lower back and lower limbs. Patients described dysesthesia both at the time of its occurrence and later, indicating more than 2 descriptors (most often "burning", "freezing" and "tingling"). The chronicity of dysesthetic pain was associated with the expansion of pain areas, with the transformation of the pain pattern (from pain attacks to constant pain), with a decrease in pain intensity.

Key words: multiple sclerosis, neuropathic dysesthetic pain, occurrence, clinical evolution.

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ВИНИКНЕННЯ ТА КЛІНІЧНА ЕВОЛЮЦІЯ НЕЙРОПАТИЧНОГО ДИЗЕСТЕТИЧНОГО БОЛЮ ПРИ РОЗСІЯНОМУ СКЛЕРОЗІ (2-РІЧНЕ ПРОСПЕКТИВНЕ ДОСЛІДЖЕННЯ)

Вивчено виникнення та еволюцію нейропатичного дизестезичного болю у пацієнтів з розсіяним склерозом протягом 2-річного періоду спостереження. Залучено до дослідження 241 пацієнт. Дизестезичний біль діагностувався за опитувальником PainDETECT. Пацієнтів із вперше виявленим (рецидивним) дизестезичним болем обстежували на початку дослідження, через 1, 3 та 6 місяців залежно від тривалості болю. За 2-річний період кумулятивний ризик виникнення дизестезичного болю становив 15,6 % (11,4 %–21,0 %), а кумулятивний ризик рецидиву – 8,8 % (3,0 %–23,0 %). Вперше виявлений (рецидивний) дизестезичний у двох третинах випадків тривав більше 3 місяців. Вперше виявлений (рецидивний) дизестезичний переважно локалізувався в нижній частині спини та нижніх кінцівках. Пацієнти описували дизестезичний як на момент його виникнення, так і пізніше, вказуючи більше 2 дескрипторів (найчастіше «печіння», «морозіння» та «поколювання»). Хронізація дизестезичного болю асоціювалася з розширенням ділянок болю, з трансформацією больового паттерну (від больових нападів до постійного болю), зі зниженням інтенсивності болю.

Ключові слова: розсіяний склероз, нейропатичний дизестезичний біль, виникнення, клінічна еволюція.

The study is a fragment of the research project "Optimization of diagnosis, prognosis and prevention of neuropsychological disorders in organic diseases of the nervous system", state registration No. 0120U104165.

Clinical neurologists and neuroscientists have focused on dysfunctions in neurological diseases in the last 10 years that go beyond physical disability [2]. Multiple sclerosis (MS) besides well-known functional disabilities, has a wide variety of other disorders, including pain syndromes [1]. Classifications of pain in MS distinguish between neuropathic pain (NP), nociceptive pain and mixed pain [13]. NP is most directly related to the pathology of MS and its prevalence has been estimated to be 29 % in a meta-

analysis [5]. NP is of particular attention in MS patients, as it produces the greatest effects on adaption of patients and present significant therapeutic difficulties [8]. NP in MS patients is of central origin (as result of somatosensory system lesions in the brain and (or) spinal cord) and is represented by neuropathic dysesthetic pain (NDP), Lhermitte's phenomenon, and trigeminal neuralgia. In patients with MS, NDP is the most commonly reported type of NP, having a prevalence of 17.5 % (13.7 %–22.0 %) [1]. Patients often find NDP difficult to describe and these conditions are not always recognized by doctors [15].

Until now there are a few longitudinal studies devoted to NP in MS [6, 7]. Moreover, prospective studies of pain in MS patients had large time intervals between obsevations, they did not distinguish type of pain, did not assess pain incidence between definite time points, did not study pain evolution over time [4, 9, 14]. For the better understanding the NP charactericstics in MS patients it would be useful to detail the occurrence as well as clinical evolution of NDP as the most common type of NP in this population.

The purpose of the study was to reveal peculiarities of development and further course of neuropathic dysesthetic pain in patients with multiple sclerosis.

Materials and methods. Totally we examined 321 patients. Inclusion criteria: clinically definite MS according to McDonald's 2017 criteria, age over 18 years, patient's written consent to participate in the study. Exclusion criteria: severe speech and writing disorders, diseases that could be the cause of NP, presence of NP at baseline examination. Among 268 eligible patients, 241 consented to take part in the 2-year study (follow up rate 89.9 %).

Every patient who signed consent to participate in the study was given PainDETECT questionnaire (PDQ) and was instructed how to fill it out. Patients were asked to report any new painful sensations in any convenient way. If a patient did not contact us every 3 months we called him/her and asked about any new painful sensation during the last 3 months. If a patient reported new pain, he/she was invited to visit clinic. If a patient with a new pain could not visit clinic, he/she was asked to fill out and send to us PDQ. NDP was diagnosed in cases of >18 points on PDQ, in cases of ≤18 points pain was considered as non-NP. Patient with NDP were asked to detalize pain characteristics by choosing one or more actual pain descriptors: "burning", "freezing", "tingling", "painful numbness", "tightening", "squeezing", "shooting".

Patients with newly diagnosed (recurred) NDP were examined in clinic (or interviewed remotely with PDQ and detalizing pain characteristics) at 1, 3 and 6 months after pain occurrence. If NDP was already absent during 1 or 3-months visits, patients were not invited to the next scheduled visit.

Analyzing PDQ also included: 1) NDP intensity on 10-point scale; 2) body localization of NDP; 3) pain behaviour pattern (patients chose one of the 4 proposed courses of pain according to PDQ).

23 of 241 patients due to various reasons prematurely stopped participating in the study period (dropout rate 9.5 %).

The study was conducted at the Poltava regional Center for MS patients. The study has been reviewed by the Ethics Committee of Poltava State Medical University and the subjects have signed informed consents.

Categorical variables were presented as proportions with 95 % confidence interval (CI). Differences in proportions were compared using Fisher exact test. Quantitative values were presented as median (Me) and interquartile range (Q1 – Q3). For multiple comparisons Friedman's test was used with post hoc analysis (Dunn's test). Differences at $p<0.05$ were considered as significant.

Results of the study and their discussion. The observation group consisted of 69 men (28.6 %) and 172 women (71.4 %). The patients' median age was 39.5 (32.0–47.0) years (ranged from 21 to 60 years). The median duration of MS diagnosis was 12.0 (6.0–18.0) years (ranged from 1 to 29 years). 178 patients had relapsing-remitting (73.9 %), 2 patients – primary progressive (0.8 %) and 61 patients – secondary progressive (25.3 %) course of MS. The Expanded Disability Status Scale score was 4.5 (3.5–4.5) points (ranged from 1.5 to 7.5 points). During the 2-year period we identified 34 cases of newly diagnosed NDP and 3 cases of newly recurred NDP.

Cumulative incidences of NDP during 1st year were 6.9 % (4.3 %–10.9 %), during 2nd year – 8.3 % (5.3 %–12.7 %), during the 2 years' observation period – 15.6 % (11.4 %–21.0 %). The corresponding rates for non-NP were 16.8 % (12.6 %–22.2 %), 6.1 % (11.8 %–21.5 %) and 33.9 % (28.0 %–40.5 %), respectively. The cumulative incidences of NDP during each observation time interval were significantly lower ($p<0.05$) than the same values for non-NP.

Cumulative recurrence of NDP during 1st year were 6.3 % (1.1 %–28.3 %), during 2nd year – 5.9 % (1.6 %–19.1 %), during the 2 years' observation period – 8.8 % (3.0 %–23.0 %). The corresponding rates for non-NP were 38.5 % (24.9 %–54.1 %), 44.6 % (33.8 %–55.9 %) and 64.9 % (53.5 %–74.8 %), respectively. The cumulative recurrences of NDP during any observation time interval were also significantly lower ($p<0.05$) than cumulative recurrences of non-NP.

Duration of newly diagnosed (recurred) NDP had the following structure: <1 month – 13.5 % (5.9 %–28.0 %), 1–3 months – 24.3 % (13.4 %–40.1 %), 3–6 months – 51.4 % (35.9 %–66.6 %), >6 months – 10.8 % (4.3 %–24.7 %). So, in most cases duration of NDP was from 3 to 6 months. Due to the clinical criteria of chronic pain (persistent or recurrent pain lasting longer than 3 months [12]), in 23 cases (62.2 % (46.1 %–75.9 %)) newly diagnosed (recurred) NDP would be chronic.

Distribution of newly diagnosed (recurred) NDP localisations in body areas: head – 8.1 % (2.8 %–21.3 %), face – 10.8 % (4.3 %–24.7 %), neck – 2.7 % (0.5 %–13.8 %), upper back – 10.8 % (4.3 %–24.7 %), lower back – 24.3 % (13.4 %–40.1 %), chest – 5.4 % (1.5 %–17.7 %), abdomen – 13.5 % (5.9 %–28.0 %), right upper limb – 13.5 % (5.9 %–28.0 %), left upper limb – 16.2 % (7.7 %–31.1 %), right lower limb – 43.2 % (28.7 %–59.1 %), left lower limb – 48.7 % (33.5 %–64.1 %). So, newly diagnosed (recurred) NDP could be located in any body areas but predominantly localized in the lower half of the body (lower back and lower limbs).

Table 1 shows that newly diagnosed (recurred) NDP in majority of cases was limited to 1 or 2 body areas. If NDP was still present at the 3-month visits it was spread, as rule, on 3 or 4 body areas.

Table 1

Longitudinal characteristics of newly diagnosed (recurred) NDP distribution in body areas

Time point	The number of affected body areas			
	1	2	3	4
baseline	29.7 % (17.5 %–45.8 %)	48.7 % (33.5 %–64.1 %)	16.2 % (7.7 %–31.1 %)	5.4 % (1.5 %–17.7 %)
1 month	31.3 % (18.0 %–48.6 %)	50.0 % (33.6 %–66.4 %)	15.6 % (6.9 %–31.8 %)	3.1 % (0.6 %–15.8 %)
3 months	17.4 % (7.0 %–37.1 %)	13.1 % (4.5 %–32.1 %)	47.8 % (29.2%–67.0%)	21.7 % (9.7 %–41.9 %)

For statistical analysis of NDP distribution over time we dichotomized patients into those who had 1 or 2 and those who had 3 or 4 body areas with NDP. At 3-month visit the proportion of patients who had NDP in 3 or more body areas was significantly higher, according to exact Fisher test, compared to the same values at baseline and at 1-month visit (p=0.0004 and p=0.002, respectively). So, NDP chronification in MS patients was followed with increasing number of affected body areas.

As shown in Table 2, regardless of observation time, MS patients described NDP with the use of more than 2 descriptors, most frequently using “burning”, “freezing” and “tingling”. Over time, the frequencies of using each specific descriptor were not critically changed.

Table 2

Longitudinal characteristics of newly diagnosed (recurred) NDP descriptors

Time point	Descriptor						
	burning	freezing	tingling	painful numbness	tightening	squeezing	shooting
baseline	67.6 % (51.5 %–80.4 %)	62.2 % (4.6 %–75.9 %)	51.4 % (35.9 %–66.6 %)	40.5 % (26.4 %–56.5 %)	35.1 % (21.8 %–51.3 %)	29.7 % (17.5 %–45.8 %)	21.6 % (11.4 %–37.2 %)
1 month	53.1 % (36.5 %–69.1 %)	56.3 % (39.3 %–71.8 %)	59.4 % (42.3 %–74.5 %)	34.4 % (20.4 %–51.7 %)	21.9 % (11.0 %–38.8 %)	25.0 % (13.3 %–42.1 %)	18.8 % (8.9 %–35.3 %)
3 months	65.2 % (44.9 %–81.2 %)	56.5 % (36.8 %–74.4 %)	65.2 % (44.9 % – 81.2 %)	34.8 % (18.8 %–55.1 %)	47.8 % (29.2 %–67.0 %)	21.7 % (9.7 %–41.9 %)	21.7 % (9.7 %–41.9 %)

At the baseline the most frequent clinical course of newly diagnosed (recurred) NDP was “pain attacks without pain between them” (in 48.7 % (33.5 %–64.1 %) cases) whereas 3 months later it was found almost equal distribution of 4 proposed pain behavior patterns (“persistent pain with slight fluctuations”, “persistent pain with pain attacks”, “pain attacks without pain between them”, “pain attacks with pain between them”). According to the exact Fisher test, there was a trend towards a decrease in the proportion of pain pattern “pain attacks without pain between them” at the 3-month visit (21.7 % (9.7 %–41.9 %)) compared to the baseline value (p=0.06).

NDP chronification was followed with significant decreasing (p=0.02) of its intensity, according to 10-point scale, at 3-month visit (3.0 (2.0–4.0)) compared to the baseline value (4.0 (3.0–5.0)).

We revealed during 2-year period in MS patients that risk of NDP incidence was 15.6 % (11.4 %–21.0 %) and risk of NDP recurrence was 8.8 % (3.0 %–23.0 %), respectively.

Regarding the prospective studies devoted to pain occurrence in MS, there is only one study about cumulative incidence of general pain in MS – among 949 MS patients during the 1st year new pain occurred in 32.7 % cases, during the 2nd year – in 35.2 % cases (overall – in 45.7 % cases); occurence of disruptive pain was recorded in 19.6 % cases during the 1st year and in 20.5 % cases during the 2nd year (overall – in 31.3 % cases) [4].

As for pain recurrence in MS, to date, there is no research on this issue.

In all other prospective studies about pain in MS, it had been investigated only pain prevalence with controversial results. Among 94 patients, pain was diagnosed in 65 % cases at baseline whereas 7 years later, among 74 patients who remained in the study, pain prevalence was 79 % [7]. In population of 26 thousand patients with MS around 59 % patients reported pain at the onset, around 77 % after 15 years, and around 85 % after 30 years [9]. In 410 patients with newly diagnosed clinically isolated syndrome (CIS) or MS, pain was in 39.5 % cases at baseline and in 36.1 % of cases after 4 years [6]. In 230 newly diagnosed adults with CIS or MS pain prevalence at 1, 2, 3, 6, 9, and 12 months after MS diagnosis was much less stable and ranged from 58 % to 61 % [14].

Up to now only two prospective studies with multi-year interobservational intervals have examined the prevalence of NP in MS patients. Among 94 patients at baseline 60.7 % were diagnosed with NDP, 6.6 % with trigeminal neuralgia whereas 7 years later, among 74 patients who remained in the study the same indexes were 48.6 % and 10.8 % respectively [7]. Among 410 patients with newly diagnosed CIS or MS, NP prevalence, according to PDQ, was 2.4 % at baseline and after 4 years – 5.0 % [6]. It is very likely that in these studies authors dealt with different episodes of NP because due to our findings NP mostly lasts only within 6 months.

We found that newly diagnosed (recurred) NDP was predominantly localized in the lower back and in the lower limbs. Other studies also revealed that in MS central NDP was predominantly localized in the lower limbs (especially in the feet) [3]. The latter phenomenon could be partially explained by the longest length of spino-thalamic pathway's part that innervates lower extremities that consequently increases the likelihood of its demyelinating damage [15]. Moreover, at the level of the brain, thalamocortical pathways carrying information from the distal parts of the legs pass in the immediate vicinity of the lateral ventricles and are consistently more frequently involved in the pathological process, with plaques in the periventricular locations being typical of MS.

In our study, in majority of cases patients described new diagnosed (recurred) NDP at baselinene as well as over time as "burning", "freezing" and "tingling". In cross-sectional studies most frequently used descriptors of NDP were "pins and needles" and "tingling" [10]. Up to now only one prospective study about descriptors of general pain in patients with MS revealed decreasing of mean number of pain descriptors from 3.1 at baseline to 2.4 after 7 years [7]. But in the latter study due to large time interval between examination most likely it was studied descriptors of different pain.

Our prospective observation of NDP revealed evolution of its characteristics in the cases of pain duration more than 3 months.

The first feature of NDP chronification was pain expansion. In cross-sectional study, among MS patients with NP (evaluated by DN4 questionnarie), 58 % presented with three or more painful body sites [10]. There are different data about changes in the pain distribution over time in MS patients, but anyway designs of these studies dealt with general pain and multi-year interobservational intervals (the latter suggests the analysing of different pain cases). In 94 patients at baseline and in 74 patients who remained in the study after 7 years, the mean number of body areas with pain remained unchanged [7]. Among 26 thousand patients, no significant changes in pain localization were recorded after 15 and 30 years compared to the baseline [9]. In 70 patients increasing was noted in the number of cases when pain spread to the other half of the body (bilateral pain in the limbs, trunk, face) after 10 years in comparison with the first examination [15].

The second feature of NDP chronification was the trend of pain behaviour transformation. At baseline the most frequent clinical course of newly diagnosed (recurred) NDP was "pain attacks without pain between them", but 3 months later the proportions of all 4 pain behavior patterns were much less equal.

Finally, the third feature of NDP chronification was statistically significant decreasing of pain intensity compared to the baseline value by 10-point scale.

In the cross-sectional study the mean NP intensity (according to DN4 questionnaire), as measured by the visual analogue scale (VAS) score was 4.9±0.1, and 36.8 % of the respondents had NP of moderate to severe intensity (≥4/10) [10]. In prospective studies different trajectories of general pain intensity had been reported in patients with MS. However, results of these studies should be evaluated taking into account large time intervals between examinations which makes it unlikely to observe the evolution of individual episodes of pain. There were no significant differences in pain intensity due to VAS after 7 years, compared to initial scores (5.2±2.1 vs. 5.3±2.5), but at the same time, proportion of patients with "severe" pain increased from 13.1 % to 28.4 % [7]. In patients with newly diagnosed CIS or MS, initial intensity of pain

according to VAS was 1.2±1.9 and 4 years later – 1.2±2.0 [6]. In patients with newly diagnosed CIS or MS, pain intensity was stable in a series of observations during the following year [14].

The strengths of the study are prospective design and large population of MS patients that were retained during the 2-year obervation. Anyway, up to now this is the first study about NDP incidence, recurrence and longitudinal evolution of NDP in MS patients.

This study must be interpreted taking into account its main limitations. We included in analysis results of remote interviews if patients can't visit hospital, that could be followed with response biases and misdiagnosing of NDP. In cases when patients did not contact us during 3 months period and we ourselves called them it can't be ruled out that patients denied any new pain due to reluctance to visit clinic and (or) to fill in PDQ. Due to cases of non-adherence or partial adherence to pregabalin patients could not be matched on pain therapy with subsequent results biases.

Conclusion

In MS patients NDP incidence and recurrence were significantly lower compared to non-NP. In MS patients newly diagnosed (recurred) NDP in two-thirds of cases would be chronic. NDP chronification followed with pain evolution in form of its spreading on body areas, increasing of cases with persistent pain and decreasing of pain intensity.

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Стаття надійшла 15.05.2022 р.