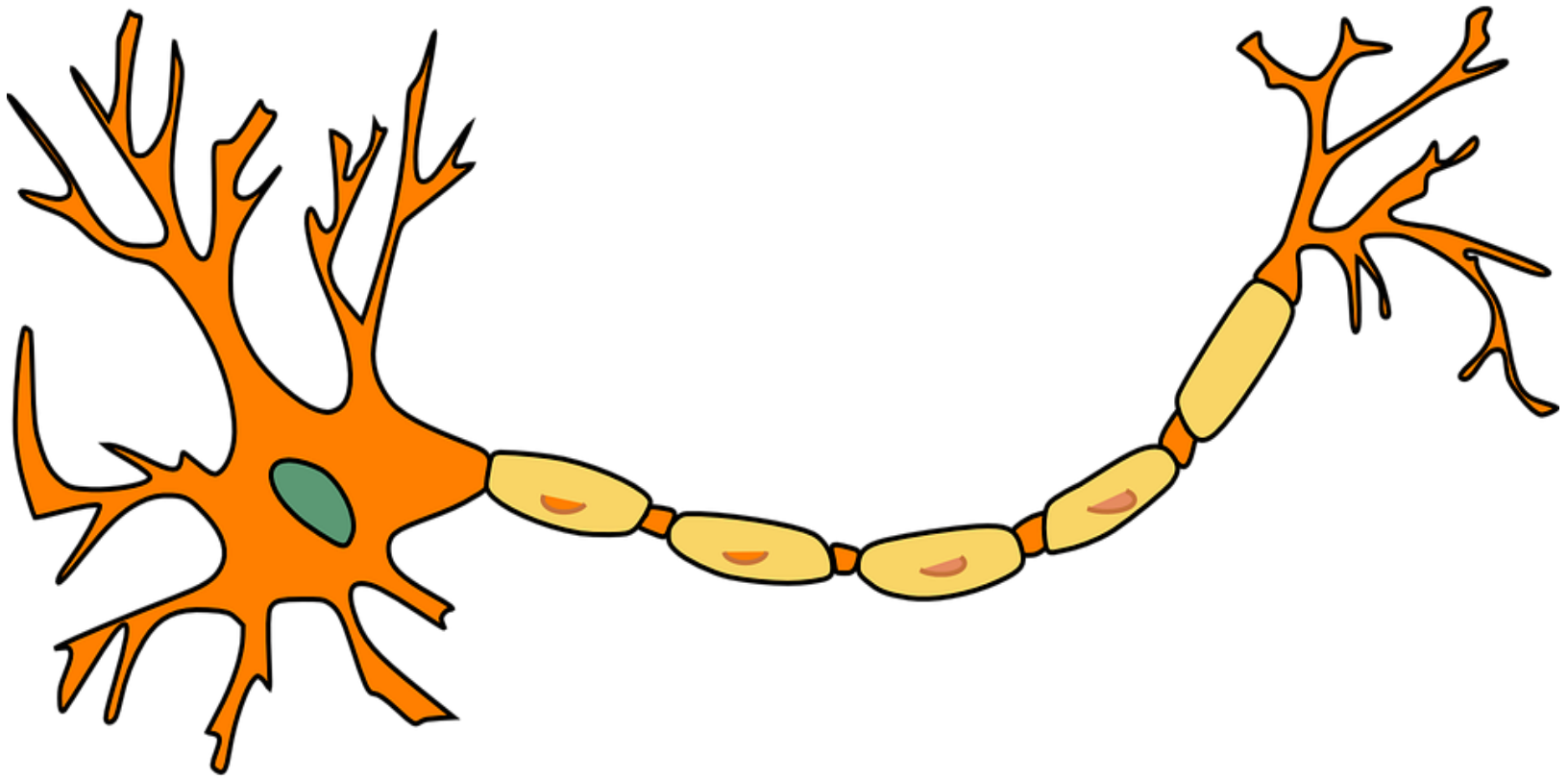
FLEX CEUs

Multiple Sclerosis and Pain Conditions



Pain in Multiple Sclerosis: Prevalence and Characteristics of Various Pain Conditions

Abstract

Introduction: Pain is a key symptom in patients with multiple sclerosis (MS), but the prevalence of pain in MS and its impact on quality of life of the patients is still underestimated.

Objective: The aim of the study was to examine the occurrence of pain in MS patients, to identify the pain conditions and the relationship to important demographic variables (age, gender, type of MS) and to determine its impact on quality of life.

Methods: Questionnaires on pain and health-related quality of life were sent to 307 patients with definitive MS diagnose. All patients with painful sensations were examined with aim to diagnose central and peripheral neuropathic and nociceptive pain.

Results: Out of 220 responders 92% reported at least one type of pain or unpleasant pain sensation. Pain was more frequent in relapsing-remitting form of MS than in secondary progressive MS ($p<0.0001$) and less frequent in males than females ($p=0,001$). The ratio of different pain types was as follows: 51.38% headache, 57.94% neck or low back pain, 40.91% central neuropathic extremity and trunk pain, 5.91% trigeminal neuralgia, 34.26% Lhermitte's sign, 2.47% peripheral neuropathic pain. The commonest location of pain was lower extremities (84.09%) and the commonest pain quality was painful stiffness. Two and more concurrent pain locations were reported by 87.2% of patients and the total number of pain locations significantly increases with disease duration ($p<0.0001$). Pain limited the activities of daily living in 61.5% of patients.

Conclusion: Our study confirmed the heterogenity of pain experienced in MS, the capacity to experience more than one type of pain simultaneously and inadequate pain treatment. Therefore pain is an important therapeutic target in MS.

Keywords: Multiple sclerosis; Pain; Prevalence; Neuropathic pain; Central pain; Nociceptive pain; Health-related quality of life

Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) with unpredictable course and a changeable, interindividually varying complex of symptoms with a lifelong progression which may result in disability. Since the disease is so far incurable, proper symptomatic treatment is very important in its management in addition to the disease modifying treatments.

Pain in MS is a very common symptom, with prevalence in patients ranging from 29 to 92% [1-14]. The existing research has proven pain is a key problem in patients with MS. Svendsen et al. found that pain in MS patients was reported by similar proportions of MS patients and sex and age- stratified group from the general population, however pain intensity, the need for analgetic treatment and pain interference with activities of daily living were much higher in MS patients [4]. Kalia and O'Connor compared MS patient's SF-36 bodily pain scores with those of rheumatoid arthritis and osteoarthritis finding, that all three groups had comparable levels of pain severity [15]. Ehde et al. reported severe pain (score 7-10) in 27% from 442 patients with MS [3]. Pain was the worst symptom of MS in 12% patients and 68% of patients reported dissatisfaction with the care of the physicians [16]. Also Solaro et al. reported as results of his work disruption in daily life activities, work, mood, recreation and general enjoyment of life, low satisfaction with treatment [5]. Brochet et al. found out that 73.5% of patients had pain at the onset of their MS and in 44% of patients pain significantly interfered with daily activities [12]. In an article by Marchettini et al. several cases were presented with pain as an initial sign of MS. Most of these patients reported pain as their only symptom for some time before further signs of MS began to appear [17].

Several different types of pain can by identified in patients with MS, including continuous or intermittent central neuropathic, nociceptive pain and mixed neuropathic and non-neuropathic pain. Pain in MS patients is classified according to causal mechanism in order to facilitate mechanism-tailored treatment strategies [18]. This mechanism-based classification of pain in MS distinguishes nine types of MS-related pain: trigeminal neuralgia and Lhermittes phenomenon (paroxysmal neuropathic pain due to ectopic impulse generation along primary afferent), on-going extremity pain (deafferentation pain secondary to lesion in the spino-thalamo-cortical pathways), painful tonic spasms and spasticity pain (mixed pains secondary to lesions in the central motor pathways but mediated by muscle nociceptors), pain associated with optic neuritis (nerve trunk pain originating from nervi nervorum), musculosceletal pains (nociceptive pain arising from postural abnormalities secondary to motor disorders), migraine (nociceptive pain favored by predisponong factors or secondary to midbrain lesions) and treatment-induces pains.

Pain in MS stemming from the disease itself includes acute pain syndrome (trigeminal neuralgia, Lhermitte's sign, painful tonic seizures, segmental burning dysaesthesia, neuralgia, migraine) or chronic pain syndrome (chronic dysesthetic pain, painful leg spasms, and optic

neuritis). In many patients, pain results from disability, immobility, poor posture, decubital ulcer, peripheral nerve lesions due to chronic pressure, e.g. from poorly fitted braces, or MS treatment. In our study we tried to better understand the epidemiology of pain in MS, which could potentially improve pain management in MS patients. Details from the study on prevalence of central pain in MS was analysed in detail in a separate study.

Patients and Methods

The analysed group consisted of 307 patients (225 female and 82 male) aged 21 to 69 (with the average age of 37) with definitive MS in the patient register at the Department of Neurology of the University Hospital in Bratislava, Slovakia. The patients were sent a questionnaire focusing on basic demographic characteristics (age, sex), disease specifics (onset of first MS symptoms, the year of diagnosis confirmation, form of the disease course, and disability score) and pain. They also filled in a standardized health-related quality of life questionnaire, *SF-36v2* [19]. Questions relating to pain experiencing during the course of the disease were created on the basis of existing literature sources and our own clinical experiences. Responders were asked, if they had suffered from such types and qualities of pain as follows: headache (tension, migrenous), back or neck pain, trigeminal neuralgia, Lhermitt´s sign, unpleasant painful sensations in upper legs, lower legs or other parts of the body (burning, cramping, stabbing, pressing, picking, stiffness, coldness) and secondary pain (due to urinary tract infection, spasticity, immobility, decubitus). Pain was measured by using the pain intensity and interference items from the Bodily Pain Scale of the SF-36 [20,21]. Participants were asked about pain intensity by rating how much bodily pain they experienced during the past 4 weeks ranging from 1 (none) to 6 (very severe). They also rated how much pain interfered with normal work, including both work outside the home and housework, on a scale ranging from 1 (not at all) to 6 (extremely). Questionnaire replies received along with patient´s informed consent were included in the study patient database and revised. All patients with unclear pain history were interviewed by telephone or examined at the outpatient clinic. All patients with unpleasant painful sensations in extremities and trunk were examined with aim to diagnose central or peripheral neuropathic-peripheral neuropathy or radiculopathy [22] and nociceptive pain. Patients with dementia or psychiatric conditions were excluded from the study. Back pain, spasticity pain, headache were considered as nociceptive pain in our study. Trigeminal neuralgia et Lhermitte sign were considered as type of central pain. Non-painful paresthesias of central etiology were not considered as central pain. A control group could not be formed for too low a number of painless MS patients participating in the study.

Statistical Analysis

The patient's data was subsequently evaluated and interpreted using descriptive and inductive statistics methods. Data normality was checked graphically and by the Shapiro-Wilk test. Each set of data was summarized in contingency tables and displayed graphically in bar and pie charts. To test significance of proportions, binomial tests were used for univariate analysis and chi-squared tests for bivariate analysis. In case of numerical calculability, exact tests were applied. Significance of medians was tested using the Mann-Whitney test. The differences are presented along with the 95% Confidence Interval (95% CI). To establish association between variables, we used corresponding bivariate or multivariate regression analysis methods. Chi-squared tests were used to determine the dependence between qualitative variables. The strength of the relationship was assessed using the Goodman-Kruskal gamma correlation coefficient. Significance of expected or published predictors of the incidence of central pain was tested by bivariate and multivariate logistic regression and it is quoted with corresponding odds ratio (OR) and the 95% confidence intervals. For all statistical analyses, we used the significance level alpha=5%. All analyses were conducted using Microsoft Office Excel 2003 (Microsoft Corporation) and StatsDirect 2.6.6 (Stats Direct Ltd., Cheshire, UK) software.

Results

Demographic data of the analyzed group of patients are presented in Table 1. The questionnaire was sent in by significantly less males than females ($p<0.0001$), 95% CI (21.50 to 33.66%). The age or disability score were not substantially different between respondents and non-respondents. Both groups had rather lower scores on the Expanded Disability Status Scale (EDSS), which indicates a higher representation of less disabled persons in our study. Both groups featured significantly more patients with relapsing-remitting MS ($p<0.0001$). The average disease duration (in our study time since diagnose) was similar in both groups (8 years for respondents, 10 years for non-respondents).

Prevalence of Pain in MS Patients

Out of 220 respondents 203 (92%) reported at least one type of pain or unpleasant pain sensation. Prevalence of pain in case of excluding headache from analyse was 90.45%. The results of our study show males to be significantly less susceptible to pain than females (Fisher's exact test, ($p=0.0011$, 95% CI (0.04 to 0.55). Pain was significantly more frequent in relapsing-remitting form of MS than in secondary progressive MS ($p<0.0001$), 95% CI (0.64 to 0.77).

Prevalence of pain does not correlate with the age of the patient. The highest incidence of pain was found in MS patients in their 40s and 50s, and then it progressively decreased (Table 2). The total chi-square test shows a statistically non-significant ($P=0.052$) association between the gender (i.e., between the counts of male and female patients with pain) and age decade, however, this association is plausible, since the age category is ordered and we have found a significant linear trend ($P=0.042$).

Our study found, that 87.2% patients reported two and more and 31.05% reported three and more concurrent pain locations (i.e. including all types of pain) and the total number of pain locations

	Patients		Sex		Age at examination		EDSS		Disease duration (years)	
	Number	%	W	M	Range	Mean	Range	Mean	Range	Mean
Responders	220	71	160	60	21-69	39	2–6.5	2.5	6-29	8
Nonresponders	87	29	65	22	22-58	36	1-5	2	7-34	10
All patients	307	100								
	Course of multiple sclerosis									
	RR		SCHP	PCHP						
Responders	72.00%		26.60%	1.40%						
Nonresponders	85.00%		15.00%	0.00%						

EDSS: Expanded Disability Status Scale; RR: Relapsing-Remitting; SCHP: Secondary Progressive; PCHP: Primary Progressive

Table 1: Demographic characteristics.

significantly increases with disease duration (p<0.0001), 95% CI (from 0.15 to 0.32). Significantly more concurrent pain locations per patient were found in females than males–Fisher-Freeman-Halton exact test (p<0.0001), 95% CI (from -0.69 to -0.24).

Prevalence of Different Types of Pain in MS Patients (Table 3)

Headache (Neuropathic, nociceptive, psychogenic pain)

In our study, we found headache in 51.4% of patients. Out of them 46.8% suffered from at least one another type of pain. Headache was the only painful symptom of MS in four (1.8%) patients. The results show that headache is significantly less frequent in males than females (p=0.016, OR=0.26). Our results confirmed there is no association between headache and EDSS (p=0.53). The same finding was obtained for disease duration (p=0.54). In our study headache occurred significantly more frequent in patients with relapsing-remitting form of MS compared to other forms of MS (p=0.081).

(n=201)	D:3	D:4	D:5	D:6	D:7	Suma
W	28	40	47	36	3	**154**
M	11	20	9	8	1	**49**
Total	**39**	**60**	**56**	**44**	**2**	**203**

Table 2: Age decades of MS patients with pain in years.

Back pain (Nociceptive pain)

Cervical or lumbar back pain was found in 57.94% of patients. The results of our study show that females suffer from back pain significantly more than males (p=0.0028), 95% CI (from 0.20 to 0.69). The prevalence of back pain significantly increase with the EDSS score (p=0.078). This condition was significantly more frequent in patients with relapsing-remitting form of MS (p=0.013). The presence of back pain was not associated with disease duration (p=0.7).

Secondary pain (Nociceptive pain)

Secondary pain was found in 31.8 of our patients (84% female). The results indicate that males are less susceptible to secondary nociceptive pain than females (OR=0.37).

The prevalence of secondary pain significantly increase with the EDSS score (p=0.0085).This condition was not associated with disease duration (p=0.82). The same finding was obtained in types of multiple sclerosis (p=0.18).

Trigeminal neuralgia (Central neuropathic pain)

The prevalence of trigeminal neuralgia in our study is 5.91%. The risk of this condition to occur was found to be equal in males and females (OR=0.45).

Lhermitte's sign (Central neuropathic pain)

The prevalence of Lhermitte's sign in our study is 34.26%.

Type of pain	Number of patients	% of patients	W	%	M	%
Headache	112	**51.38**	86	76.78	26	23.21
Back or neck pain	124	**57.94**	101	81.45	23	18.55
Secondary pain (Due to urinary tract infection, spasticity, immobility, decubitus)	69	**31.8**	58	84.05	11	15.94
Lhermitte´s sign	74	**34.26**	57	77.03	17	22.97
Trigeminal neuralgia	13	**5.91**	11	84.62	2	15.38
Upleasant painful sensations in lower legs	185	**84.09**	142	76.76	43	23.24
Upleasant painful sensations in upper legs	134	**61.19**	101	75.37	33	24.63
Upleasant painful sensations	81	**37.85**	67	82.72	14	17.28
Upleasant painful sensations	65	**30.09**	54	83.08	11	16.92

W: Women; M: Men
Headache (Nociceptive, Neuropathic, Psychogenetic pain)

Table 3: Prevalence of individual types of pain in MS patients.

Location of unpleasant painful sensations	n/resp	% out of resp	n/W	n/M	%/W	%/M
Lower extremity	220	**84.09**	185	35	70.71	13.38
Upper extremity	219	**61.19**	134	85	37.44	23.75
Half of the body	214	**37.85**	81	133	14.33	23.52
Trunk	216	**30.09**	65	151	9.05	21.04

n: number; W: Women; M: Men; resp: respondent

Table 4: Quantitative analysis of unpleasant painful sensatios occurring concurrently in patients.

Unpleasant painful sensations	Localisation of unpleasant painful sensations							
	Lower limbs		Upper limbs		A half of body		Trunk	
	Number	%	Number	%	Number	%	Number	%
Burning	59	29.06	20	9.9	17	8.59	7	3.52
Cramping	81	39.9	29	14.36	18	9.09	11	5.53
Stiffness	127	62.56	74	36.63	50	25.25		
Stabbing	25	12.32	22	10.89	13	6.57	14	7.04
Coldness	76	37.44						
Pressing							40	20.1
Other types	49	24.14	58	28.71	21	10.61	1	0.5

Table 5: Qualitative analysis of unpleasant painful sensations occurring concurrently in patients.

This condition was found equally frequent in males and females (OR=0.45).

Neuropathic extremity and trunk pain (Central neuropathic pain)

Out of 220 respondents, central neuropathic extremity and trunk pain was found in 40.91%. Female were significantly more affected than male ($p<0.0001$).

Peripheral neuropathic pain

Five respondents reported peripheral neuropathic pain, which represents the prevalence of 2.4%.

Trigeminal neuralgia, Lhermitte's sign, Neuropathic extremity and trunk pain as a central neuropatic pains were analyzed in detail in upcoming separate study.

Lower extremities were the commonest location of unpleasant pain sensations (84.09%, Table 4). The commonest pain quality in all the mentioned body locations (upper and lower extremities and the trunk) was stiffness (Table 5). On the trunk, it was mostly manifested as "girdling" around the body.

Evaluation Subgroups "Bodily Pain" of the SF-36v2

Verbal pain intensity scale has shown that during the past 4 weeks (before the completion of a questionnaire) 55.6% of patients experienced mild to moderate pain and 10% severe to very severe pain.

Within the 5-point verbal scale, which assesses the extent to which pain limits the patient's activities of daily living; we found moderate degree of limitation in 34% and severe degree of limitation in 27.5% of patients.

Discussion

According to available literature sources, there have been several studies looking into different pain conditions accompanying MS, but a thorough differentiation between nociceptive, peripheral and central neuropathic pain – which is essential for the appropriate treatment of patients–has, to our knowledge, been reported in only one study [6].

Representativeness of sample

Based on the assumption that in our analysis of 200 patients (approx. 5% of the MS population in Slovakia), there is an even distribution of characteristics within the population, our sample might be considered as representative. Regarding proportional representation by age our set of patients is consistent with epidemiological data on MS [23]. Regarding proportional representation by gender, it correlates with epidemiological data concerning MS [24,25]. Finally, from the viewpoint of proportional representation of patients stratified by MS forms, we found our sample to be just as consistent with epidemiological data [23].

Prevalence of pain

There are significant differences in the prevalence of pain in MS. They result from geographical and demographic factors of the prevalence of MS itself as well as from different classifications of pain conditions, various sets of patients and control groups, and methodological differences.

The prevalence of pain in our set of patients is 92%, which is not significantly different from other published studies [4,11,26]. Compared to other findings however [3-6,10], the prevalence of pain in our study turned out to be higher. We supposed that important factor in high prevalence of pain found in our study might have been headache, since headache was previously excluded from most studies and according to literature sources prevalence of primary headache in MS patients is higher than in the general population [28], headache may develop as a consequence of MS [29, 30] and can be a treatment induced [18,27,28,31,32].

To assessing the impact of headache on the overall prevalence of pain in patients with MS we decided to analysed the data excluding headache. The obtained result has not confirmed our assumption, because despite the exclusion of headache prevalence was too high. Based on these results MS specific treatment (interferon-beta, glatiramer acetat) and antidepressants probably has not fundamentally influenced the overall prevalence of pain in MS, since existing studies have confirmed their effect mainly on headache.

The high prevalence in our set of patients might have been caused by other factors.

Probably the most important factor is that the questionnaires might have mostly been filled in and returned by more motivated MS patients (experiencing pain). This hypothesis is supported by the fact that the questionnaires were sent in by significantly less male than female patients, which is in line with our finding that pain is more significant in females than males. Also, the results of demographic data analysis showed that we had significantly more patients with relapsing-remitting MS, which was found to be accompanied with pain significantly more frequently than other forms of MS [27,35].

Another factor that must have played a role in high prevalence of pain was the inclusion secondary pain to the study.

As our study found, the prevalence of pain in MS does not correlate with the age of the patient, which is consistent with the study by Österberg et al. but inconsistent with findings by Clifford et al. or Moulin et al. who reported pain in MS patients to increase with the age. This could be explained by predominance relapsing-remitting MS form associated with pain in our study as well as the fact that relapsing-remitting MS form is more common in younger patients. According to our study, the prevalence of pain is significantly higher in females than males, which is also consistent with literature report [6,15,33,34].

We found pain to be significantly more frequent in relapsing-remitting MS, which can possibly be explained by a higher incidence of headache and paroxysmal pain symptoms during relapses in this form of MS. This could also be consistent with Pöllmann et al. [27] and study by Togha et al. who has shown that headaches are more common during a relapse [35].

Furthermore, our study confirms that MS patients have concurrent pain in many locations of the body on average [7,36]. Our results show that the total number of pain locations (i.e., including all types of pain) in MS patients significantly increases with disease duration, with significantly more pain locations being present in females. To our knowledge, none of such results have so far been reported in literature. According to literature lower extremities are the commonest location of unpleasant pain sensations. The commonest pain quality in our study was found to be painful stiffness and then cramping pain, which may be present in the form of acute or chronic complaints. On the one hand, it may be manifested as nociceptive pain, for instance due to spasticity, muscle pain arising from an abnormal body position, or pain caused by arthropathies. On the other hand, it may be manifested as central pain, includes painful spasms, cramps or tightness such as "feeling like a belt" around the leg, or possibly as peripheral neuropathic pain. Often it is a combination of more than one mechanism.

Prevalence of individual types of pain

The incidence of headache (as based on IHS Classification and diagnostic criteria for headache disorders) in patients with MS is higher than in general population, several (mostly prospective) studies show. Variable frequencies ranging from 4 to 61.8% have been reported in the prevalence of headache in MS [14,35,37-39]. Our study found the prevalence of headache to be 51.38%, which is within the mentioned range. Prevalence of headache was significantly higher in relapsing-remitting form of MS, which is in agreement with the results of several studies. [28,35,43,44]. Headache is a unique clinical problem that must be discussed in any review of MS-related pain, because there appears that the process of demyelination may be a factor in headache production, but there is still limited evidence about it. A little data is also on MS related treatment, comorbidities and MS disability on headaches, especially migraine.

In many MS patients, pain is not directly related to the process of the disease; rather, it results from the consequences of their disability. Frequently occurring back pain and lumbar sciatic syndrome are mostly stemming from wrong posture in patients with paresis, spasticity, dyscoordination of movements, and osteoporosis due to immobility and corticoid therapy. In our sample of patients, we found cervical or lumbar back pain in 57.94%, which is not very much different from the prevalence of 50% as reported by Bashir and Whitaker [40], but higher as 20% reported by Foley et al. [14]. Significantly higher prevalence of back pain in relapsing-remitting form of MS in our study could support the clinical suspicion that back pain is not only consequent to spondyloarthritis, but could be in some cases related to inflammatory episodes involving the meninges or to meningeal reaction to underlying myelitis. Chronic nociceptive pain may also be caused by bedsores, chronic uroinfection, tendonitis, and arthralgias. In our study, these were present in 31.8% of patients and significantly increase with the EDSS score. Females were significantly more susceptible to chronic nociceptive pain than males. The same was found to be true about back pain.

The prevalence of peripheral neuropathic pain (polyneuropathy, peripheral nerve lesion, e.g. as part of chronic pressure due to poorly fitted braces, or isthmus syndrome due to using crutches, etc.) in patients with MS has so far been examined in detail only in the study by Österberg et al. [6] (with all the investigated patients having undergone EMG examination) who reported the prevalence of 2%. In our study, peripheral neuropathic pain was found in five patients, which corresponds to the prevalence of 2.4%.

Unlike nociceptive pain, which was found to be significantly more present in female patients, Lhermitte's sign and trigeminal neuralgia occur equally frequently in males and females, according to our study. Lhermitte's sign was present in 34.7% of our patients. In literature, data on the prevalence of this disorder vary considerably from 9 to 41% [5,14,41]. Our results showed trigeminal neuralgia to be present in 5.91% of MS patients, which is consistent with the published data reporting the prevalence frequencies ranging from 1.6 to 18% [4,5,6,38,42]. Our research found central neuropathic extremity pain in 90 patients (40.91%), which is more than refered Truini et al. [18] or Foley et al. [14], but comparable with study reported by Österberg et al. [6].

Effects on quality of life of patients pain

A comprehensive evaluation of the SF-36v2 in order to assess the proportion of pain on quality of life of MS patients in this study could not be implemented for very small control group of patients without pain. Be able to evaluate a subset of the questionnaire "bodily pain". In this respect, our results in line with other literature confirm that the majority of patients (55%) felt the intensity of mild to moderate pain that 60% of patients with moderately to severely limit their daily activities [3,4,12].

Replies to questions related to bodily pain in the health-related quality of life questionnaire showed that pain intensity is moderate to severe in 55.6% patients, while in 60% pain interferes with normal work moderately to "quite a bit", which is not very different from data reporting moderate or higher intensity of bodily pain within the prior 4 weeks in 69% of the sample and 71% reporting pain-related interference that was moderate or greater [11].

Conclusion

Our study confirms high prevalence of pain in MS, significantly more frequent in relapsing-remitting MS and being significantly higher in females, includes several pain syndromes and number of pain locations which significantly increases with disease duration and female gender and confirms too, that pain is an important symptom influences quality of life of the patients.

Appropriate treatment of MS patients experiencing pain requires a thorough differentiation between nociceptive, peripheral neuropathic and central neuropathic pain. Each type of simultaneously occurring pain must be paid special attention to. Many types of pain in MS are often unrecognised by clinicians, because of difficulties for many people with MS with finding the right words to describe the painful sensations they experience. In taking a medical history, we must actively communicate with the patient and ask questions about the presence of pain or unpleasant pain sensations in order to determine the right treatment strategy.

Central Pain in Patients with Multiple sclerosis

Abstract

Central pain (CP) is little recognized and diagnosed type of pain in multiple sclerosis.

Objective: This second part of our work related to pain in multiple sclerosis is concentrated on occurrence of CP and defined its characteristics.

Methods: Questionnaires on pain were sent to 307 patients with definitive multiple sclerosis diagnose. Patients admitting to CP were examined with aim to diagnose CP. The dates were statistically processed.

Results: Out of 220 responders 92% reported pain during the course of their multiple sclerosis. CP was found in 57.72%, including 40.91% with central neuropathic extremity and trunk pain (CNEP), 5.91% with trigeminal neuralgia (TN), and 33.18% with Lhermitte's sign (LS). In 28.8% of all patients, CP was an initial multiple sclerosis symptom. The prevalence of CP does not increase with age, disease duration, or the Expanded Disability Status Scale (EDSS). Lower extremities were the commonest location of CNEP (74.5%) and burning was the commonest painful sensation. Three and more concurrent unpleasant painful sensations experienced 68.9% of patients, which were in 46.7% located in the lower extremities. Three and more concurrent CP locations (including TN and LS) were reported by 89% of patients. Number of locations in CP increases significantly with age and EDSS, in contrast to group with nociceptive and peripheral neuropathic pain (n=113), where does not increase with age, EDSS and multiple sclerosis duration. The group with nociceptive and peripheral neuropathic pain featured significantly less patients with only one pain location ($p=0.0269$) and only one pain quality. In contrast to the other group, In CP increases significantly the number of patients with increase the number of concurrent pain qualities ($p<0.0001$).

Conclusion: CP is not only a frequent complaint among persons with multiple sclerosis, but is a distinctive type of pain requiring special attention and their identification remains still the major challenge.

Keywords: Multiple sclerosis; Pain, Prevalence; Neuropathic pain; Nociceptive pain

Introduction

Multiple sclerosis is a chronic, often disabling neurological disease with unpredictable and variable course. Among symptomultiple sclerosis, which vary from one person to another, pain is very common. Little recognized and diagnosed is central pain (CP). In practice, it is often overlooked, especially in the case of coexistence of several types of pain. CP is for the patient new feeling and different from pain as he knows before. Because of difficulties for many people with multiple sclerosis to find the right words to describe the painful sensations they experience ttherefore some CP sensations is being often unrecognised by clinician. Based on pathophysiological mechanism, the central pain is considered as neuropathic pain. According the mechanism-based classification of pain in multiple sclerosis distinguishes nine types of multiple sclerosis-related pain: trigeminal neuralgia and Lhermittes phenomenon (paroxysmal neuropathic pain due to ectopic impulse generation along primary afferent), on-going extremity pain (de-afferentation pain secondary to lesion in the spino-thalamo-cortical pathways), painful tonic spasms and spasticity pain (mixed pains secondary to lesions in the central motor pathways but mediated by muscle nociceptors), pain associated with optic neuritis (nerve trunk pain originating from nervi nervorum), musculosceletal pains (nociceptive pain arising from postural abnormalities secondary to motor disorders), migraine (nociceptive pain favoured by predisponong factors or secondary to midbrain lesions) and treatment-induces pains. According to the International Association for the Study of Pain, CP is pain caused by a lesion or disease of the central somatosensory nervous system [1]. CP is commonly thought of as being excruciating pain with a bizarre character, covering small or large areas of body, mostly constant, but it may by intermittent or paroxysmal, varies in type and intensity among individuals [2]. No one pain quality is pathognomic for central pain, but concurrently more than one pain quality is occurring in multiple sclerosis patients [3] and the resulting pain is their combination. Almost any kind of lesion in the brain or spinal cord can cause CP, which is associated with sensory disturbances, dominated by abnormalities in the sensibility to temperature and pain. CP is long-lasting, heavily tolerable, causing a great deal of suffering, while heat, pressure, as well as physical and mental overwork may increase the symptomultiple sclerosis. Often is extremely intense and intolerable during the night [4] with a significant impact on the quality of life (QOL) of the patients [5]. Central pain frequently develops at an interval of weeks or months after the occurrence of the lesion, does not seem to be dependent on etiology and may be the first symptom of multiple sclerosis, which may occur alone or together with other multiple sclerosis symptom-multiple sclerosis [6,7]. CP can be difficult to diagnose. The pain may be widespread and may seem unrelated to any injury or lesion. No single test is available to enable your doctor to diagnose CP. CP is very challenging to treat and may not respond to pharmacological agents routinely used for peripheral neuropathic pain [7]. As such, its management is troublesome. For all these reasons it is important to be familiar with the distinguishing features of central

neuropathic pain [7]. Results on prevalence studies of CP in multiple sclerosis are heterogenous, ranging from 14% to 64% among studies [4,6-11]. The most common type of central pain in multiple sclerosis is non-paroxysmal, continuous extremity pain (dysaesthesias or ongoing pain) of the arms, legs or trunk occurring in 14-29% of multiple sclerosis patients [4,6-11]. The common paroxysmal central pains in multiple sclerosis are trigeminal neuralgia with reported prevalence from 1.6 to 18% [5,6,11-14] and Lhermitte´s sign with prevalence from 9 to 41% [1,11,13,15]. Appropriate treatment of multiple sclerosis patients experiencing pain requires a thorough differentiation between nociceptive, peripheral neuropathic and central neuropathic pain. Each type of simultaneously occurring pain must be paid special attention to. Therefore, it is a great challenge to recognize and distinguish central pain from other types of pain.

Patients and Methods

The analysed group consisted of 307 patients (225 female and 82 male) aged 21 to 69 (with the average age of 37) with definitive multiple sclerosis in the patient register at the Department of Neurology of the University Hospital in Bratislava, Slovakia.

The patients were sent a questionnaire focusing on basic demographic characteristics (age, sex), disease specifics (onset of first multiple sclerosis symptom-multiple sclerosis, the year of diagnosis confirmation, form of the disease course, disability score) and pain.

Questions relating to pain were created on the basis of existing literature sources and our own clinical experiences. Responders were asked on onset of first painful sensations and if they had suffered from such types and qualities of pain as follows: headache, back or neck pain, trigeminal neuralgia, Lhermitte´s sign, unpleasant painful sensations in upper legs, lower legs or other parts of the body (burning, cramping, stabbing, pressing, picking, stiffness, coldness) and secondary pain (due to urinary tract infection, spasticity, immobility, decubitus). Questionnaire replies received along with patient´s informed consent were included in the study patient database and revised. All patients with unclear pain history were interviewed by telephone or examined at the outpatient clinic.

All patients with unpleasant painful sensations in extremities and trunk were examined with aim to diagnose central, peripheral neuropathic (peripheral neuropathy or radiculopathy) and nociceptive pain. Patients with dementia or psychiatric conditions were excluded from the study. Back pain, spasticity pain, headache and optic neuritis pain were considered as nociceptive pain in our study. Trigeminal neuralgia and Lhermitte´s sign was considered as central pain. Non-painful paresthesias of central etiology and non-painful Lhermitte´s sign were not considered as central pain. Painful tonic spasms were not included in the central pain. A control group without pain could not be formed for too low a number of painless multiple sclerosis patients participating in the study. In order to find out the same differences of patients with central pain we created a control group of multiple sclerosis patients with all others types of pain in multiple sclerosis. The group consisted of 113 patients (including 71 women) aged 25-53 years (mean 39 years).

The patients´ data were collected and subsequently evaluated and interpreted using descriptive and inferential statistics. Categorical variables are presented as counts/percentages in tables and/or displayed graphically in the bar and pie charts. Continuous or interval-scaled variables were first checked for normality using graphical methods and the Shapiro-Wilk test. Differences in the proportions between responders and no-responders as well as between CNEP and non-CNEP groups were tested with binomial tests. Categorical variables grouped in two-way contingency tables were analysed using chi-square tests. In case of numerical calculability, exact tests were applied. Interval and continuous variables were tested using the Mann-Whitney test. To establish association between variables, we used corresponding bivariate or multivariate regression analysis methods. Chi-squared tests were used to determine the dependence between qualitative variables. The strength of the relationship was assessed using the Goodman-Kruskal gamma correlation coefficient. Significance of expected or published predictors of the incidence of central pain was tested by bivariate and multivariate logistic regression and it is quoted with corresponding odds ratio (OR). All estimated statistics are presented along with the respective 95% Confidence Interval (95% CI). Our statistical significance reporting criteria for comparison between data sets was $p<0.05$ (Figure 1). All analyses were conducted using Microsoft Office Excel 2003 (Microsoft Corporation) and StatsDirect® 2.6.6 (Stats Direct Ltd., Cheshire, UK) software.

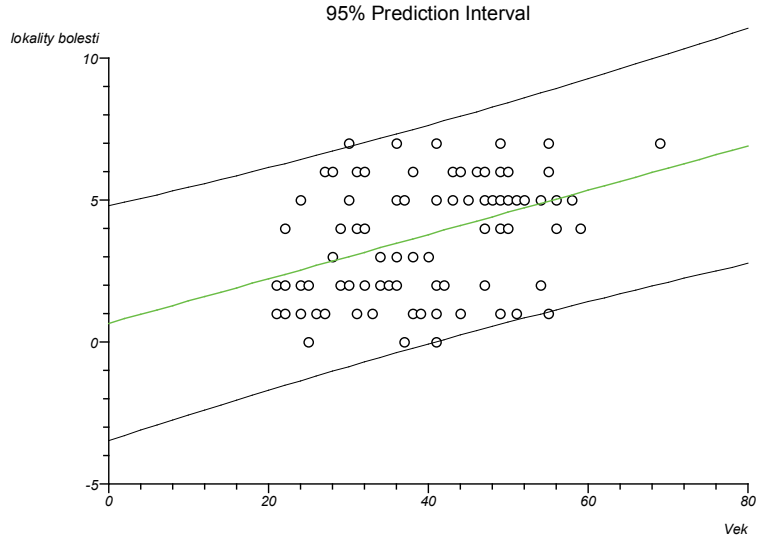


Figure 1: 95% prediction interval.

Details from the study on prevalence of other types of pain than CP in multiple sclerosis was analyzed in detail in a separate study [17].

Results

Demographic data of the analyzed group of patients are presented in Table 1.

Questionnaires replies with informed consent were received from 220 patients (responders, i.e., the response rate was 71.7% (160 female and 60 male) aged 21 to 69 (with the average age of 39). Replies were not received from 87 patients (non-responders) (65 female and 22 male) aged 22 to 57 (with the average age of 36). The age, proportion of genders or disability score was not substantially different between responders and non-responders. Both groups had rather lower scores on the EDSS, which indicates a higher proportion of less disabled persons in our study. Both groups featured significantly more patients with relapsing-remitting multiple sclerosis (p<0.0001). The average disease duration (time since diagnosis) was similar in both groups (8 years for responders, 10 years for non-responders).

Prevalence of pain in multiple sclerosis patients

Pain during the course of disease reported 203 (92.3%) of responders. Details from the study on prevalence at other than central pain in multiple sclerosis was analysed in detail in a separate study [17].

Prevalence of central pain in multiple sclerosis patients

CP was found to be common in 127 patients (57.72%) of responders including those with central neuropathic extremity and trunk pain (CNEP) (90, 40.91%), with trigeminal neuralgia (TN) (13, 5.91%) and those with Lhermitte's sign (LS) (73, 33.18%) (Table 2). All three types of CP occurred concurrently in four patients. CP occurred as an initial symptom of multiple sclerosis in 28.74% of responders (as CNEP in 28.74% and in 1.36% together with LS).

The prevalence of CP did not increase with age decades (the output from chi-square test: p=0.78), and the presence of CP was not associated with age (the output from bivariate logistic regression: p=0.65; OR=0.99, 95% CI (from 0.96 to 1.02).

The prevalence of CP was not associated with the EDSS score (p=0.31; OR=0.89, 95% CI (from 0.71 to 1.12). Also regression analysis did not confirm EDSS as an independent predictor for manifestation of central pain.

The same finding was obtained for disease duration (p=0.68; OR=0.98, 95% CI (from 0.93 to 1.04). Multivariable logistic regression did confirm non-significance of all three above mentioned predictors.

Trigeminal neuralgia

In our study, we found TN in 5.91% of patients; while in 2 patients (15%) was bilateral. TN was the only painful sign of multiple sclerosis in one patient. Our results confirmed there is not an association between TN and EDSS (p=0.51). The same finding was obtained for form of multiple sclerosis (p=0.7). The risk of this condition to occur was found to be equal in males and females (OR=0.452). We were not able to use the chi-squared test due to low counts; instead, we used the Fisher exact test. Our results confirmed there is no significant difference between males and females in the occurrence of trigeminal neuralgia (p=0.32), 95% CI (from 0.06 to 1.90). The average age of persons with this condition was 41 years (the age range of 25–56), the average duration of trigeminal neuralgia was 13 years and the average time from diagnosis multiple sclerosis was 11 years. This condition was significantly more frequent in early-stage of disease duration and correlated with time since diagnosis multiple sclerosis (p=0.031; OR=1.05, 95% CI (from 0.09 to 0.18).

Lhermitte's sign

The prevalence of painful LS was 73 patients (33.18%), while in 36 responders (16.36 %) LS was only painful symptom of multiple sclerosis and in three patients (1.36%) onset of LS was in accordance with onset of the first symptomultiple sclerosis of SM, thus occurred at the disease onset. This condition was found equally frequent in males and females (p=0.26; OR=0.686; 95% CI (from 0.35 to 1.30).No correlation was found between Lhermitte's sign and age, EDSS and disease duration.

Central neuropathic extremity and trunk pain

CNEP was identified in 90 patients (40.91%), while in 28.74% of responders onset of CNEP was in accordance with onset of the first symptomultiple sclerosis of SM. CNEP was only painful symptom of multiple sclerosis in 47 patients (21.36%) 10 patients (4.54%) reported CNEP together with NT. Female were significantly more affected with CNEP than male (p<0.0001), 95% CI (from 0.70 to 0.87). OR=0.537, 95% CI (from 0.27 to 1.03). 67 patients (74.5 %) reported unpleasant painful sensations located on lower extremities, 58 patients (64.4%) on upper extremities, 39 patients (43.3%) on a half of body and 31 patients (34.4%) on a trunk (Table 4). The commonest quality of pain was burning (56.6%) (Table 3). 64 patients (68.9%) reported three and more concurrent qualities of pain, which were in 46.7% of them located in the lower extremities. The commonest location of CNEP in 74.5% of the patients was lower extremities (Table 4). Three and more CP locations (including trigeminal neuralgia and Lhermitte's sign were reported by 89% of the patients.

	Patients		Sex		Age at examination		EDSS		Disease duration (years)	
	number	%	W	M	range	mean	range	mean	range	mean
Responders	220	71	160	60	21-69	39	2-6.5	2.5	29-Jun	8
Nonresponders	87	29	65	22	22-58	36	5-Jan	2	Jul-34	10
All patients	307	100								
EDSS: Expanded Disability Status Scale; RR: Relapsing-Remitting; SCHP: Secondary Progressive; PCHP: Primary Progressive										

Table 1: Demographic characteristics.

Central pain types	No. of patients	patients %	female	male	female %	male%
Central neuropathic extremity and trunk pain	90	**40.91**	72	18	80	20
Trigeminal neuralgia	13	**5.91**	11	2	84.6	15.4
Lhermitte's sign	73	**33,18**	57	17	77,03	22,97

Table 2: Prevalence of central pain types in patients with MS.

Unpleasant painful sensations	Lower limbs		Upper limbs		A half of body		Trunk	
	n	*%T/%CP*	*n*	*%T/%CP*	*n*	*%T/%CP*	*n*	*%T/%CP*
Burning	52	23.6/55.9	16	7.3/17.2	16	7.3/17.2	5	2.3/5.4
Cramping	36	16.4/38.7	12	5.5/12.9	9	4.1/9.7	8	3.6/8.6
Pressing Stiffness	47	21.4/50.5	34	15.5./36.6	27	12.3/29.0	21	9.6/22.6
Stabbing	15	6.8/16.1	14	6.4/15.1	8	3.6/8.6	8	3.6/8.6
Painful coldness	39	17.7/41.9	-	-	-	-	-	-
Other types	21	9.6/22.6	25	27.78	10	4.6/10.8	0	0/0

Table 3: Qualitative analysis of painful sensations occurring concurrently in patients with central neuropathic extremity and trunk pain.

n: 90	Lower limbs		Upper limbs		A half of body		Trunk	
sensations	n	%	n	%	n	%	n	%
None	23	25.6	32	35.6	51	56.7	59	65.6
One	9	10	28	31.1	21	23.3	21	23.3
Two	16	17.8	18	20	10	11.1	10	11.1
Three	13	14.4	12	13.3	6	6.7	0	0
Four	20	22.2	0	0	1	1.1	0	0
Five	8	8.9	0	0	1	1.1	0	0
Six	1	1.1	0	0	0	0	0	0
One	9	10	28	31.1	21	23.3	21	23.3
Two	16	17.8	18	20	10	11.1	10	11.1
Three and more	42	46.7	12	13.3	8	8.9	0	0
n: number								

Table 4: Quantitative analysis of the number of concurrently occurring painful sensations in patients with central neuropathic extremity and trunk pain.

The number of locations of CP in the patient increased significantly with the age (p=0.0006, correlation coefficient Gamma=0.292, 95% CI (from 0.14 to 0.39).

The number of locations of CP increased significantly with EDSS (p=0.0006; correlation coefficient Gamma=0.325, 95% CI (from 0.16 to 0.52).

The number of locations with CP in the patient did not increase with duration of the disease (correlation coefficient Gamma=0.153; 95% CI (from -0,001 to 0.27; p=0.08).

Comparison of CP and other as CP (nociceptive and peripheral neurophatic-NCP)

Groups of patients with CP and NCP were highly significantly different in terms of the number of pain qualities, which were in one patient present simultaneously (Table 5). While in the CP group the number of patients was growing with an increase of pain qualities occuring concurrently in one patient, in the NCP group with the increasing number of pain qualities the number of patients decreased (Fisher-Freeman-Halton exact test, p<0.0001).

Groups of patients with CP and NCP were highly significantly different in terms of the number of pain sites, which were simultaneously present in one patient (Table 6). The number of patients with only one site of pain was significantly higher in the NCP group (Fisher-Freeman-Halton exact test, p=0.0269).

From our study was further revealed, that the number of NCP locations in the patients did not increase with the age (correlation coefficient Gamma=0.040, (p=0.5724), 95% CI 95% CI (from 0.14 to 0.39), the number of NCP locations in the patients did not increase with EDSS (correlation coefficient Gama=0.090, (p=0.242), 95% CI (from –0.03 to 0.19) and the number of locations with NCP in the patients did not increase with duration of the disease (correlation coefficient Gama=0.021, (p=0.791), 95% CI (from -0.12 to 0.16).

	0-1	2-4	5-8	9 and more	all
(n=90)					
CP (n)	15	23	24	28	90
CP (%)	16.67%	25.56%	26.67%	31.11%	100%
(n=113)					
NCP (n)	18	52	33	10	113
NCP (%)	13.85%	49.35%	29.11%	7.69%	100%

Table 5: Comparison of the number of pain qualities in MS patients occurring concurrently in CP or in NCP.

	H:0	H:1	H:2 and more
CP (n)	3	15	72
CP (%)	3.33%	16.67%	80%
NCP (n)	12	9	109
NCP (%)	9.23%	6.92%	83.85%
n: number, H: number of pain locations, CNEP: Central Extremity and Trunk Pain, NCNEP: Other as Central Extremity and Trunk Pain (Non-Central Extremity and Trunk Pain)			

Table 6: Comparison of the number of pain sites occurring concurrently in patients with CP or NCP.

Discussion

Representativeness of sample

Based on the assumption that in our analysis of 200 patients (approx. 5% of the multiple sclerosis population in Slovakia), there is an even distribution of characteristics within the population, our sample might be considered as representative. Regarding proportional representation by age our set of patients is consistent with epidemiological data on multiple sclerosis [18]. Regarding proportional representation by gender, it correlates with epidemiological data concerning multiple sclerosis [15,19]. Finally, from the viewpoint of proportional representation of patients stratified by multiple sclerosis forms, we found our sample to be just as consistent with epidemiological data [18].

Prevalence of central pain

Concerning to the effort to specify the prevalence of central pain in patients with multiple sclerosis, there was done an estimation of the necessary number of the patients with multiple sclerosis. The estimated size of the group in terms of characteristics obtaining we set up in accordance to the population incidence of clinically confirmed central pain and the difference was considered as an acceptable deviation of ± 20% from percentage of prevalence. Estimation of prevalence rate we did on the base of published articles and the level of reliability of the estimation we set up to 95%. Result for the needed selection from patients´ population with SM (8000) and for a published middle-sized prevalence is 218. This corresponds with our group of patients.

Our research found central pain in more than half of the patients (57.72%), which is comparable with other published studies [20-22]. Compared to other findings [4,6,9,11] the prevalence of central pain in our study turned out to be higher. This might have been caused by geographical and demographic factors of the prevalence of multiple sclerosis itself, differing patients samples, study design and by our opinion on recognition this very distinctive type of pain by patients, because of difficulties to find the right words to describe this new painful feeling and also insufficient attention to obtain reliable information about painful sensations from the patients and thus to diagnose pain of central neuropathic origin by physician.

Our results could be influenced by inclusion of some types of neuropathic pain, which were not included in some previous studies. According to literature sources most of the studies reported as central pain only neuropathic extremity pain alone or in combination with trigeminal neuralgia [4,6,13,20] Only in the, study by Foley, where investigators used pooled prevalence estimates, explored heterogeneity using meta-regression, and analysed prevalence during the disease course using both estimates at disease milestones and longitudinal studies, was in central neuropathic pain included neuropathic extremity pain (7.1%–52.8%), Lhermitte's sign (9.7%-25.0%) and trigeminal neuralgia (2.0%-6.0%) with pooled prevalence of CNEP 26%, LS 16% and TN 3.8%. The prevalence of central pain, according to our results, does not increase with patient age, disease duration or EDSS [4]. Thus it appears that neither the increasing age of the patient, EDSS score nor duration of multiple sclerosis increases the risk for development of CP. This conclusion is in accordance with my own clinical experiences partly in accordance with study by Österberg et al. where it was found out, that CP prevalence does not increase with higher degree of disability and out of the results of their study was concluded, that it appears that neither increasing age nor increasing duration of disease increase the risk for developing CP. These interesting results contradict previous findings on the prevalence of overall pain in patients with multiple sclerosis, where it was found that the pain prevalence increased with age [4,8,10,13] disease duration [13,23] as well as increasing disability [10,13,23]. As in studies on prevalence of overall pain in multiple sclerosis except central neuropathic extremity pain and trigeminal neuralgia, there were nociceptive and peripheral neuropathic pain included and according Osterberg finding, that prevalence of peripheral neuropathic pain in multiple sclerosis is very low, thus it appears that responsible for different results of the studies could be nociceptive pain [6]. Based on the above findings, it can be assumed that the increasing age, increasing EDSS and duration of the disease in patients with multiple sclerosis increase the risk for developing nociceptive, but not for central neuropathic, especially central neuropathic extremity pain. Further studies are needed to confirm this theory.

Characteristics of types of central pain

Trigeminal neuralgia: After revision all our patients with TN confirmed criteria according Cruccu et al. Our results showed TN to be present in 5.91% of multiple sclerosis patients, which is much higher than in general population (from 0.1% to 0.7%) [24]. This is consistent with published data reporting the prevalence range TN in multiple sclerosis from 1.6% to 18% [3,8,19,11,24]. The age of onset of multiple sclerosis- associated TN in patients has been noted to be about 10 years younger than in patients without multiple sclerosis [25-27]. In our study the average age of persons with this condition was 41 years (the age range of 25-56), while average duration of trigeminal neuralgia was 13 years and average time from diagnosis multiple sclerosis was 11 years, which pointed to onset in the early period of multiple sclerosis and at young age. These results are in accordance with published studies about early age of onset of multiple sclerosis-associated TN than in patients without multiple sclerosis [24-27] and have more years to develop recurrence, also are more likely to be medically intractable because their multiple sclerosis symptomultiple sclerosis are often worsened by the anti-seizure medicines used to treat TN [28], thus suffer much.

Lhermitte's sign: According to the **Multiple sclerosis Foundation** approximately 38 percent of multiple sclerosis patients will experience Lhermitte's sign at one time or another. In literature, the data on prevalence of this disorder vary from 2% to 41% [11,13,29-31]. The possible explanation for differences in prevalence of Lhermitte´s sign may be the fact, that there is some multiple sclerosis patients for which an electric feeling passing down the back to the legs on flexing the neck (the common form of Lhermitte´s sign) could be painless. One-quarter of patients with Lhermitte's sign had never told their physicians of these symptom-multiple scleroses (Al-Arai). In literature, there are few studies which concentrate their attention to LS as painful symptom in multiple sclerosis. Our questionnaire of pain was focusing on description of perceiving painful sensations, thus in our study LS was presented as painful. The prevalence of 34.7% is within the published range. No correlation was found between Lhermitte's sign and age, EDSS and disease duration. This is according with study by Beckmann. Furthermore we found out, that in a half of patients with LS, it was only painful symptom of SM and in 1.36% of the patients LS occurred at the disease onset, which isn´t much different from 3% published by Paty and Poser. Because of limitation in current knowledge regarding LS in multiple sclerosis, there is a need for future studies that would increase understanding in this area.

Central neuropathic extremity pain: The most common painful symptomultiple sclerosis of neuropathic pain in our population and often one of the first symptomultiple sclerosis of pain perceived at the beginning of multiple sclerosis is pain felt in the extremities [9]. Most of these painful symptomultiple sclerosis are of central neuropathic origin. In our series 40.91% of patients experienced central neuropathic extremity and trunk pain, which is in the range of published studies (7.1%-52.8%) examined by Foley [4].

The prevalence of CNEP as part of the onset symptomatology of multiple sclerosis was not surprising very high (28.74% of responders), because this type of pain is a directly consequence of the multiple sclerosis lesion. In accordance with literature sources [5,6,22,32] the most commonly perceived quality of pain in our study were burning and painful cold. Compared with the general population experiencing chronic neuropathic pain, multiple sclerosis patients were more likely to use the pain adjectives of painful cold, tingling, itching, and numbness [33]. Such descriptors of neuropathic pain in multiple sclerosis patients could be related to central mechanisms, whereas in the general population, neuropathic pain is mostly due to peripheral mechanisms [22].

The significant interindividual differences have been found in quality of pain perceiving by the patients, who often indicate more than one type of pain [6], and the resulting pain is their combination.

So pathognomonic for central pain is not certain quality of pain, but the combination of different qualities of pain [34]. In the present study more than two third of CNEP patients experienced three and more concurrent unpleasant painful sensations on lower extremities and almost two third on upper extremities, which is in line with the study conducted by Leijon et al. [18] for central pain after stroke (stroke) and study by Österberg et al. [19] and also Moisset [20] for central pain in multiple sclerosis.

The most important finding was that among our patients with CP, 89% were presented with three and more painful sites at the same time.

The number of locations in CP patients increases significantly with patient age, increasing degree of the EDSS and a hint of the trend is the duration of SM. The number of locations in NCP patients did not increase with the age, EDSS and duration of the disease. Such a correlation could not be found in many other studies.

Conclusion

Our study confirms that central pain is a frequent and unique complaint among persons with multiple sclerosis for which is patognomic combinations of different concurrent pain qualities, no one quality of pain, which are experiencing in multiple sites at the same time. The prevalence of CP is high and in nearly 30% of the patients are present in the early stages of the disease together with other symptom-multiple sclerosis, while during the disease the number of painful sites and the qualities of pain experienced by patients is raising. On the basis of these facts is extremely important to pay great attention to this type of pain not only by researchers but by doctors too.

This finding, along with other results of our study highlights the special status of central pain in SM. Necessary but further studies to improve our knowledge and assess the significance of central pain and its place within the complexity of the patients with multiple sclerosis.