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Prevalence of pain in patients with multiple sclerosis and its association with anxiety, depressive symptoms and quality of life

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Summary

Pain is one of the most frequently reported symptoms of multiple sclerosis (MS). It affects the daily functioning of patients, limits the ability to work and reduces the joy of life.

Aim. The aim of the study was to analyze the impact of pain on quality of life as well as symptoms of anxiety and depression in patients with MS.

Material and methods. The study included 144 patients with diagnosed MS (mean age 41±12 years, mean illness duration 10.3±8.6 years). The study was carried out on the basis of the author's survey on current and previous pain – *the Quality of Life Self-esteem Questionnaire* (EuroQol5D) and *the Hospital Anxiety and Depression Scale* (HADS).

Results. Among all respondents, 117 (81.3%) reported current pain, and 120 (83.3%) declared the occurrence of pain in the past. Currently, patients have reported: pain in one or more extremities – 79 people (54.9%), headache and facial pain – 72 (50%), back pain – 72 (50%), painful muscle spasms – 54 (38.6%), ocular pain – 37 (25.7%), Lhermitte's sign – 32 (22.2%). Patients reporting pain experienced significantly more severe symptoms of anxiety and depression (HADS-L: 8.0±4.3 vs. 5.1±4.3; $p< 0.01$; HADS-D: 6.0±4.2 vs. 3.4±3.7; $p< 0.01$), and had significantly worse quality of life (EQ 5D: 8.1±1.9 vs. 6.3±1.4; $p< 0.0001$).

An association between presence of pain and gender ($p< 0.01$), age ($p< 0.05$), the degree of disability ($p< 0.05$), education ($p< 0.001$), and the professional activity ($p< 0.01$) was found.

Conclusions. Pain in MS is associated with more severe symptoms of anxiety and depression, and worse quality of life. Female sex, older age, lower level of education, greater disability, and lack of occupational work predispose to the occurrence of pain in MS.

Key words: multiple sclerosis, pain, anxiety, depression

Introduction

Pain – as defined by the International Association for the Study of Pain (IASP) – is a subjective unpleasant and negative sensory as well as emotional impression arising under the influence of stimuli damaging tissues (nociceptive) or threatening malfunctions. Pain is considered as mental phenomenon. There are two types of pain: receptor – nociceptive pain (somatic or visceral), which is caused by irritation of the receptors of sensory nerve (nociceptors), e.g., by inflammatory mediators, and non-receptor – neuropathic pain, which is caused by compression or destruction of the structures of the nervous system [1–3].

Pain is one of the most frequent symptoms accompanying patients who suffer from neurological diseases. It is also reported by patients with multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system (CNS). Symptomatology of MS varies widely and results from location of damage. Movement disorders, sensory abnormalities, damage of cranial nerves, fatigue, vegetative, and psychological symptoms can be present [4–6].

According to the literature, pain is reported by 23–92% of patients with MS [7–12]. There are following types of pain: primary pain – resulting from demyelinating changes in the CNS, secondary pain – caused by other factors associated with the disease, for example, the therapy, and MS-independent pain – associated with the accompanying disease. Pain affects the daily functioning of MS patients, limits the ability to work, reduces their careers, causes sleep problems, mood disorders and anxiety, reduces social contacts, and limits the joy of life [13–15].

Little is known about presence of pain in Polish patients and the literature data on pain and its associations with clinical and psychosocial features are rather contradictory [16]. Therefore, the aim of this study was:

1. to assess the type and prevalence of pain in patients with MS and its association with clinical features and social factors;
2. to assess the association between pain in MS and anxiety, depression, and quality of life.

Material and methods

Subjects were recruited among188 patients diagnosed with MS treated at the Neurological Outpatient Clinic, Medical University of Silesia in Zabrze. Out of this group, 144 patients (76.6%) agreed to participate in the study and signed the written consent. The research was conducted between September 2014 and January 2015.

It was a non-invasive study, therefore the consent of the bioethical commission was not necessary.

Each patient was interviewed using an author's questionnaire consisting of questions concerning sociodemographic and medical data. Questions concerned age, sex, course of the disease (age at first symptoms and diagnosis, current symptoms, frequency of relapses, previous and current pharmacological treatment), education, professional activity, marital status, and number of children. Detailed questions concerned current and previous pain (pain in upper and lower extremities, headache, facial pain, back pain, painful muscle spasms, ocular pain, Lhermitte's phenomenon). Intensity of pain was assessed using *the Visual Analogue Score* (VAS). It determines the intensity of pain on the scale from 1 to 10, using a ruler 10 cm in length where '0' indicates no pain, and '10' the strongest imaginable pain [17].

Quality of life was assessed by *the European Quality of Life-5 Dimensions* (EuroQol 5D), which consists of two parts: EQ-5D (Five Questions of the EEQ-5) and EQ-VAS (Visual Analogue Scale of the EuroQol 5D). The EQ-5D contains five questions concerning: motor skills, taking care of oneself, normal daily activities, the presence and severity of pain, and mood disorders. There are three possible responses to each question. For purposes of this study, the following scoring was established: from 1 (no problem) to 3 points (significant problems) for each question, and then the sum was calculated. The maximum possible score was 15 [18, 19]. A Polish validated version of the questionnaire was used [20]. A permission to use this questionnaire in the study was obtained from the EuroQol Research Foundation.

The EQ-VAS is an analogue visual scale assessing the general health status and disease activity from 0 (the worst imaginable health) to 100 (the best possible health). Most often it is presented as a vertical line100 mm long, on which the patient marks the horizontal line corresponding to his own assessment of the severity of the disease. The result is obtained by measuring (in millimeters) the distance from the beginning of the scale to the place selected by the patient.

The depressive symptoms and anxiety were assessed by *the Hospital Anxiety and Depression Scale* (HADS) by Zigmond and Snaith, which is a self-assessment questionnaire. The patients are asked to choose one response from the four given per each question. The questions related to anxiety are marked with 'A' (7 questions), and to depression – marked with 'D' (7 questions). They are arranged in an alternating way. The scores (from 0 to 3) for each question, separately for 'A' and 'D', are added together to obtain two results: regarding the severity of depressive symptoms (D) and anxiety (A). A total score of 0–7 points indicates no abnormalities, 8–10 – borderline score, and of ≥11 points suggests anxiety (A) or depressive symptoms (D) [21].

Finally, neurological examination was performed. Physical disability was assessed using *the Expended Disability Status Scale* (EDSS) [22]. Course of the disease was determined based on an interview and analysis of medical documentation.

Statistical analysis was performed using STATISTICA 12, Stat Soft Poland and R 3.3.2, GNU General Public License. Data were expressed as mean ± standard deviation (M±SD) and median with interquartile range (*Me*, IQR) or percentages. The following tests were used: the chi-square test, Fischer's exact test, Shapiro-Wilk test, Student's

t-test or Mann-Whitney *U* test, and a Spearman correlation analysis. A *p*-value of $p < 0.05$ was considered significant.

Results

The study included 144 patients diagnosed with MS (mean age 41±12 years, mean disease duration since first symptoms 10.3±8.6 years). There were 110 women (mean age 40.8±11.6 years) and 34 men (mean age 42±12.8 years). The course of MS was relapsing-remitting (RR) in 114 patients, and secondary progressive (SP) – in 30 patients. The mean EDSS score was 3.2±1.9 points. The mean time from the last relapse was 22.7±31.2 months. The annual relapse ratio (ARR) was 1.3±1.3.

Declared education was as follows (no data in 4 patients): primary – 2 patients (1.4%), vocational – 37 patients (26.4%), secondary – 53 patients (37.9%), and higher – 48 patients (34.3%). Among all the participants, there were 68 (48.6%) professionally active people, and 72 (51.4%) professionally inactive individuals (no data in 4 patients). 50 patients (35.4%) were single (maiden, bachelor, widow, widower, divorced), 91 (64.6%) were married or in concubinage (no data in 3 patients); 98 patients (68.1%) had children: three or more – 13 (9%), two – 33 (22.9%), one child – 52 (36.1%).

85 patients (59.1%) were treated with the following immunomodulatory or immunosuppressive medications: interferon beta 1a – 25 (17.4%), interferon beta 1b – 35 (24.3%), glatiramer acetate – 4 (2.8%), mitoxantrone –2 (1.4%), fingolimod – 15 (10.4%), daclizumab – 3 (2.1%), natalizumab – 1 (0.7%).

Among all respondents, 117 people (81.3%) reported current pain, and 120 patients (83.3%) declared the occurrence of pain in the past (Table 1). In 52 patients (36.1%), first symptoms of MS were associated with pain. 52 patients (36.1%) were treated with analgesics at the time of the study (paracetamol and NSAIDs) and 58 (40.3%) used analgesics in the past (no data about usage of analgesics in 34 respondents). In addition, patients were treated with antiepileptic drugs (2 persons; 1.4%), benzodiazepines (3 persons; 2.1%), SSRI and SNRI antidepressants (8 persons; 5.6%).

Table 1. **Occurrence and intensity of pain among MS patients (N = 144)**

Localization of pain	Pain reported currently N (%)[a]	Intensity of current pain [0÷10] M±SD Me (IQR)[b]	Pain reported in the past N (%)[a]	Intensity of pain in the past [0÷10] M±SD Me (IQR)[b]	p[c]
Pain in one or more extremities	79 (54.9)	5.7±2.3 5.0 (4.0)	86 (59.7)	5.8±2.4 5.5 (4.0)	R = 0.85 p < 0.0001
Headache	72 (50)	5.5±2.2 5.0 (16.6)	94 (65.3)	6.4±2.5 7.0 (10.8)	R = 0.64 p < 0.0001
Facial pain (trigeminal neuralgia)	9 (6.3)	5.4±1.7 5.0 (3.0)	19 (13.2)	5.6±2.3 5.0 (5.0)	R = 0.60 p = 0.280

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Back pain	72 (50)	5.6±2.4 5.0 (4.0)	68 (47.2)	6.2±2.3 6.0 (3.0)	R = 0.87 p < 0.0001
Painful muscle spasms	54 (38.6)	5.6±2.3 5.0 (3.0)	62 (43.1)	5.9±2.3 5.0 (4.0)	R = 0.85 p < 0.0001
Ocular pain	37 (2.7)	4.4±2.8 3.5 (4.5)	39 (27.1)	5.1±2.3 5.0 (4.0)	R = 0.72 p < 0.001
Lhermitte's sign	32 (22.2)	4.5±2.8 4.0 (3.0)	37 (25.7)	5.3±2.6 5.0 (3.0)	R = 0.75 p < 0.010

[a] – data presented as number and percentage; [b] – data presented as mean±standard deviation (M±SD) and median with interquartile range – Me (IQR); [c] – assessment of the relationship between the occurrence of pain at present and in the past (Spearman's coefficient).

Table 2. **Results of the questionnaires and their association with presence of current pain and the use of analgesics**

Questionnaire	Examined patients N = 144	Current pain		p[b]	Analgesics		p[b]
		Yes N = 117	No N = 27		Yes N = 58	No N = 52	
	M±SD Me (IQR)[a]	M±SD Me (IQR)[a]	M±SD Me (IQR)[a]		M±SD Me (IQR)[a]	M±SD Me (IQR)[a]	
Symptoms of anxiety HADS-A [0÷21]	7.5±4.4 7.0 (6.0)	8±4.3 8.0 (6.0)	5.1±4.3 4.0 (7.0)	p < 0.010	8.5±4.2 9.0 (6.0)	6.3±4 6 (5)	p < 0.010
Symptoms of depression HADS-D [0÷21]	5.5±4.2 5.0 (7.5)	6.0±4.2 6.0 (6.0)	3.4±3.7 2.0 (6.0)	p < 0.010	5.9±4.4 5.0 (6.0)	5.2±3.9 5.0 (8.0)	p = 0.480 NS
Quality of life EQ-5D [0÷15]	7.8±1.9 8.0 (3.0)	8.1±1.9 8.0 (6.0)	6.3±1.4 6.0 (2.0)	p < 0.0001	8.2±1.9 8.0 (3.0)	7.4±1.7 7.0 (2.0)	p < 0.050
Health status EQ-VAS [0–100%]	67.5±19.5 70.0 (20.0)	64.5±19.2 68.0 (30.0)	76.6±17.8 80.0 (20.0)	p < 0.010	64.6±20 70.0 (30.0)	74.5±14.2 78.5 (20.0)	p < 0.050

[a] – data presented as mean with standard deviation – M ± SD and median with interquartile range – Me (IQR); [b] – the Student's t-test / the Mann-Whitney U test; HADS-A – Hospital Anxiety and Depression Scale – Anxiety; HADS-D – Hospital Anxiety and Depression Scale – Depression; EQ-5D – 5 questions of EuroQol 5D; EQ-VAS – Visual Analogue Scale of EuroQol 5D

Presence of current pain and its intensity correlated with pain in the past and its intensity (Table 1). The results of the questionnaires (EQ5D, EQ-VAS, HADS) are

shown in Table 2. Patients who reported current pain experienced significantly more severe symptoms of anxiety ($p < 0.01$) and depression ($p < 0.01$), had significantly worse quality of life ($p < 0.0001$) and worse self-assessed health status ($p < 0.01$). In the study group, only 3 patients (2.1%) were treated in a Psychiatric Outpatient Clinic and had been previously diagnosed with depression and/or anxiety disorder.

An association between presence of current pain and gender ($p < 0.01$), education ($p < 0.001$), having a job ($p < 0.01$), and age ($p < 0.05$) was found (Table 3). MS patients who declared presence of current pain had significantly higher degree of disability (3.5±1.8 points in the EDSS) in comparison to MS patients without pain (1.5±1.0) ($p < 0.05$). Course and duration of the disease, ARR, time from the last relapse, and current medication did not influence the occurrence of pain.

Table 3. **Association between pain and gender, age and sociodemographic factors in the examined patients with MS (N = 144)**

Factor		No data N[a]	Current pain		p[c]
			Yes N (%)[b]	No N (%)[b]	
Gender N = 144	F	0	96 (88.1)	13 (11.9)	p < 0.01
	M		21 (65.6)	11 (34.4)	
Marital status N = 141	Marriage/concubinage	3	76 (83.5)	15 (16.5)	p = 0.990 NS
	Single		41 (82.0)	9 (18)	
Children N = 141	No	3	36 (81.8)	8 (18.2)	p = 0.990 NS
	Yes		81 (83.5)	16 (16.5)	
Number of children N=97	1	0	41 (80.4)	10 (19.6)	p = 0.960 NS
	2		29 (87.9)	4 (12.1)	
	3 or more		11 (84.6)	2 (15.4)	
Education N = 140	Primary/Vocational	4	39 (100)	0 (0)	p < 0.001
	Secondary		43 (81.1)	10 (18.9)	
	Higher		35 (72.9)	13 (27.1)	
Professional activity N=140	Yes	4	50 (73.5)	18 (26.5)	p < 0.010
	No		66 (91.7)	6 (8.3)	
Age [years] M±SD Me (IQR)		0	42.4±12.1[d] 41 (19)	35.37±9.1[d] 36 (11.5)	p < 0.050[e]

[a] – data presented as number of patients; [b]– data presented as number and percentage; [c] – the chi-square test / the Fischer's exact test; [d] – data presented as mean with standard deviation – M±SD and median with interquartile range – Me (IQR); [e] – the Student's t-test / the Mann-Whitney U test

Analgesics were more often used by women (53% of those who reported pain) than men (33%) ($p < 0.01$). Other social and clinical factors did not influence usage of analgesics.

Discussion

Pain is a very common symptom in patients with MS – it can affect more than 80% of patients, as it was observed in this study. There are few reliable studies on the evaluation and treatment of pain in MS, and these studies differ in patient selection and data collection methods, which makes it difficult to compare them [7–12, 23–29]. Probably one of the reasons for so little interest in the problem of pain in MS is the doctors' focus on other symptoms of the disease and thus ignoring and underestimating this important problem.

As shown in this study, in patients who reported current pain, anxiety and depression were significantly more severe and their quality of life was lower compared to people without pain. Co-morbidity of pain and depression or pain and anxiety is supposed to exist in up one third of MS patients [23, 25–29]. This co-morbidity is also evident in some other neurological diseases. It is difficult to say whether depression is a result of pain or pain is a symptom of depression. It should also be emphasized that some other factors like fatigue or sleep disorders (not examined in the present study) may be associated either with depression or pain syndromes [25, 29–31]. This study also confirmed previous observations on the association between lack of professional activity and the presence of pain in MS [32, 33].

In patients with MS there are several types of pain, which is important for the choice of therapy. Central neuropathic pain is the most common; it could be chronic or paroxysmal (recurrent). In addition, musculoskeletal (somatic) pain and mixed pain are distinguished [12, 16].

The cause of neuropathic pain in MS is a damage to the spinal-thalamic-cortical pathways following demyelinating foci (damage to inhibitory GABA interneurons). Pain is classified as central neuropathic pain after exclusion of peripheral, somatic, and mental illness. In most patients with central neuropathic pain, neurological examination reveals surface sensory disturbances and a reduced threshold for pain sensation. The patient determines this pain as burning, tingling, numbness, needle sting.

Chronic neuropathic pain mostly affects lower limbs, rarely upper limbs and the spine [12, 16]. In this study, lower extremity pain was reported by more than one third of the subjects, while upper extremity pain – by one sixth of them.

On the other hand, paroxysmal neuropathic pain is most often characterized by trigeminal neuralgia, glossopharyngeal neuralgia, and Lhermitte's syndrome. Trigeminal neuralgia may be due to the presence of demyelinating lesions in the pons or could be caused by vascular-nerve conflict [8, 10]. In this study, trigeminal neuralgia was reported at the tie of the study by 6.3% of respondents, while 13.2% declared its occurrence in the past. These results are close to the observations of some authors [7, 23]. None of the surveyed patients reported glossopharyngeal neuralgia.

Lhermitte's syndrome is associated with the occurrence of demyelinating lesions in the posterior part of the spinal cord, most often in the cervical segment, and is described as severe pain, "feeling of the current along the spine" after the neck flexion. This symptom may also affect the lower part of the spine as well as may be felt in one or more limbs. In this study, Lhermitte's syndrome was reported by about one fifth of MS patients, as in other reports [23].

Musculoskeletal pain in MS is divided into painful muscle spasms, pain associated with spasticity, spine pain, and pain in wheelchair patients. This type of pain may also be caused by the causal treatment of MS – for instance myalgia after interferon beta has been described, while treatment with steroids during relapses causes osteoporosis, which in turn is responsible for vertebral fractures [12, 16].

Painful muscle spasms lasting less than 2 minutes can be spontaneous or induced by touch, hyperventilation, motion or stress, and occur many times within 24 hours. They are associated with damage to the upper motor neuron – lesions are mostly located in the basal ganglia, inner capsule, cerebral peduncle, medulla oblongata, and spinal cord. Painful muscle spasms result from the spread of spontaneous discharges generated by demyelinated axons. In this study, painful muscle spasms have been reported at the time of the study by one third of patients and almost half of them declared its occurrence in the past. This is a higher percentage than that reported by other authors [23].

We have also observed frequent back pain in patients with MS – in half of the respondents. The percentage reported by other authors was about 30% [23]. Back pain is aggravated by prolonged sitting or lying down. It is associated with progressive muscle weakness, spasticity, disability, and limited motility.

Headache is the most common type of mixed pain in MS. It occurs much more often than in the general population – according to the literature data, in 13–57% of patients with MS [9, 23]. Most often tension headache or migraine were described. According to the literature, the incidence of migraine in patients with MS is 2.6 times higher than in the general population [9]. In patients with MS and migraine, demyelinating lesions in fMRI were found in the substantia nigra, red nucleus, and midbrain [9]. In this study, headache was reported by half of the respondents.

In patients with MS, ocular pain is mostly associated with retrobulbar inflammation. It was present at the time of the study in 3% of our respondents and almost in one third in the past.

We found that pain was reported more frequently by women than by men, as in most other studies [5, 6, 8]. We also observed, that people who reported pain were significantly older. The correlation between older age and occurrence of pain was also noticed by other researchers [23]. There are also reports that people with MS and pain were younger [9].

Similarly to the majority of authors, the course and duration of the disease, number of relapses and time from the last relapse did not influence our results [7, 23]. Only functional status was associated with the results – people who reported pain symptoms had significantly higher EDSS scores.

Some studies have found a relationship between presence of pain and one or more MS factors such as duration of the disease, course of the disease, or disability [6, 10,

34, 35]. Some authors suggested a strong inverse correlation between relapses and pain. They found that each relapse after the second one reduced the chance of experiencing the pain by 46% and suggested that this finding might indicate a possible role of focal inflammation in the prevention of pain [36]. In turn, others found an association between pain and primary progressive course of the disease and higher EDSS score but not with the duration of MS [23]. Pain in MS may be also associated with cognitive impairment [37, 38].

Similarly to the majority of authors, presence of pain was not associated with any of medication used in the treatment of MS [9, 36]. But others described that interferon beta may induce pain associated with flu-like syndrome, myalgias and headache. Injections of the drug can also cause pain [12, 16]. Maybe lack of association between pain and medication was caused by small groups of patients treated with different immunomodulatory drugs in our study.

Pharmacological and non-pharmacological methods are used to treat pain in MS. Antidepressants (especially SSRIs and SNRIs, e.g., duloxetine, venlafaxine), antiepileptics (especially of so-called new generation, with fewer side effects, like pregabalin or gabapentin), opiates (tramadol, tapentadol), and cannabinoids (in Poland only one preparation is registered and available – cannabis extract, administered as an oral mucosal spray). Baclofen, benzodiazepines, gabapentin, and carbamazepine are used for the treatment of painful muscle spasms. In spasticity, it is most often recommended to use tizanidine, baclofen (in severe cases in the form of baclofen pump), cannabinoids, botulinum toxin injections. When planning a pharmacological treatment for pain in patients with MS, co-occurrence of other diseases, especially depression and anxiety syndrome, should be considered. Also, one should remember about non-pharmacological methods, including relaxation techniques, cognitive-behavioral programs, physiotherapy (electrotherapy, magnetic field, laser therapy, light therapy, ultrasounds, thermotherapy, massages), acupuncture, or interventional methods (blockades, thalassotherapy, neuromodulation). Treatment of pain in MS should be complex and the use of non-pharmacological methods allows to limit the intake of analgesics [12–16].

Conclusions

Pain in MS patients is associated with anxiety and depression, and worse quality of life. Female sex, older age, greater disability, worse education, and lack of professional activity predispose to the occurrence of pain in MS patients.

People who take care of MS patients should consider high prevalence of pain in this disease and its association with quality of life. Also, such co-morbidities like presence of pain and depression or anxiety may be considered when symptomatic treatment is established. One should remember about referring patients with such symptoms to a psychiatrist or psychologist.

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