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Review article

Symptomatology and pathogenesis of different types of pain in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is a progressive disease of the central nervous system. It is characterized by disseminated foci of demyelination, which are responsible for the diverse clinical picture of MS. Pain is a frequent but underestimated symptom of multiple sclerosis. It is estimated to affect 29–86% of MS patients in various stages of the disease and severely influences rehabilitation and quality of life. The pain experienced by MS patients is generally caused by nervous system damage during the course of the disease process and can usually be characterized as central neuropathic pain (less frequently as peripheral or nociceptive pain). The most frequent symptoms include dysesthetic extremity pain, painful tonic spasms, Lhermitte's sign, trigeminal neuralgia, headaches and low back pain. This paper discusses the probable mechanisms behind the development of pain in MS, the prevalence, classification, types of pain, as well as the most effective treatment methods.

1. Introduction

Multiple sclerosis is a progressive, inflammatory demyelinating disease of the central nervous system (CNS) of an unknown etiology [1]. Its prominent feature is the presence of disseminated foci of demyelination, mainly in the white matter; in most cases, demyelination occurs periventricularly. The complex pathomechanism of the disease and its disseminated nature make both the clinical picture and the course of MS exceptionally diverse. The symptoms include movement, visual and sensory disturbances, cerebellar symptoms and sphincter control disturbances [1]. Pain is a frequent yet underestimated symptom of multiple sclerosis. For years, multiple sclerosis was thought of as a painless condition; however, as early as 1872, *Charcot* described pains in the shoulder and pelvic girdle region accompanying the disease [2]. In 1924, Lhermitte described the phenomenon of an electrical-like sensation running down the back, which is characteristic of MS [1–3]. However, the theory of a painless course of multiple sclerosis was only definitively invalidated at the close of the XX century. Recently, pain has been recognized as a factor that significantly affects quality of life [3–5]. The study conducted by Warnell [6] showed that among MS

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patients suffering from various types of pain, 40% had difficulty working, 44% had difficulty sleeping and 34% reported troubled interpersonal relationships [6].

2. Prevalence of pain

Pain is rarely observed at the initial stages of MS and is estimated to be its first symptom in only 1% of patients [3,7,8]. However, it frequently accompanies the advanced stages, being a nagging symptom that severely limits the patient's functioning, treatment and rehabilitation. Pain is estimated to occur in approximately 29–86% of patients at different stages of MS [3,8–12]. Pain present in the month preceding the evaluation was diagnosed in 53–79% of patients, whereas pain during the evaluation was present in 43–54% [5,8–11]. In 15% of patients, pain is acute (usually paroxysmal), but it is chronic in the straight majority [6,7,10]. Kalia et al. and Khan et al. estimated that chronic pain is present in 64–69% of MS patients [4,11]. According to the majority of authors, central pain is the most frequent type of pain [3,9–12]. In Osterberg's study, this type of pain was reported by 27.5% of patients [12]. However, Svendsen et al. reported that muscular (39.6% of patients) and articular pain (41.9%) are among the most frequent pain symptoms [5].

In a Polish study, Fryze et al. diagnosed various types of pain in 70.2% of MS patients [2]. In 8% of these patients, it was their first symptom of multiple sclerosis. The most frequently occurring symptoms were dysesthetic extremity pain (45%), back pain (34%) and painful tonic spasms (22%). Chronic pain was diagnosed in 60% of patients [2]. On the other hand, Kwolek et al. found various types of pain in 83% of patients (mainly painful muscle spasms and painful paresthesia) [13].

This large discrepancy in the results stems from the different definitions of pain that were adopted in the studies, different methods of pain assessment, and the different stages of disease progression and disability in the studied populations. It is usually assumed that pain affects approximately half of MS patients, and all studies confirm that it is more frequent in people with multiple sclerosis than in those who are not affected by the disease [3,7–13].

The frequency of pain increases with the progression of MS and may be the dominating syndrome in its advanced stages. However, it should be noted that pain may occur at all stages of MS, and it is reported by as many as 11–23% of newly diagnosed patients [4,9–11]. Risk factors for pain in MS include older age, female gender (F/M = 2.2/1), longer duration of illness, higher EDSS score, concomitant depression or mental disorders, unstable course of illness, lower education and primarily- or secondarily-progressing type of MS [3,4,8,12,14].

3. Pathophysiology of pain in patients with multiple sclerosis

It is believed that most MS-related pain symptoms are of a neuropathic central type [3,8,15,16]. Neuropathic pain caused by peripheral nervous system damage, nociceptive pain caused by irritation of peripheral nerve endings in the nociceptive system and psychogenic pain are less frequent [3,15,16].

Central pain results from a primary CNS injury, but its pathomechanism has not yet been fully elucidated. The demyelination and axonal damage in the brain and spinal cord lead to distinct mechanisms and central hyperexcitability [14–16]. The pain is associated with damage of the thalamus or the parietal cortex, in which projection areas for the sensory tract are located, and it is usually secondary to lesions in the spino-thalamo-cortical pathways [23].

It is postulated that the lack of normal afferent impulses in the area of the lesion causes quantitative and qualitative changes in sodium and calcium channels, which increase neuronal excitability [8,14–17]. The pain symptoms are thought to result from the ephaptic spread of spontaneous ectopic discharges generated by demyelinated axons. Consequently, the spinal cord is constantly inundated with false information about painful stimuli, which in fact are non-existent [17]. The CNS has demonstrated the ability to modify its functions, which causes an enormous variety of pain symptoms depending on the time and place of their occurrence, pathological processes, individual variability, age and many other factors [17,18]. One of the most important roles in these processes is played by NMDA (N-methyl-D-aspartate) receptors for excitatory amino acids and NK-1 neurokinin receptors situated postsynaptically in the posterior horns of the spinal cord [27]. There is evidence that NMDA receptors take part in triggering the long-term excessive pain response to a slight, repetitive irritating impulse, due to the 'wind-up' effect [15–18]. This phenomenon is similar to the kindling effect observed in epileptic foci and is responsible for the creation of abnormal discharges [16,17]. An increased calcium ion concentration in cells leads to a rise of enzymatic activity. This result, for example, in the enhanced synthesis of nitrogen oxide, which takes part in the neuropathic pain mechanisms, most likely via an intensified release of neurotransmitters from presynaptic terminals [18,27].

Central pain involves large areas such as the whole side of the body and is usually one-sided. It is not associated with movement disturbances but may be aggravated by external stimuli. It is characterized by acute, burning or stinging sensations, sensory disturbances and poor (or no) response to standard analgesic therapy [8,18]. Central pain usually lasts for a short time and may take the form of a seizure. However, it may also be chronic with recurring relapses. It is usually moderate in intensity but can aggravate significantly during the attacks and in response to heat, cold or touch. In almost all cases, the pain is associated with other symptoms of CNS damage such as sensory disturbances, paresis or ataxia [8,17,18]. Central pain includes psychogenic and overlapping pain [8].

Peripheral neuropathic pain is less frequent in multiple sclerosis. In most patients, it manifests itself as a chronic, searing, burning pain of a dysesthetic type (unpleasant sensation arising spontaneously or following a stimulus) or as a paroxysmal pain that is usually severe, short-lasting, stinging and ''electric-like'' [16]. Its onset is spontaneous and may be triggered by movement. It is frequently accompanied by mechanical or thermal allodynia (pain in response to touch or hot/cold temperature), hyperalgesia (increased

sensitivity to pain), hyperpathia (increased pain reaction to mildly painful stimulus with delayed effect, radiating outside the damaged nerve and lasting longer than the stimulus), hypoalgesia (a decreased sensitivity to painful stimuli) [17–19].

Muscular and articular pain may be associated with musculoskeletal complains. It is usually nociceptive but may also result from central pain. Some types of MS-related chronic pain may not be ascribed to any of the categories above. Headache in patients with MS is a prevalent example of this type of pain condition, which involves a complex mixture of neuropathic, inflammatory and musculoskeletal mechanisms [3].

4. Classification and types of pain

The literature provides different classifications of pain types in multiple sclerosis. They are usually divided into primary and secondary pain syndromes. The primary types of pain are directly associated with the disease and its pathology (painful tonic spasms in the extremities, Lhermitte's sign, trigeminal neuralgia, glossopharyngeal neuralgia). Secondary syndromes result from the already-existing symptoms of the disease (radiculalgia and low back pain are secondary to faulty posture and gait disturbances due to limb paresis or other movement disturbances) [1].

With regard to duration, pain syndromes are divided into acute and chronic [3,12,18]. It is postulated that most types of acute pain syndromes are associated with the essence of the disease, while their pathophysiology is associated with lesions located in the pons, brainstem and the nerve itself. Such syndromes include paroxysmal burning pain of the lower extremities, painful tonic spasms of extremities and Lhermitte's sign. Chronic syndromes include painful lower limb dysesthesia and back pain.

The World Health Organisation (WHO) distinguishes three types of pain occurring in MS: neuropathic, somatic and psychogenic [20].

In 2008, O'Connor et al. [3] suggested the most widely used classification of pain according to its pathophysiology (Table 1).

In 2013, Truini et al. proposed a new mechanism-based classification of pain associated with MS (Table 2) [21].

Table 1 – Classification of pain conditions associated with multiple sclerosis (adapted from O'Connor et al. [3]).

Pain classification	Examples
Continuous central neuropathic pain	Dysesthetic lower extremity pain
Intermittent central neuropathic pain	Trigeminal neuralgia Lhermitte's sign
Musculoskeletal pain	Lower back pain Muscle spasms Painful tonic spasms
Mixed neuropathic and non-neuropathic pain	Headache

5. Painful dysesthesias (dysesthetic extremity pain)

Painful dysesthesias belong to the category of continuous central neuropathic pain and usually affect the lower extremities; however, they may also involve the trunk, upper extremities or head. In a study by Osterberg, 87% of dysesthesias were located in lower and 31% in upper extremities. They were more frequent in patients with the primary progressive type of MS, mostly bilateral (76%), with 88% occurring during the day [12]. Only 2% of patients complained of paroxysmal pain. The pain was intense with small to moderate spontaneous variation [12].

Painful dysesthesia is the most frequent type of pain occurring in MS [5,7,10]. Its prevalence is estimated at 17–26% [3,9,10]. Fryze et al. found this type of pain in 45% of patients [2]. Painful dysesthesias are described by patients as a ''continuous burning pain'' (searing, burning, tingling, piercing, ''electric-like''), which worsens with exposure to heat or weather changes [5,7]. Allodynia and hyperalgesia are typical as well.

This type of pain is typically bilateral, affecting the legs and feet; it is usually worse at night and can be exacerbated by physical activity [3–5]. It must be distinguished from other conditions that could cause bilateral extremity pain, including musculoskeletal pain and pain associated with peripheral neuropathy [3,5–7].

Because painful dysesthesias are a type of neuropathic central pain, antiepileptic and antidepressant drugs are administered. The recommended first-line treatments include amitriptyline and other tricyclic antidepressants, as well as gabapentin and pregabalin [22–27]. Among all antidepressant drugs, the tricyclic antidepressants and especially amitriptyline, play the most crucial role. If amitriptyline causes some adverse effects, nortriptyline should be used [22,23]. In addition, some new generation antidepressant drugs (selective serotonin-reuptake inhibitors, SSRI) show efficiency comparable to the performance of classical antidepressants, with the added benefit of a lower rate of side effects [23–27]. The best therapeutic results have been observed for duloxetine and venlafaxine [28]. The antiepileptic drugs used so far, such as carbamazepine and valproic acid or phenytoin, are currently believed to be less efficient than the new generation drugs. Most studies are aimed at assessing the effectiveness of gabapentin and pregabalin [22–28]. Lamotrigine and topiramate may also be effective [22–28]. If antidepressant and antiepileptic drugs do not bring about satisfactory results in the treatment of central pain, the European Federation of Neurological Societies (EFNS) recommends starting opioids. However, none of the studies confirmed their effectiveness in the treatment of pain in multiple sclerosis [28]. A positive effect was observed for cannabinoids, as evaluated in several randomized controlled trials [29–31]. Most of the studies confirmed the effectiveness of these drugs in relieving chronic and paroxysmal pain, especially in painful dysesthesias. However, it should be borne in mind that the primary endpoint of these studies was the evaluation of spasticity [29–31]. Cannabinoids are currently recommended as a second-line treatment in some cases of treatment-resistant pain. When

Table 2 – Mechanism-based classification of pain in multiple sclerosis (according to Truini et al. [21]).

Types of pain	Possible mechanisms
Neuropathic pains	
Dysesthetic extremity pain	Deafferentation pain secondary to lesions in the spino-thalamo-cortical pathways
Trigeminal neuralgia	Paroxysmal high-frequency discharges ectopically generated by intra-axial inflammatory demyelination and extra-axial mechanical demyelination of the trigeminal primary afferents
Lhermitte's phenomenon	Paroxysmal neuropathic pain due to high-frequency ectopic impulse generated by demyelination of the dorsal column primary afferents
Nociceptive pains	
Pain associated with optic neuritis	Nerve trunk pain originating from endoneural inflammation intraneural nociceptors of the *nervi nervorum*
Musculoskeletal pains	Nociceptive pain related to postural abnormalities secondary to motor disturbances
Back pain	Consequence of postural anomalies
Migraine	Nociceptive pain favored by predisposing factors or secondary to midbrain/periaqueductal grey matter lesions
Tension-type headache	Probably coexisting conditions
Treatment-induced pains	Interferon beta (flu-like symptoms, myalgias, and headache) Glatiramer acetate (pain at the injection site) Corticosteroids (osteoporosis and secondary pain)
Mixed pains	
Painful tonic spasms	High-frequency discharges ectopically generated by demyelinating lesions in the cortico-spinal pathways induce tonic spasm which, in turn, induce ischemic muscle pain
Spasticity pain	Mixed pain secondary to lesions in the central motor pathways but mediated by muscle nociceptors
Other pains	Psychogenic and overlapping pain Pain in other illnesses not related to MS

pharmacotherapy is ineffective, various forms of surgical treatment are used, including the following: damaging certain zones of the thalamus or DREZ (dorsal root entry zone) lesions by microsurgically cutting the dorsal roots in the spinal entry area. Today, these methods are being replaced with the stimulation of specific structures of the nervous system [30,31].

6. Lhermitte's sign

Another type of central pain in MS is Lhermitte's sign, which is usually observed in the initial stages of the disease and is more frequently observed in patients with primary progressive MS [8]. Al-Araji and Oger describe it as 'a transient short-lasting sensation related to neck movement felt in the back of the neck, lower back or in other parts of the body' [32]. It is a feeling described as an 'electric shock', vibration and tingling lasting less than 2 s, triggered by neck flexion with immediate relief upon cessation of the flexion. It has been associated with lesions in the posterior columns of the cervical spinal cord and is thought to be caused by the hypersensitivity of demyelinated cervical sensory axons to stretching. The prevalence of Lhermitte's sign ranges from 9% to 16% during the period with no relapses and approximately 40% during MS exacerbation [3,7,32–35]. Fryze et al. observed this symptom in 26% of patients [2]. In most cases, Lhermitte's sign remits within 4–6 weeks. The high frequency of central pain evident in various subtypes of MS places it among the most frequent symptoms of the disease [3,8,32–35].

The treatment of Lhermitte's phenomenon is similar to that of other central neuropathic types of pain. One controlled study showed a positive effect of intravenously injected lidocaine and oral mexiletine [36].

7. Painful tonic spasms (PTS)

Painful tonic spasms (PTS) are diagnosed in 11–15% of MS patients [3,7,9,10]. The seizure-like, involuntary dystonic spasms may be one- or two-sided and are usually brought on by movement. Previously, they were referred to as 'painful tonic seizures'. However, electroencephalography showed that there were no epileptiform discharges during such an episode; thus the term was abandoned [37]. The attacks are often preceded by an aura. In addition to movement, they are also brought on by touch, hyperventilation or emotions [1,2,38]. They usually occur several times a day and last for less than 2 min [1–3,38]. However, they may also occur at night and disturb sleep. They usually have a stereotypical course and can be chronic or recurrent, with repeated episodes every several days or months. In some cases, the pain directly precedes the spasm, which indicates that the pain may not be caused by the muscle spasm itself. Additionally, the spasms do not necessarily have to be painful [1,2]. MRI showed lesions in the areas of basal ganglia, internal capsule, cerebral peduncles, medulla and spinal cord in patients with attacks of painful tonic spasms [37]. It is postulated that the symptoms result from ephaptic spreading of spontaneous discharges triggered by demyelinated axons [37,38].

Painful tonic spasms may be managed with antiepileptic drugs including carbamazepine, phenytoin and gabapentin, as well as intravenous infusions of lidocaine [27,28]. Some authors suggest injecting botulinum toxin [23,24]. Botulinum toxin injections may also be used if a patient is suffering from localized, focal spasticity. Injections are repeated every three to four months.

8. Musculoskeletal pain

Musculoskeletal pain, also known as nociceptive pain, is the most common pain in multiple sclerosis [3,4,11,15]. Nociceptors are free nerve endings located in all types of body tissues, except the brain, that detect stimuli and interpret them as pain. This pain is caused by tissue damage detected by the nociceptors, while neuropathic pain is related to nervous system lesions [3]. Musculoskeletal pain is usually secondary to muscular weakness, spasms, spasticity and imbalance. It is most often seen in the hips, legs and arms and is most often seen when muscles, tendons and ligaments remain immobile for a long time.

Lower-back pain and neck pain can occur as a result of irregular, asymmetric movement patterns and postures, and changes in muscle strength, tone (spasticity) or length (contracture). Pain associated with spasticity and muscle spasms can include muscle aching, cramping or pulling [4]. These symptoms are often worse at night or early in the morning [3].

The prevalence of low back pain is 10–20% [4,7,10,39]. The observed prevalence depends upon the selected sample, but it increases in older people. Asymmetric posture and difficulty in ambulation can be predisposing factors to back pain. Lumbar spasticity is also a possible cause of lower-back pain, due to increased muscle tension and its effect on lumbar spine joints [39].

It is postulated that pain within muscles and joints is associated with musculoskeletal complaints; however, it may also be a manifestation of central pain [5,12].

Secondary musculoskeletal pain can also be caused by the drugs used to treat MS. Interferon beta frequently causes muscular pain, while long-term steroid treatment may result in osteoporosis and, consequently, vertebral compression fractures [3,7,12].

Pharmacotherapy of musculoskeletal pain is usually started with non-steroid anti-inflammatory drugs, which bring the desired effect only at the initial stage of treatment. The basic procedure in this case is physiotherapy aimed at improving the stability of proximal muscles and teaching individuals to maintain good posture while standing and sitting. Electrotherapy, cryotherapy, magnotherapy and hydrotherapy belong to the most frequently used physical methods [40,41]. Electrotherapy is mainly used in symptomatic treatments to treat pain and excessive spasticity.

9. Trigeminal neuralgia

Trigeminal neuralgia (TN) is most likely the best known neuropathic pain syndrome in multiple sclerosis. It appears in the trigeminal innervation area and is characterized by paroxysms of shooting, piercing, stinging, 'electric-like' pain. The pain has a sudden onset, is extremely strong and is often accompanied by a characteristic facial grimace. It lasts from several to several dozen seconds, exceptionally up to a few minutes, and disappears. The pain may occur spontaneously or be caused by stimuli in specific areas of the face or mouth. A gentle touch or irritation of the so-called trigger zone causes pain [42]. The risk of the appearance of the symptomatic TN is 20 times higher in patients with multiple sclerosis than in the general population [43]. Studies show that the prevalence of trigeminal neuralgia in patients with multiple sclerosis falls in the range between 1.9% and 6.3% [10,12]. The clinical symptoms are the same as in the idiopathic form, with no dysesthesia and the presence of points triggering the paroxysms of pain. Neuralgia occurs most often (in approximately 90% of patients) in the area of the V2 and V3 branches [44]. Post-mortem studies show that trigeminal neuralgia in patients with multiple sclerosis is related to demyelination plaques in the pons. Studies with the use of MRI indicate one- or two-side demyelination plaques in the course of nerve V [45]. High signal lesions along the trigeminal nerve have been observed both in the pons [44] and the brainstem nuclei [46]. Although it occurs relatively rarely in patients with multiple sclerosis, trigeminal neuralgia is very painful and has a significant impact on the patients' quality of life [47].

Glossopharyngeal neuralgia (a severe pain in the posterior pharynx, tonsils and the base of the tongue) is extremely rare in patients with MS [48].

Carbamazepine is the first-line drug for the treatment of trigeminal and glossopharyngeal neuralgia in the course of multiple sclerosis, as in the case of the idiopathic forms [45–48]. However, it can cause side effects, leading specifically to a reversible exacerbation of multiple sclerosis symptoms [49]. Alternatively, oxcarbazepine or lamotrigine and gabapentin can be used [27,28].

10. Headaches

Worldwide, almost 50% of general population suffers from at least one of the following types of headache: tension headache, migraine, cluster headache or chronic daily headache [50]. Therefore, it may be presupposed that headaches will also be more frequent in patients with MS. From the neurological point of view, the MS-related inflammatory demyelinating lesions may evoke headaches due to damage of the pathways associated with the pathology of migraine, tension-type headache (TTH) and trigemino-autonomic cephalalgia.

The most recent studies (mainly prospective and case–control ones) conducted in various countries according to the Guidelines of the International Headache Society of 2004, showed that the prevalence of TTH is similar in patients with MS and in the control group (TTH was reported by 21–48% of patients with MS) [51–53].

The relationship between the onset of MS and TTH was assessed in one study [54]. Nearly two thirds of patients experienced their first headache before the onset of multiple sclerosis [54]. Because headache generally precedes the onset of MS and is not significantly modified by the disease, it seems that in most MS patients TTH may not be considered a reactive or secondary disorder. One could agree with the hypothesis that TTH, although not necessarily more frequent in patients with multiple sclerosis than in healthy control group patients, may be caused by demyelination damaging the tracks engaged in TTH pathogenesis.

A possible relationship between migraine and multiple sclerosis was suggested over half a century ago by Compston and McAlpine [55], who reported that 2% of MS patients had experienced migraine during the 3 months preceding the onset of the disease. The results were later confirmed in a retrospective review of 1113 MS patients, 18 (1.6%) of whom complained of a migraine attack preceding MS onset and 26 of whom experienced headache during the aggravation of MS. They frequently showed symptoms of a posterior fossa mass lesion [56]. The coincidence of time between migraine and the bout of multiple sclerosis suggests that migraine headaches may be a secondary symptom in some MS patients.

A double-blind study with two control groups, conducted before interferon therapy was introduced, showed that 21% of MS patients had migraine compared to 10% in patients with neurological diseases other than MS (control group) [57]. The beginning of headaches preceded symptoms of MS by an average of 7 years [57]. In addition, not all studies revealed a higher prevalence of migraine in MS patients [58,59].

Studies using scans suggest a greater probability of engagement of the brainstem and diencephalon structures in migraine-suffering MS patients in comparison to those patients who do not suffer from migraines [60,61]. Another study also showed a greater frequency of gadolinium-enhanced lesions in the brainstem of headache-suffering patients [62], which indicates the potential participation of these structures in the generation of migraines. On the other hand, no differences were found in the number or distribution of T2 lesions or gadolinium-enhanced lesions between the groups of multiple sclerosis patients with and without migraine [63].

Available data indicate that the age of MS onset, the duration of the disease and the degree of patient's disability are similar in MS patients with and without migraines [51,57,62,63]. On the other hand, most researchers [52,53,63], though not all of them [54], report a correlation between migraine and relapsing remitting multiple sclerosis. Women are overrepresented in the MS-migraine group, in comparison to the MS-no headache group [63].

The standard treatment for migraine and tension headache is usually effective.

11. Pain in retrobulbar optic neuritis

Retrobulbar optic neuritis is the first symptom of multiple sclerosis in 20% of cases [64]. It is characterized by blurred vision or the complete loss of vision. Color vision deficiency and contrast sensitivity frequently decrease proportionally to visual acuity loss. Visual field defect (especially central scotoma) is typical of optic neuritis [65]. The symptoms subside suddenly, within 10–20 h. They are accompanied by pain, in most cases originating from behind the eye and frequently preceding the disturbances of visual acuity. Ninety percent of patients with optic neuritis suffer from periocular pain, which may be present before the onset of vision loss [66]. However, patients may not initially complain of pain. It may be helpful to ask if the pain is associated with eye movements. The pain may even involve the whole head and range from moderate to severe. It usually accompanies the visual symptoms (at least initially). MRI of the optic nerve reveals lesions of demyelination of approximately 1 cm in diameter within the course of the optic nerve (there may be several of them) [67]. In two-thirds of cases, the lesions are located in the retrobulbar section of the optic nerve. Rapid visual recovery occurs within 2–3 weeks after the onset of symptoms and the symptoms stabilize within several subsequent months [22]. Approximately 70–80% of patients experience a complete recovery of vision. In the rest of the patients, color vision deficiency and contrast sensitivity remain, while the visual acuity is normal. A minority of patients may experience permanent visual disturbances, including blindness.

First-line drugs for the treatment of pain in retrobulbar optic neuritis are corticosteroids.

12. Psychogenic pain

The cause of psychogenic pain has not been established. It is believed to be associated with emotional and behavioral factors and is triggered by psychological factors, thus it tends to be treated as central pain [6–8]. It may resemble any type of organic pain, even if morphological changes that could cause the pain are excluded. It is frequently associated with an emotional conflict or psychosocial problems. Psychogenic pain is also often associated with depression, sleeping disturbances and fatigue syndrome [68,69]. As a consequence of the persistent pain, the patient usually draws more attention from family and healthcare providers. The origin of the psychogenic pain is related to the transmission of impulses from the limbic system responsible for emotions to the brainstem nuclei, which consequently leads to trigeminal vascular reflex causing vasogenic headaches and other pain-related reflex phenomena [8]. Psychogenic pain may be local or generalized. Local pain is closely limited, usually to one or several small areas. It is frequently located at the surface of the face or head. Generalized pain may involve the whole body, half of it, or just one limb [3–9]. Its prevalence in multiple sclerosis is highly individual and hard to assess.

13. Overlapping pain

Overlapping pain is a sum of the psychological reaction to pain and the physical pain resulting from the illness or accompanying it. It increases the patient's sense of illness and is supposed to convince people around the patient of the immense suffering he is going through and the seriousness of the condition. This attitude is frequently used to pursue certain claims or judicial decisions.

14. Other types of pain in MS

It should be borne in mind that a patient with multiple sclerosis may also present with pain in internal organs (bladder infection, gastrointestinal disturbances). Additionally, it must not be presupposed that pain is always caused by MS because there may be a different cause requiring independent treatment. The adverse effects of the pharmacotherapy should also be taken into account. They may include the following: flu-like symptoms,

headaches, muscular pain (interferon beta), tightness or pain in the chest (glatiramer acetate) or glucocorticoid-induced osteoporosis with frequent vertebral compression fractures.

Conflict of interest

None declared.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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