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## **Non-motor symptoms in Multiple Sclerosis**

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### **Abstract**

Multiple sclerosis (MS) is the most common disease of the brain and spinal cord in young people. European doctors started talking about a new epidemic: multiple sclerosis came out on top among the diseases leading to disability of young people. In the course of the disease, an autoimmune inflammation occurs, which causes damage to the myelin layer surrounding the nerve cells. Damage occurs in numerous foci of the brain and spinal cord. Currently, there are more than 2 million patients with MS in the world [1].

Multiple Sclerosis (MS) is an autoimmune disease that leads to a demyelination process. The clinical picture of the disease is complex, and an important part of it are the non-motor symptoms, such as: dysphagia, sleep disorders, fatigue and pain, and the bladder function disorders. Some questionnaires were used to assess some of the dysfunctions listed above.

The treatment of non-motor symptoms in patients with multiple sclerosis is based on the use of a various forms of therapy: pharmacotherapy, physiotherapy and surgical treatment. The aim of these is to improve the quality of life of the patient.

The aim of this work is to present non-inguinal disorders occurring in patients with MS. The bibliographic databases were searched: PubMed, MedLine, Polish Medical and others. Bibliography. Articles in Polish and English were used.

**Key words: multiple sclerosis, non-motor symptoms, dysphagia, fatigue in MS**

### Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system with an autoimmune background, classified into the group of demyelinating disorders. The disease is more often diagnosed in women, and the peak of incidence falls in the period of full life activity - between 20 and 30 years of age. The literature reports that the incidence is 3-5 cases per 100,000. The number of patients in Poland is not well known, there is no register and the Polish Society of Multiple Sclerosis only provides estimated numbers of patients [2, 3, 4, 5, 6].

In the course of multiple sclerosis, demyelination and axonal loss occurs. The etiology of the disease has not been fully understood. It is believed that the occurrence of this disease is influenced by many factors – such as environmental, exogenous as well as genetic [2].

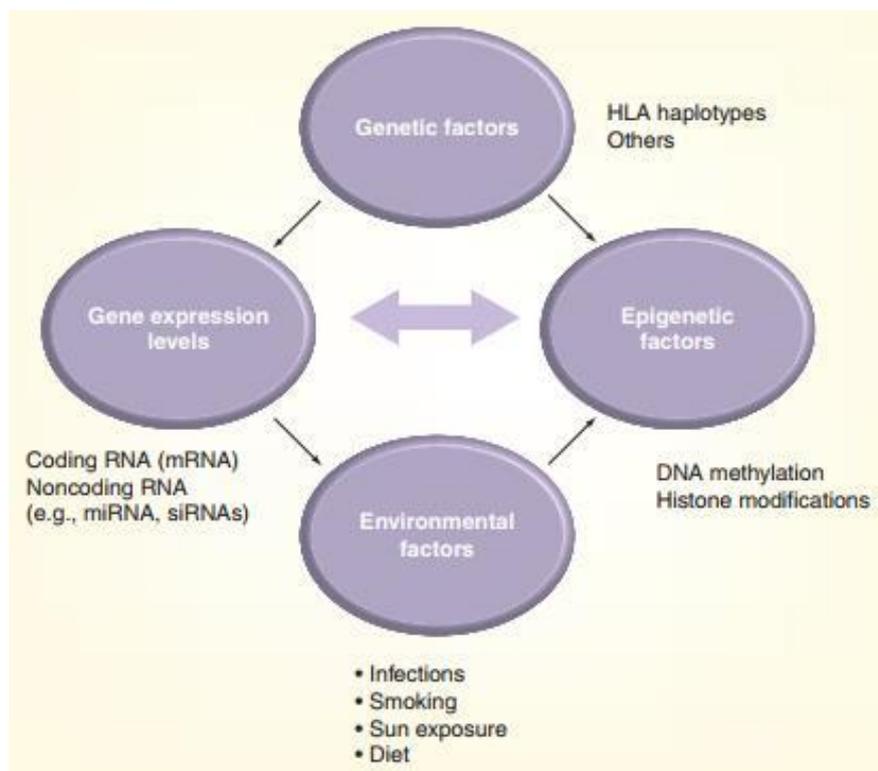


Figure 1. Potential causes of the pathogenesis of multiple sclerosis [7].

The disease is characterized by various clinical symptoms, among which one can distinguish motor symptoms - paresis, the presence of pathological reflexes, increased muscle tone. Neurological deficits also cause disorders of the bladder function, swallowing as well as speech which are non-motor symptoms of this disease. A significant proportion of patients also suffers from excessive fatigue and pain. In the case of 40% of patients, the onset of MS precedes optic neuritis [2, 8].

The course of MS is different, therefore the clinical forms of the disease are distinguished: secondary-progressive and relapsing-remitting, primary-progressive and benign. The disease is incurable and leads to disability, which is why comprehensive treatment of patients with MS is important, which includes: causative treatment, treatment of relapses, symptomatic treatment and appropriately selected rehabilitation procedures [2, 6].

### **Dysphagia**

Swallowing disorders in MS are associated with the weakening of the active muscles during swallowing, which progresses with the development of the disease. Such factors as dysfunctions within the brainstem and cerebellum, cognitive dysfunction or paresis of the lower cranial nerves are also affected. According to research, dysphagia is present in 33-43% of patients with MS [9, 10, 11].

The first symptoms reported by patients are mainly: cough, difficulty in swallowing, excessive salivation, choking during meals, gag reflex or feeling of scratching in the throat [9, 12]. In the study by Alali et al. [13] the most common problems associated with dysphagia reported by patients with MS were: cough during or immediately after a meal (66%), sticking food to the throat (63%). 17% of subjects were drooling and sticking to the mouth.

Swallowing disorders in patients with MS are very dangerous, as they may lead to aspiration pneumonia, malnutrition and dehydration and even death. This also adversely affects the quality of life of patients with MS. In the diagnosis and treatment of dysphagia, an interdisciplinary team of specialists takes part, consisting of: a neurologist, ENT specialist, physiotherapist, dietitian, gastrologist and speech therapist [12, 14].

Diagnosis of dysphagia is based on a physical examination, a neurological assessment and diagnostic examinations - videofluoroscopy, fiberoptic endoscopic examination of swallowing (FEES). Not all centers have an access to such diagnostic equipment, therefore questionnaires are also useful in diagnosing swallowing disorders [15].

One of the questionnaires used to assess dysphagia is DYMUS (Dysphagia in Multiple Sclerosis). It consists of a 10 questions and assesses dysphagia of both solid and

liquid foods. The affirmative answer to at least 1 question indicates the occurrence of dysphagia [15].

Another questionnaire is EAT-10 (Eating Assessment Tool 10). The patient answers 10 questions and each item is graded from 0 to 4 points. Obtaining the 3 and more result suggests the occurrence of swallowing disorders [16].

One of the forms of treatment of this disorder is the rehabilitation of swallowing. It includes mouth and tongue exercises to improve the range of movement and muscle strength. An appropriately modified diet is also important - the introduction of foods with high protein content, mineral salts and vitamins. It is also recommended to eat meals in a liquid and pasty form. In the case of failure of the above-mentioned methods of therapy, surgical treatment - percutaneous endoscopic gastrostomy or other enteral nutrition methods [10, 17].

### **Fatigue**

Fatigue, as a symptom in multiple sclerosis, can have a different severity and duration. Literature reports that almost 80% of patients with MS reports fatigue during the first year of the disease. It follows that this is a common symptom, with 55% of patients claiming to be one of the most troublesome symptoms [18, 19].

Along with the duration of the disease, fatigue is reported by a growing number of patients. Although the disorder affects a significant number of patients, its pathomechanism is still not fully understood. Fatigue can be primary or secondary. Factors affecting the occurrence of primary fatigue includes [20]:

- disorders of the central nervous system, as a result of demyelination and the inflammatory process neuron functions are disturbed,

- neurotransmitter disorders,
- immunocompromised,
- endocrine factors, disorder of the hypothalamic - pituitary - adrenal axis

Secondary fatigue arises as a result of other disorders, such as [20]:

- sleep disorders,
- some medicines,
- pain,
- psychological factors – depression.

Fatigue affects the patient's quality of life, it leads to withdrawal from social life and resignation from a physical activity because of the fear of exacerbating symptoms. Special questionnaires are used to diagnose fatigue. The most commonly used are: Modified Fatigue

Impact Scale (MFIS), Fatigue Severity Scale (FSS) and Chalder Fatigue Scale (CFQ). It is very important to quickly diagnose a problem and take appropriate therapeutic steps, because chronic fatigue can lead to other problems such as depression. In the treatment of tiredness, as in the case of sleep disorders, pharmacological and non-pharmacological methods are used. The literature lists several drugs that can be used in this disorder, but amantadine is the most commonly used one [21].

As in any therapy, in the therapy of fatigue it is important to modify the lifestyle. Physical activity can not be given up by the patient. However, activities should be adapted to the patient's ability, it need to avoid the overworking of the body and it is important to balance the time of an effort and rest. Properly selected activity is essential for improving the comfort of life. In the scientific literature, there are researches confirming the positive effect of cooling the body before and after physical activity to reduce the level of fatigue. However, the evidence is limited, which makes it necessary to conduct further research on this subject. Fatigue therapy is also helpful in occupational therapy. In addition to improving manual efficiency it has the relaxation effect. Among the forms of therapy for patients with MS, application of water therapy can be found. According to data available in the literature, exercises in water have a positive effect on reducing fatigue and improving the quality of life [18, 19, 22].

Complex rehabilitation procedures combined with psychotherapy and symptomatic therapy are currently considered to be the most effective way of symptomatic management in patients with MS. Considering the complex effect of fatigue on the body, an interdisciplinary rehabilitation approach is required, which includes both pharmacological and non-pharmacological methods. At the same time, further research is needed regarding the impact of rehabilitation interventions in the therapy of fatigue in patients with MS.

### **Sleep disorders**

Sleep disorders are non-sharply manifested symptoms of the MS that significantly affect the quality of life of patients. These disorders are a complex problem and affect about 60% of patients. Unfortunately, the pathophysiology of sleep disorders has not been fully understood. Among the causes of their occurrence are disorders of melatonin pathways as well as disturbed level of proinflammatory cytokines. Their increased level may cause disorders of the body's homeostasis, which in turn leads to circadian rhythm disorder. Among the factors affecting the occurrence of sleep disorders, the undesirable effects of some drugs are mentioned [23]. The most commonly reported disorders are:

- insomnia, during which there are difficulties with falling asleep, waking up and early waking up
- restless legs syndrome, it is a condition manifested by involuntary movement of legs constantly during sleep
- narcolepsy, it is a disorder consisting of several times a day falling asleep against will
- breathing disorders during sleep, the most common of them is sleep apnea, which involves stopping or reducing amount of breathing during sleep.

For the diagnosis of sleep abnormalities, questionnaires such as the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS) are used. PSQI evaluates seven areas of sleep: subjective sleep quality, sleep delay, sleep time, normal sleep efficiency, sleep disorders, the use of a sleeping pills and daytime disorder during the last month. The patient gives from 0 to 3 points, where 0 means that the disorder does not occur. ESS, on the other hand, assesses the likelihood of a patient falling asleep in eight typical situations from everyday life. Also in this questionnaire the patient gives from 0 to 3 points. A score below 10 points is the correct result, while over 14 points to excessive sleepiness. In the diagnosis of sleep disorders, the polysomnography method is used. It is a technique that allows the assessment of brain function during sleep. It allows you to assess individual stages of sleep. It is particularly useful in diagnosing breathing disorders during sleep, including sleep apnea [24, 25].

Difficulties in recognizing the causes of sleep disorders are also a problem in their treatment. Beneficial effects are brought by the use of a pharmacological agents such as sleep inducing pills or melatonin supplementation. It is equally important to follow certain rules known as "sleep hygiene". These are general recommendations to improve the quality of sleep. It is important to establish a constant sleep period, avoiding mental activities before going to bed, avoid coffee, tea and alcohol during the evening, and stop smoking. These are just a few recommendations that must be followed to ensure sleep quality. Due to the fact that sleep disorders affect other aspects of life such as fatigue and the occurrence of depression, a comprehensive approach to this problem is important. Only an appropriate diagnosis of the problem and combining pharmacological and non-pharmacological methods allows for therapeutic success.

## **Pain**

In patients with multiple sclerosis pain is very common. Pain in this group of patients is most often the result of damage to the nervous system by the basic disease process. It may be of a different nature - peripheral or central neuropathic pain, receptor, idiopathic, iatrogenic or mixed pain. Pain in MS may be paroxysmal or chronic [26].

Characteristic for patients with MS is optic neuritis, occurring in about 20% of patients with MS and is often its early symptom. Symptoms of optic neuritis are: unilateral pain in the eye, which intensifies during eye movements, with one-sided visual disturbances. It occurs as a result of the inflammatory process in the area of the nerve trunk. In the treatment of it, the most common are corticosteroids, after which the pain is quickly reduced [26, 27].

The most common pain complaints occurring in this group of patients are, among others, spastic pain in the limbs and painful tonic muscle contractions. Symptoms of increased muscular tension of the spasticity type occur in 50-75% of patients with MS and constitute one of the inherent, characteristic symptoms of this disease. Some movements increase spasticity or cause spasm, and patients may experience pain regardless of exacerbations and spasms. Spasticity is associated with impaired spinal cord injury. Treatment consists in reducing pain due to pharmacological agents and reducing spasticity where the main intervention is physiotherapy [28, 29].

Painful tonic spasm occurs in 6-11% of patients with MS. It can be single- or double-sided. It is a muscular contraction independent of a will, lasting less than 2 minutes, appearing several times a day. It results from the "pseudosynaptic" spread of spontaneous discharges generated by axons that have undergone demyelination. It can be triggered by touch, movement, hyperventilation or a change in emotional mood. It begins on the face and spreads to the neighboring areas of the body, e.g. the shoulder. Half of the patients describe it as a high-intensity pain that lasts for weeks or months and then suddenly disappears. In the treatment of painful tonic spasm, pharmacotherapy is widely used [28, 30].

An additional cause of pain in patients with advanced stage of MS may also be changes in the skin (sores and decubitus) - the priority in this case is prevention (physical therapy, frequent change of position, massages). In the case of pressure ulcers, their proper surgical development is necessary, and a good analgesic effect may be obtained by surface therapy with the use of local anesthetics and opioids, used together with the systemic administration of analgesics [31, 32].

## **Bladder disorders**

In the course of multiple sclerosis, some of the more troublesome symptoms includes bladder control disorders. The most common is urinary incontinence caused by the presence of a spastic bladder (automatic). It is based on imperative urination in small portions due to uncontrolled contractions of the detrusor muscle. These spasms are a consequence of damage to the corticospinal tracts. These roads inhibit the reflex bend that provides urination. This dysfunction is manifested by the occurrence of a sudden urge to urinate and the impossibility to stop micturition. Much less frequent disorders of sphincter control in MS concern the difficulty of urinating due to atonal bladder or due to bladder dyssynergy. The bladder disorder is characterized by uncoordinated contraction of the detrusor muscle and simultaneous contraction of the internal urethral sphincter muscle. Clinically, this leads to difficulties in the micturition process and even its retention. In the case of atonic bladder, a patient with MS experiences difficulty urinating or has urinary retention. The micturition is stopped due to demyelinating lesions located in the spinal cord on the way of conditioning the reflex. Over time, patients develop involuntary urination due to overflowing bladder [33, 34, 35].

In the treatment of spastic bladder, the most commonly used drugs to alleviate its symptoms are: oxybutynin and anticholinergic drugs, such as propantelin or tolterodine. In the case of atonic bladder with retention of urine, a frequently used therapeutic method is a program of independent and frequent catheterization aimed at emptying the bladder. Cholinergic drugs such as tanachol, carbachol and pyridostigmine help to empty the bladder, but are effective only in some patients. In acute urinary retention, the drug of choice is fenoxylbenzamine. The most challenging are disorders associated with detrusor dyssynergy and external sphincter. In this case, it is recommended to use a combination of oxybutynin with baclofen, tizanidine or  $\alpha 1$  receptor blockers (terazosin, doxazosin or tamsulosin), and periodic self-healing. In patients with sphincter disorders, it may be necessary to keep the catheter permanently despite the increased risk of urinary tract infection. One of the newer methods supporting the treatment of bladder disorders is physiotherapy. These include electrotherapy treatments - internal and external electrical stimulation, and pelvic muscle exercise kinesitherapy [36, 37, 38].

It is worth mentioning that patients with multiple sclerosis are exposed to frequent infections of the genitourinary system. The reason is the urine remaining in the bladder, which becomes a source of bacteria that are the source of infection. Any infection in patients with MS may produce symptoms mimicking the disease - in particular a combination of

inflammation and elevated body temperature may result in transient, mimicking disease symptoms that disappear after healing the infection [33, 36].

### **Discussion**

Non-motor disorders in patients with multiple sclerosis are an important part of the overall clinical picture. In many available studies, the authors present the occurrence of individual non-inguinal disorders in this group of patients.

Dysphagia is a significant problem in patients with neurological diseases. In addition to multiple sclerosis, swallowing disorders occurs, e.g. at amyotrophic lateral sclerosis, Parkinson's disease, stroke or Alzheimer's disease. In the study of Alali et al. [9], 38% of patients with MS reported swallowing problems. In addition: gender, diagnosis time, age and type of multiple sclerosis did not affect the increased incidence of dysphagia. It was noted that the higher EDSS score (Expanded Disability Status Scale) correlates with increased swallowing problems. A similar relationship was noticed in the 2017 study by Tarameshlu et al. [39]. Tenekeci et al. [11] used the DYMUS questionnaire to assess the incidence of dysphagia. As many as 45.3% of respondents answered yes to one or more questions, which indicates the occurrence of swallowing disorders in this group of patients. Similar results were obtained by Payouh et al. [40], using the same questionnaire. Dysphagia occurred in 52.4% of patients with MS. The prevalence of dysphagia in people with multiple sclerosis is high, and discrepancies in individual studies may result from varying numbers of study groups.

Deterioration of the quality of life is a serious problem that MS patients are struggling with. This is related to the onerous symptoms that occur during the illness. The occurrence of sleep disorders in the MS population compared to the healthy group was assessed by Bøe Lunde et al. [41]. It was observed that patients achieved higher scores in the PSQI questionnaire, which indicates the occurrence of sleep disorders. These disorders occurred in 67.1% of patients with MS and in 43.9% of subjects in the control group.

In the study Tabrizi FM et al. [42] the relationship between the occurrence of fatigue, sleep disorders and the degree of disability and the quality of life of MS patients was assessed. The study found the occurrence of sleep disorders in 82 patients, which accounted for 70.1% of the subjects. Fatigue was found in 59% of respondents. There was a high positive correlation between results in the physical and mental QOL domain and fatigue and sleep quality.

Łabuz-Roszak et al. [43] conducted studies on fatigue and its relationship with sleep disorders, symptoms of depression and anxiety in patients with MS. Fatigue occurred in 75 MS patients (61.5%). Excessive sleepiness during the day was observed in 20.5% and

insomnia in 59.8% of patients. The symptoms of depression according to the Montgomery-Asberg Depression Rating Scale (MADRS) were found in 27% and according to Hospital Anxiety and Depression Scale (HADS) in 12.3% of the respondents. In addition, there was a relationship between the occurrence of fatigue and sleep disorders.

There are many types of pain in patients with MS. However, the basic problem is the symptoms are associated with excessive spasticity and painful muscle spasms. Baclofen is the drug most commonly used in these conditions. Recent studies have confirmed the efficacy of cannabinoids in neuropathic pain in patients with MS. Research conducted by Osborne et al. Indicates that pain is more severe in women than in men [44, 45].

In bladder disorders in patients with MS, pharmacotherapy is the most common therapeutic method. Berkowicz T. and Selmaj K. [46] point to oxybutynin, tolterodine, terazosin, doxazosin, tamsulosin as agents that are recommended for this dysfunction. An increasing number of clinical trials concern non-pharmacological methods, mainly physiotherapy in the treatment of bladder disorders such as urinary incontinence, also in patients with multiple sclerosis. Pereira et al. [38] in 2017 described the case of a 55-year-old female MS patient with diagnosed mixed urinary incontinence. The patient underwent a therapy involving the use of physiotherapy to reduce the symptoms. Internal electrical stimulation and pelvic floor muscle exercises were performed. The patient decreased incontinence incidence and remained at the same reduced level for 5 months, which also increased the quality of life of the patient.

### **Summary**

Multiple sclerosis is a disease entity that is a challenge in planning and implementing treatment. The main therapeutic activity is focused on a symptomatic treatment. Occurring disorders significantly affects the quality of life in this group of patients. The majority of clinical trials on the effectiveness of symptomatic treatment for non-motoric disorders are conducted on a small groups, often not statistically significant. Researches combining both pharmacological and nonpharmacological methods in the treatment of extrinsic disorders in order to obtain the best therapeutic effects should be carried out. Therefore, further research is needed with a solid methodology and more participants to justify the impact of the interventions used on the treatment of non-cardiac symptoms in MS patients.

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