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Review

Cognitive and Emotional Disorders during Multiple Sclerosis — Exogenous and Endogenous Conditions, Contemporary Methods of Treatment and Prevention

Zaburzenia poznawcze i emocjonalne w przebiegu stwardnienia rozsianego — egzogenne i endogenne uwarunkowania, współczesne metody leczenia i profilaktyki

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Abstract

Multiple sclerosis (SM) is an autoimmune, demyelinating disease of the central nervous system. The disease affects patients of all ages, with a higher incidence in women. The etiopathogenesis of SM is not fully understood — it is believed that autoreactive lymphocytes play a key role in the development of the disease, although genetic predisposition and environmental factors also play a role. Diagnosis is based on the McDonald criteria, and the disease has different clinical presentations. Treatment is based on immunomodulation, aims to control the disease, and prevent recurrence. Frequent symptoms of the disease are motor, sensory, and cognitive disorders. Cognitive impairment, which is common in multiple sclerosis patients, has numerous consequences in everyday life (mental, social, economic) that significantly reduce the quality of life. Psycho-cognitive dysfunction, which can occur at any stage of the disease, is associated with changes in the central nervous system. Prevention of these disorders includes the early application of treatment methods that modify the natural course of the disease and the implication of pro-health behaviors, such as quitting smoking, proper diet and physical exercise. Pharmacological treatment shows limited effectiveness. Rehabilitation involving the use of compensatory strategies, remedial methods aimed at brain neuroplasticity and cognitive training shaping new functional networks of the brain is important. The aim of this work is to present the problem of cognitive and emotional disorders in the course of multiple sclerosis, with particular emphasis on endo- and exogenous conditions, together with modern methods of their treatment and prevention. (JNNN 2023;12(3):140–146)

Key Words: cognitive disorders, emotional disorders, multiple sclerosis, nurse, prophylaxis, treatment

Streszczenie

Stwardnienie rozsiane (SM) jest chorobą autoimmunologiczną, demielinizacyjną ośrodkowego układu nerwowego. Choroba występuje u pacjentów w różnym wieku, z częstszym występowaniem u kobiet. Etiopatogeneza SM nie jest w pełni poznana, uważa się, że autoreaktywne limfocyty odgrywają kluczową rolę w rozwoju choroby, predyspozycje genetyczne, wpływ czynników środowiskowych również ma znaczenie. Diagnoza opiera się na kryteriach McDonald'a, a choroba ma różne postaci kliniczne. Leczenie opiera się na immunomodulacji, ma na celu kontrolowanie choroby i zapobieganie nawrotom. Częstymi objawami choroby są zaburzenia motoryczne, czuciowe i poznawcze. Upośledzenie funkcji poznawczych, często występujące u pacjentów ze stwardnieniem rozsianym ma liczne konsekwencje w życiu codziennym (psychiczne, społeczne, ekonomiczne), znacznie obniżające jakość życia. Dysfunkcja psychicznopoznawcza, mogąca wystąpić na każdym etapie choroby związana jest ze zmianami w ośrodkowym układzie nerwowym. Profilaktyka tych zaburzeń obejmuje wczesne stosowanie metod leczenia modyfikujących naturalny przebieg choroby oraz implikowanie zachowań prozdrowotnych, takich jak rzucenie palenia, właściwa dietę i wysiłek fizyczny. Leczenie farmakologiczne wykazuje ograniczoną skuteczność. Ważna jest rehabilitacja polegająca na stosowaniu strategii kompensacyjnych, metodach naprawczych ukierunkowanych na neuroplastyczność mózgu oraz i treningach poznawczych kształtujących nowe sieci funkcjonalne mózgowia. Celem pracy jest przedstawienie problematyki zaburzeń poznawczych i emocjonalnych w przebiegu stwardnienia rozsianego, ze szczególnym uwzględnieniem schorzeń endo- i egzogennych, wraz z nowoczesnymi metodami ich leczenia i profilaktyki. **(PNN 2023;12(3):140–146)**

Słowa kluczowe: zaburzenia poznawcze, zaburzenia emocjonalne, stwardnienie rozsiane, pielęgniarka, profilaktyka, leczenie

Introduction

Multiple sclerosis (SM) is an autoimmune, demyelinating disease of the central nervous system (CNS), which is the main cause of non-traumatic neurological disability in young adults [1]. It is characterized by multifocal, temporarily progressive formation of inflammatory and demyelinating changes, the consequence of which is axonal neurodegeneration [2].

This disease occurs in patients of all ages, with a median of 24 years of age [3]. According to the Multiple Sclerosis International Federation (MSIF) statistics, nearly 2.3 million people worldwide suffer from multiple sclerosis. Epidemiological data on the Polish population oscillate between 40,000 and 60,000 cases. A certain predilection of the female sex has also been demonstrated (twice as often) [4,5].

The etiopathogenesis of multiple sclerosis is not fully understood. Disturbances in the immunocompetence mechanisms of the body are believed to be involved, in the form of autoreactive CD8+ T lymphocytes, and to a lesser extent CD4+ T lymphocytes, B lymphocytes, and plasma cells [6,7]. The most widely accepted hypothesis of the etiology of this pathology is the susceptibility to antigenic homology of the organism (molecular mimicry) in relation to pathogenic environmental factors, such as Epstein-Barr virus (EBV), Human herpesvirus type 6 (HHV-6), human T-lymphotropic virus 1 (human T-lymphotropicvirus 1 — HTLV-1), coronaviruses or bacteria such as group A streptococcus, Chlamydia bacteria. The influence of genetic factors (mutation of the HLA locus - DRB1), vitamin D3 deficiencies, obesity, nicotinism is also probable [2,6].

The diagnostic algorithm is based on the McDonald Criteria in the modification of 2017, taking into account the number of relapses, the number of foci in the Magnetic Resonance Imaging (MRI) examination (according to the MAGNIMS guidelines of 2015 and CMSC of 2016) taking into account dissemination over time and in space, and immune electophoresis of the cerebrospinal fluid for the presence of oligoclonal bands [8–10].

The clinical manifestation of multiple sclerosis depends on the location of the plaques (foci of sclerosis) and the form of the disease, among which the relapsingremitting multipole sclerosis (RRMS), secondary progressive multiple sclerosis (SPMS) and primary progressive multiple sclerosis (RRMS) forms are distinguished — PPMS), acutely progressive (Marburg's disease), Baló's concentric sclerosis, pseudotumor or early-onset multiple sclerosis [1,11–13]. The first episode of neurological dysfunction, termed clinically acquired isolated demyelinating syndrome (ADS), typically presents with unilateral retrobulbar optic neuritis (II), focal supratentorial syndrome, focal trunk syndrome, partial myelitis. At a later stage of the disease, the symptomatology includes: sensory disturbances (paresthesias, Lhermitte's sign), cerebellar syndrome, trigeminal neuralgia, diplopia (internuclear ophthalmoplegia, abducens nerve palsy (VI), spasticity of the limbs, sphincter dysfunction, myelopathy, sexual dysfunction, tiredness.

Symptoms of multiple sclerosis are characterized by the variability of symptoms — new symptoms appear, and some of the previously existing symptoms regress [2,13,14]. The use of long-term immunomodulatory treatment contributes to the inhibition of disease progression and, above all, to the prevention of relapses [14]. In recent years, attention has also been paid to non-physical aspects - depression, cognitive deficits, affective symptoms negatively affecting the quality of life in the mental, social and spiritual spheres. It is worth emphasizing that the above-mentioned disorders occur at every stage of the severity of the disease — patients with light and moderate disability according to the Kurtzke scale (EDSS - Expanded Disability Status Scale) are characterized by a high intensity of depression and anxiety symptoms [15].

The aim of this work is to present the problem of cognitive and emotional disorders in the course of multiple sclerosis, with particular emphasis on endo- and exogenous conditions, together with modern methods of their treatment and prevention.

Review

The incidence of affective disorders, such as depression or anxiety disorders, in multiple sclerosis can reach up to 50% — it is estimated that patients are at twice as high risk of developing major depression. Anxiety disorders (e.g. generalized anxiety disorder, social anxiety disorder, agoraphobia, etc.) occur in 20 to 44.5% of patients [16–18]. Multiple sclerosis is also often associated with mood disorders: emotional instability, euphoric states, dissociative symptoms, involuntary emotional expression syndrome, manifested by episodes of laughing or crying inappropriate to the presented emotional state. Their clinical manifestations are caused by disorders of the cortico-subcortical pathways [17].

Deterioration of cognitive and cognitive functions occurs in about 70% of patients with multiple sclerosis, regardless of the stage and form of the disease, however, the greatest intensity of the described symptoms is observed in the secondary progressive form [19].

Risk Factors and Etiology

Progressive inflammation, demyelination, degeneration of neurons in the white matter of the CNS, together with overlapping predisposing factors (demographic, environmental, personality, behavioral) affect the incidence of cognitive and emotional disorders in the course of multiple sclerosis. The occurrence of affective symptoms may be favored by factors such as: low socioeconomic status, older age, male sex, place and region of residence. Young age of onset (early-onset form) increases the risk of disorders.

Aspects related to the primary and secondary support system, self-efficacy, level of emotional selfcontrol, high emotional sensitivity, low self-esteem, maladaptive coping strategies, and other mood disorders are commonly considered predictors of depression, anxiety, and cognitive-behavioral disorders in multiple sclerosis. Pharmaceuticals used in both acute relapse and chronic treatment, such as glucocorticoids, diseasemodifying drugs (interferon-β, glatiramer acetate, mitoxantrone, siponimod, natalizumab, ocrelizumab) may reduce the risk and delay the onset of mood disorders, depressive episodes, mania and psychoses [15,16,19-21]. People using stimulants such as nicotine, alcohol, cannabinoids (tetrahydrocannabinol - THC) and other narcotic substances show higher cognitive dysfunctions compared to the control group (people who do not use them), especially in terms of information processing speed, processing speed and memory. The authors linked this relationship with a reduced volume of gray and white matter of the CNS [21].

The etiology and pathogenesis of psycho-cognitive disorders coexisting with multiple sclerosis are still unclear [15,16,20]. Advances in neuroimaging techniques have led to the emergence of several leading etiopathogenetic hypotheses. One of the dominant ones is the correlation of depression along with cognitive dysfunction with progressive demyelination in the anatomical components of the limbic system, gray and white matter. Analyzes of the MRI results showed a significant relationship between the results of memory performance and the quantitative and qualitative features of the plaques. The latest reports of researchers emphasize the significant impact of destructive and atrophic changes located in the frontal and temporal lobes as a factor distinguishing patients suffering from multiple sclerosis with coexisting depression and those without mental and cognitive disorders [15,18,19].

Reduced sleep quality occurring in more than half of patients with multiple sclerosis is also conducive to emotional dysregulation, reduced cognitive abilities, mood changes and is associated with achieving higher rates of fatigue [22]. Chronic fatigue syndrome, which occurs in 80% of patients with multiple sclerosis, leads to disorders in the spheres of information processing, attention, working memory, and executive functions, thus reducing the quality of life of patients. Physical exhaustion may result from the progression of the disease, depression overlapping syndromes, side effects of the therapy [15,19,23]. In recent years, intensified cause-and-effect analyzes of affective disorders in the course of multiple sclerosis have shown that they manifest themselves at an early stage of the disease, even during an isolated clinical syndrome and remain stable for at least 3 years and longer [15].

Available research data point to the role of cognitive reserve in the context of multiple sclerosis and its impact on cognitive disorders. According to it, the level of development and intellectual potential correlates with the neuroplasticity of the brain, which contributes to slower development and less severe cognitive symptoms. Patients suffering from multiple sclerosis with higher education, with a rich vocabulary, having interdisciplinary interests, remaining professionally active, are characterized by a higher cognitive reserve. It is suggested that its higher level is a predictive factor [24].

The full pathomechanism of mental and cognitive disorders in multiple sclerosis remains unclear. Conclusions from current retrospective cohort studies indicate a weak correlation between the above-mentioned symptoms and the severity of CNS damage in conventional MRI measurements. The pattern of cognitive impairment in MS has been defined as a disconnection syndrome or a fronto-subcortical syndrome, although other structures have also been suggested [19].

Assessment, Treatment, and Prevention

Assessment of cognitive functions at an early stage of the disease not only identifies people with cognitive impairments, but also allows for progressive analyzes of the risk of cognitive and psychological limitations in the progressive course of multiple sclerosis. Dysfunctions in the described spheres, occurring already at the stage of diagnosis of the disease in the form of i.a. slowdown of information processing, memorization and memory disorders may indicate the possibility of a rapid onset of disability. Therefore, early detection of cognitive and mental changes may lead to the implementation of targeted therapeutic interventions [21]. Clinical tools for assessing the cognitive functioning of patients are the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS), with high sensitivity and specificities in this group of patients. Processing speed is assessed by the PacedAuditory Serial Addition Test (PASAT) and the symbol-digit assignment test. The California Verbal Learning Test (CVLT) is the test used to assess learning and memory. The Delis-Kaplan card sorting test works well for the assessment of executive function, the verbal fluency test for language functions. The risk of affective disorders can be assessed on the basis of the Montgomery-Asberg Depression Rating Scale (MADRS) [25].

Pharmacological management includes preventing the progression of the underlying disease by using drugs that modify the natural course of multiple sclerosis, limiting the progression of lesions in the white and gray matter of the central nervous system. Cognitive rehabilitation based on neurofunctional networks of the brain, started early enough positively affects corticothalamic associative pathways, which is reflected in fMRI examinations (functional Magnetic resonance eimaging) [9].

The variable rate of progression of cognitive lesions in multiple sclerosis hampers the implications of innovative pharmacological approaches in controlled clinical trial environments. Until now, attempts at symptomatic treatment of cognitive disorders in this disease entity have shown mixed results. Some active substances with limited benefit have been identified: amantadine, fampridine, L-amphetamine, dexamphetamine dimesylate, memantine, rivastigmine, donepezil, ginkgo biloba. Unfortunately, there are no FDA (Food and Drug Administration) approved drugs to reduce cognitive symptoms in this group of patients. The best results were obtained with fampridine, although there are reports that do not confirm this relationship. It should be emphasized that polypharmacy, which is common in patients with multiple sclerosis, can also result in cognitive impairment and/or fatigue, therefore a careful

review of the patient's medication is recommended [21,26].

Fatigue, associated with reduced sleep quality or obstructive sleep apnea, leads to impairment of shortterm, operational, visual and verbal memory. There is a decrease in executive functions, the level of attention, the speed of information processing and reaction time decrease [21]. Therefore, recommendations were developed to optimize night rest, including short-term pharmacological interventions (benzodiazepines, drugs from the group of imidazopyridines, the so-called "Zets", selective serotonin reuptake inhibitors SSRIs) and non-pharmacological interventions such as cognitivebehavioral therapy, relaxation techniques, rationalized physical exercise. The negative impact of long-term use of hypnotics and sedatives in daytime sleepiness ("next day syndrome"), depression, increased fatigue, and reduced cognitive performance should be emphasized [22].

Telerehabilitation in the form of cognitive training with the use of multimedia tools consists in the repetitive performance of specific tasks posted on websites, dedicated software. and working memory capacity [26]. Randomized clinical trials of a multimodal exercise program in people with severe motor disabilities showed significant improvements in walking efficiency and cognitive processing speed, possibly related to increased cardiorespiratory capacity, increased maximal oxygen uptake, and reduced anaerobic cellular metabolism. A limited number of tests, carried out on a few samples, indicate a relationship between the state of the cardiovascular system and the volume of brain tissue, the effectiveness of fMRI connections. Research is underway to more accurately assess the impact of combining cognitive rehabilitation with aerobic physical training on the psycho-cognitive functioning, gait and physical condition of patients [27]. In the case of people suffering from multiple sclerosis, it is important to pay attention to the scope, level and conditions of physical training. Excessive, overloading exercises, performed especially in a hot microclimate, leading to hyperthermia, may result in exacerbation of symptoms, according to the laws of the Uhthoff phenomenon. Personalization of active kinesitherapy is a significant clinical problem [22,28].

Depression in patients with multiple sclerosis is common. Rapid diagnosis of mood disorders, anhedonia and reduced drive is difficult due to frequent overlapping syndromes and difficulties in distinguishing the causality of psychopathologies. However, depression, despite the increased risk of polypharmacy, should be treated. Research sources on the psychopharmacological treatment of depression in multiple sclerosis are the subject of numerous discussions and interpretation ambiguities. On the one hand, the available clinical trials emphasize the limitations resulting from the course of the underlying disease, and on the other hand, many studies document the effectiveness of the same methods of treating depression in the population suffering from demyelinating diseases as well as in the healthy population [28]. As in the general population, selective serotonin reuptake inhibitor (SSRI) (fluoxetine, sertraline) or selective serotonin norepinephrine reuptake inhibitor (SNRI) (duloxetine, venlafaxine) are the drugs of first choice for depression comorbid with multiple sclerosis [18]. The use of other pharmaceuticals may be limited due to nonselective blocking of numerous transmission pathways in the CNS, e.g. dopamine, or blocking alpha-adrenergic receptors. Also, the patient's age and drug interactions are of clinical importance.

No specific diet has yet been established for patients with multiple sclerosis, therefore a balanced, healthy diet is recommended. Current dietary guidelines for this group of patients indicate that a daily caloric intake of between 20 and 35 kcal/kg/day is appropriate. Consumed foods should increase the plasma concentration of unsaturated fatty acids. The supply of carbohydrates, antioxidants, vitamin D and B12 reduces symptoms such as fatigue or weakness. Cholecalciferol (vitamin D) supplementation has an immunomodulatory effect. Epidemiological studies suggest a beneficial effect of higher levels of vitamin D and exposure to solar ultraviolet radiation on the activity and progression of multiple sclerosis. Cobalamin (vitamin B12) deficiency can lead to damage to myelin sheaths and axons. Some similarities in autoimmune mechanisms have been identified between some cases of vitamin B12 deficiency and multiple sclerosis. There is also a hypothesis that in demyelinating diseases, the increased demand for vitamin B12 may result from the remyelination process - the results of previous studies, however, are not clear. A meta-analysis conducted by Cochrane in 2012 did not confirm the effectiveness of multivitamin supplementation in patients with multiple sclerosis. In the event of malnutrition, it is advisable to use foodstuffs for particular nutritional uses by mouth (in the form of drinks, puddings or powders) in order to increase the supply of calories [29].

An important element of the treatment of both cognitive and mental disorders is psychotherapy and psychoeducation. The coordinated combination of these two activities helps patients develop skills to cope with emotions, negative, persistent thoughts in the process of adaptation to the final diagnosis and accompanying symptoms of multiple sclerosis. Extensive research data confirmed the effectiveness of psychological and pedagogical interventions in this group of patients, paying attention to the effectiveness of group therapy, occupational and sensory therapy, and individual cognitive behavioral therapy (CBT). Group therapy is a particularly desirable form of support in the process of reducing the sense of alienation and ensuring acceptance, adapted to the needs of social assistance [**30**].

Health education of people with multiple sclerosis together with their family members, early screening tests, routine and systematic monitoring of the course of the disease allow for the adjustment of compensation strategies and optimization facilitating cognitive and mental functioning to the clinical condition and needs of the patient. Promoting social activities and continuing professional workare an important element of preventive measures. Attention should be paid to the patient's safety, e.g. when driving motor vehicles, working environment, adapting the conditions to the patient's limitations, so that he or she can perform normative and behavioral social roles as long as possible [21].

Nursing Care

The competence of a neurological nurse caring for a patient with multiple sclerosis is to ensure that the patient is properly educated about the disease, including information about the symptoms, course and available treatment. As part of their tasks, the nursing team is obliged to provide guidance on techniques for dealing with the occurring symptoms, provide emotional and psychological support, and help in dealing with emotional difficulties. The nurse, through cooperation with specialists, ensures comprehensive care and coordination of the treatment plan [31].

Education of the patient's family by a neurological nurse plays an important role in the care of a patient with a neurological disease. The nurse can provide your family with information about MS, including symptoms, course of the disease and potential complications. He is a competent person to answer questions and dispel doubts that may arise. Provide the family with guidance on home care for the patient. It can also teach families how to use medical aids, such as a wheelchair or assistive devices, discuss care techniques (repositioning the patient, help with daily activities, feeding, dressing and personal hygiene). The role of the nurse is to educate the family in the field of self-care, suggest among others, keeping a diary of symptoms, monitoring the patient's condition, clarifying doubts about recommendations [31].

Conclusions

- 1. Multiple sclerosis is a chronic demyelinating disease of unknown etiology.
- 2. Cognitive disorders and affective symptoms, occurring in the vast majority of patients with multiple sclerosis, have a negative impact on the patient's quality of life in the family, social, professional and other spheres.

- 3. The aim of the therapy is to prevent and restore cognitive functions using a variety of pharmacological and non-pharmacological methods (kinesitherapy, cognitive training).
- 4. The care of the patient depends on the phase of the disease, the severity of symptoms and the degree of disability of the patient.
- 5. Patients with multiple sclerosis should be systematically assessed in terms of their mental and cognitive capacity in order to promptly intervene, implement preventive and therapeutic measures.

Implications for Nursing Practice

Multiple sclerosis is a demyelinating disease that neurological nurses encounter more and more often in their practice. This professional group is responsible for holistic care, evaluating the progress of the disease, the emergence of new symptoms, including those from the sphere of affective symptoms. Systematic assessment of the care subject, early implementation of preventive and corrective measures can increase the present and future quality of life of the patient. Education of the nursing team regarding disorders of cognitive and mental functioning, awareness and knowledge of these issues is an important element of the practice of a neurological nurse.

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 $\begin{array}{l} A - Concept and design of research, B - Collection and/or compilation of data, C - Analysis and interpretation of data, D - Statistical analysis, E - Writing an article, F - Search of the literature, G - Critical article analysis, H - Approval of the final version of the article, I - Acquisition of assets [eg financial], J - Translation of the article into English \\ \end{array}$

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