BALNEO RESEARCH Balneo and PRM Research Journal
English Edition
e ISSN 2734 - 8458 p ISSN 2734 - 844X ROMANIAN ASSOCIATION OF BALNEOLOGY

Research article

Complex case of multiple sclerosis with multiple demyelinating locations

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Citation: Lungu C.M., Oprea D., Georgescu B., Stanciu L.E., Ionescu E.V., Iliescu M.G. - Complex case of multiple sclerosis with multiple demyelinating locations
Balneo and PRM Research Journal ***2024****, 15(3): 737*

Academic Editor(s):
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Received: 23.08.2024
Published: 25.09.2024

Reviewers:
Mihai Hoteteu
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Publisher's Note: Balneo and PRM Research Journal stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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Abstract: Multiple sclerosis (MS) is a chronic inflammatory disorder with an unpredictable progression that affects the central nervous system and has significant emotional, social, and professional implications. The therapeutic approach is multifactorial and requires complex management coordinated by a specialized, multidisciplinary team over the long term. Current non-pharmacological treatment strategies under study, which may improve the course of the disease, focus on the gut microbiome and include the administration of probiotics and fecal transplantation. This study presents a case of secondary progressive multiple sclerosis in a young patient, with rapidly progressive evolution despite ongoing background therapy. The study analyzed literature data regarding both medical rehabilitation programs used in secondary progressive multiple sclerosis and other therapeutic strategies that can improve the quality of life. Medical rehabilitation has no proven impact on disease progression but can enhance the quality of life for patients with multiple sclerosis through spasticity management, improved mental health, increased mobility, and muscle strength. These therapeutic strategies can improve involvement in professional activities and participation in social and family life for patients with multiple sclerosis.

Keywords: rehabilitation program, intestinal microbiome, vitamin D

1. Introduction

Multiple sclerosis (MS) is a chronic, progressive inflammatory disorder that affects the central nervous system and is the most common cause of non-traumatic disability in young adults aged 20 to 40, a period of peak socio-professional activity[1].

The estimated number of people with multiple sclerosis is continuously increasing worldwide, with a prevalence of 35.9 per 100,000 inhabitants in 2020[2].

The etiology of multiple sclerosis is multifactorial and not fully understood, involving the interaction between genetic and environmental factors. The human leukocyte antigen HLA-DRB1*1501 has been associated with an increased risk of developing multiple sclerosis[3].

Epstein-Barr virus infection increases the risk of multiple sclerosis, particularly when the infection occurs after the age of 10, as the thymic selection of autoreactive T cells slows down. The mechanisms by which the virus contributes to the development of the disease are influenced by genetic background, environmental factors, and age.

A diet rich in pro-inflammatory foods, particularly saturated fats and sugar, triggers the inflammatory cascade, leading to oxidative stress and an imbalance in the gut microbiome. Current interventions targeting the gut microbiota can alleviate symptoms, and various approaches are presented, such as direct manipulation, which involves supplementation with probiotics and treatment with antibiotics targeting pro-inflammatory gut taxa, and indirect manipulation, which modulates the gut microbiome through probiotic consumption and changes in dietary behavior[4].

Smoking increases the risk of developing the disease, raises the relapse rate, and can cause gut dysbiosis, worsening the course of the disease[5]. A body mass index (BMI) over 30 in childhood and adolescence increases the risk of multiple sclerosis, disease severity, and disability level over time. Adipose tissue is an active endocrine organ that secretes adipokines, which play a role in regulating energy metabolism, inflammation, and immune response[6].

The high prevalence of multiple sclerosis (MS) in northern latitudes has led to the hypothesis of a link between vitamin D deficiency and the disease. Vitamin D has an immunomodulatory and anti-inflammatory role and may influence the progression of MS. Most patients have insufficient levels of vitamin D at the time of diagnosis, which are not correlated with the degree of sun exposure but rather with altered vitamin D metabolism[7]. Low vitamin D levels are associated with higher relapse rates and the formation of new gadolinium-enhancing T2 lesions on MRI. During a relapse, serum vitamin D levels are lower than during remission, though it is not entirely clear whether this is a cause or an effect[8].

The pathophysiology of multiple sclerosis involves areas such as the cortical gray matter, periventricular and juxtacortical white matter, optic nerves, spinal cord, cerebellum, and meninges, and consists of two primary pathological processes—focal inflammation and neurodegeneration, which lead to both macroscopic and microscopic lesions[9].

Multiple sclerosis manifests in four clinical forms: relapsing-remitting, secondary progressive, primary progressive, and progressive-relapsing.

Relapsing-remitting multiple sclerosis (RRMS) is observed in 85% of cases and is characterized by episodes of acute neurological dysfunction followed by clinical stability, with no neurological function impairment between attacks. Relapses present as a heterogeneous group of symptoms, including visual disturbances, coordination and balance issues, motor deficits, bowel and urinary dysfunctions, sensory symptoms, vertigo, and cognitive-behavioral disorders.

The secondary progressive form of MS develops after several years in patients with untreated RRMS and is marked by gradual neurological deterioration with the progressive accumulation of disabilities. Primary progressive multiple sclerosis (PPMS) is characterized by a constant functional decline from the onset of the disease, without relapses or periods of stability. It typically begins after the age of 45, usually presenting with paraparesis as the first symptom, and predominantly affects the spinal cord. Progressive-relapsing multiple sclerosis (PRMS) is characterized by a steady functional decline from the onset, with superimposed relapses[10].

The diagnosis of multiple sclerosis (MS) is based on clinical symptoms and medical history, supported by magnetic resonance imaging (MRI) and lumbar puncture with cerebrospinal fluid examination. Laboratory tests are useful for differential diagnosis and to exclude other conditions such as Lyme disease, HIV, neurosyphilis, metabolic

dysfunctions, vitamin B12 deficiency, paraneoplastic syndromes, vasculitis, and neuromyelitis optica[10].

Current therapies can almost wholly control relapses and focal brain inflammation, but they do not provide full protection against the neurodegenerative component of the disease[11].

Clear clinical or imaging criteria do not mark the transition from the relapsing-remitting form to the secondary progressive form. The neurologist determines this shift based on the patient's history and level of disability. In secondary progressive MS, symptoms worsen insidiously, with the accumulation of permanent disabilities independent of relapses. These include chronic pain, fatigue, sleep disturbances, cognitive impairments, spasticity, bladder and bowel dysfunction, and gait dysfunction, necessitating assessment by a multidisciplinary team[12].

2. Materials and Methods

We present the case of a 38-year-old male patient, a non-smoker, residing in an urban area and working as an IT professional. The patient was admitted to the Techirghiol Balneal and Rehabilitation Sanatorium from April 15 to April 26, 2024, presenting with motor deficits of a paretic nature in the upper and lower limbs, as well as severe locomotor and self-care dysfunctions.

The patient's medical history revealed that the disease first manifested in 2012 following an episode of coordination difficulties in the lower limbs, lasting approximately three weeks. The symptoms subsequently resolved completely after self-administering vitamins and magnesium. A year later, a new relapse occurred, characterized by a decrease in muscle strength in the lower limbs. At this point, the neurologist recommended a brain and cervical spine MRI with contrast, which the patient delayed for two months, during which the symptoms persisted. After two months, the patient was admitted to the neurology department of the University Hospital in Bucharest, where clinical and paraclinical investigations led to a diagnosis of relapsing-remitting multiple sclerosis.

Initial background therapy was started with Extavia (July 2013-March 2014), during which time there was a constant progression characterized by relapses followed by incomplete recovery. Subsequently, the patient was treated with Copaxone (November 2014-March 2018), which resulted in modest clinical and imaging improvements. In 2021, treatment with intravenous Natalizumab 300 mg (one infusion every six months) was initiated. However, after the administration of the first therapeutic dose, it was decided to discontinue the immunomodulatory medication due to the presence of positive antibodies for the John Cunningham (JC) virus and the associated high risk of progressive multifocal leukoencephalopathy.

At the time of admission, the patient was not undergoing any background or symptomatic treatment. The patient's medical history includes infectious mononucleosis during childhood. The general physical examination upon admission revealed a conscious, cooperative, anxious patient, oriented in time, space, and to self, with normal weight, normally colored skin and mucous membranes, cardiovascular compensation, respiratory issues secondary to thoracic spasticity, urinary dysfunction, and slow intestinal transit for gas and feces.

The local examination revealed pyramidal signs, with a motor deficit of paretic intensity in the upper limbs, characterized by pyramidal-type spasticity graded 3/4 on the Ashworth scale. The lower limbs exhibited a bilateral paretic motor deficit graded 1/5 and significant spasticity, also graded 3/4 on the Ashworth scale. The osteotendinous reflexes were globally brisk, with a positive Hoffman sign and bilateral Babinski sign. A cerebellar syndrome was present, characterized by explosive, staccato speech and coordination disturbances in the finger-to-nose test, with dysmetria and hypermetria on the left. The upper right limb and lower limbs could not be examined. Vestibular syndrome was indicated by horizontal nystagmus on lateral gaze, and

brainstem anomalies were noted, including intermittent diplopia and occasional dysphagia for liquids. Sensory anomalies included paresthesias on the left side of the face, a positive Lhermitte's sign, and proprioceptive sensitivity disturbances in both lower limbs. Sphincter disorders were also present, including urgency and urge incontinence, along with respiratory issues secondary to thoracic spasticity and autonomic disturbances, such as intolerance to heat and cold.

Functionally, the patient was wheelchair-bound, unable to perform transfers independently from a supine to a lateral position, from lateral to sitting at the edge of the bed, or to stand up without bilateral support. Standing without support was impossible, as was walking, and the patient could not independently perform daily living activities. Paraclinically, a deficiency in 25-OH vitamin D3 was noted, with a value of 11 ng/mL.

The most recent brain and cervical spine MRI performed in July 2021 revealed inactive demyelinating lesions in the brain, both supra- and infratentorially, which remained stable in number and size. The cervical spine showed multiple newly appeared inactive demyelinating lesions, and the thoracic spine exhibited multiple inactive demyelinating lesions at the upper and lower thoracic cord level, non-gadolinium enhancing, with the lesion at the lower thoracic level measuring 21/4 mm on the sagittal plane.

At the time of admission, the following assessments were conducted: EDSS (Expanded Disability Status Scale) = 7, ADL (Activities of Daily Living) = 2/10 points, IADL (Instrumental Activities of Daily Living) = 3 points, Barthel Index = 15 points, Fatigue Severity Scale = 5 points, and MIF (Functional Independence Measure) = 13 points.

The treatment objectives at the time of admission focused on improving motor control, reducing spasticity, enhancing transfers, improving speech, restoring functional capacity, increasing quality of life, and boosting independence by improving motor control.

During the hospital stay, the patient underwent a complex physical-kinetic therapy regimen, including: cervical-dorsal-lumbar trophic massage alternated with sedative massage on the lower limbs, aimed at facilitating muscle function, Hufschmidt current therapy was applied to the lower limbs and right upper limb to relax spastic muscles through the inhibition of spastic motoneurons. For excitomotor effects on smooth muscles, tetrapolar interferential current therapy was used, with two electrodes placed suprasacrally and two suprapubically, crossed at the pelvis, set at 10 Hz. Hivamat (Deep Oscillation) therapy at 85 Hz was applied to the back and hips, providing muscle relaxation, pain reduction, and local trophic effects. VibraMoov therapy was employed to stimulate proprioceptive function and promote motor recovery. Robotic therapy was utilized for bilateral upper limb training.

Fig. 1. Therapy with sensory-motor rehabilitation system through proprioceptive functional stimulation (personal archive)

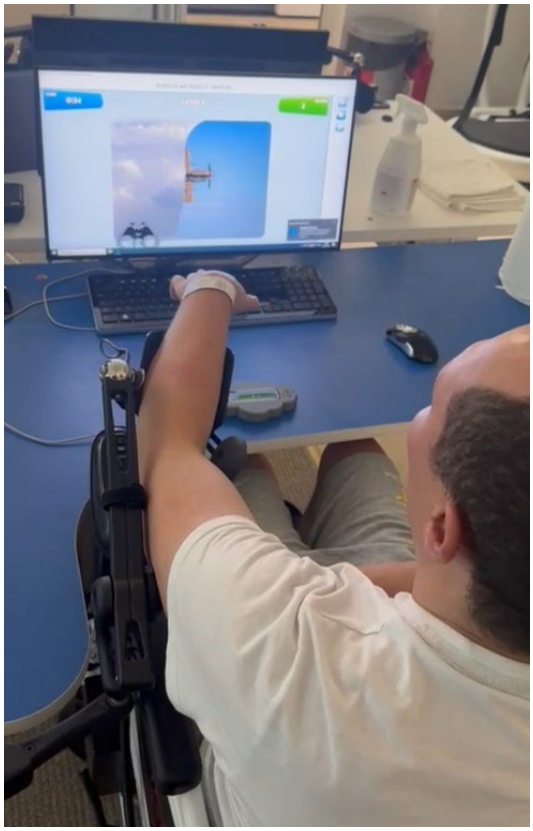

Fig. 2. Therapy with sensory-motor rehabilitation system through proprioceptive functional stimulation (personal archive)

The objectives of individual physiotherapy were to induce voluntary motor activity, improve sensory feedback, inhibit undesirable motor patterns, enhance coordination, prevent and treat joint stiffness and muscle contractures, and ameliorate cerebellar disorders. To achieve these objectives, techniques promoting muscle tone and motor activity were used, along with passive-active mobilizations associated with facilitation elements (such as brushing, and ice blocks applied to the skin over the muscle), motor facilitation exercises like slow reversal, repeated contractions, sequential strengthening, and unidirectional Kabat facilitation patterns for positive induction from well-innervated muscles. Unwanted motor patterns were inhibited using techniques proposed by Bobath, along with compensatory techniques to improve fatigue management, which included behavioral techniques to understand personal limits, activity scheduling based on daily fatigue variations, and respiratory muscle training.

3. Results

Multiple sclerosis is a complex, chronic, progressive, and unpredictable disease with a unique evolution for each individual. The progression can be aggressive, with severe stages of disability that significantly reduce the quality of life. The risk of falls and, consequently, fractures arises from visual disturbances, balance and coordination issues, loss of proprioceptive sensitivity, concentration problems, short attention span, cognitive impairments, and urinary and sexual dysfunctions.

During the hospitalization, the progression was slightly favorable, with reduced spasticity in the upper and lower limbs, and an improvement in the anxious state.

Ashworth scale	Admission	Discharge
	Upper limb 3/4	Upper limb 2/4
	Lower limb 2/4	Lower limb 3/4

Table 1. Spasticity at admission and discharge

The life prognosis (ad vitam) is reserved due to the progressive nature of the underlying disease, which can lead to death.

The functional prognosis (ad functionem) is unsatisfactory, as the patient has an EDSS score of 7. If the home physiotherapy program is continued along with recommendations related to fatigue management, heat, stress, and diet, function can be improved.

The work prognosis (ad laborem) is satisfactory at present, as the patient works online and can perform professional activities.

4. Discussion

The clinical case presented involves a young patient diagnosed during the second neurological episode, initially marked by motor abnormalities and rapidly progressing to a secondary progressive form with gradual disability accumulation, showing a poor response to baseline therapy. Male gender, pyramidal symptoms at disease onset, incomplete recovery after the first attack, and the short time interval to the second relapse are negative prognostic factors for the evolution towards the secondary progressive form[13].

Rapid progression to an EDSS score higher than 6 within 10 years from symptom onset is a marker that may classify the patient as having aggressive multiple sclerosis (MS)[14]. Vitamin D deficiency is considered a risk factor for developing multiple sclerosis and increases the risk of relapse, disability, and heightened lesion load on nuclear magnetic resonance imaging. Vitamin D can activate and proliferate lymphocytes and differentiate T-helper cells, directing its immune response regulatory effects towards self-tolerance[15]. The acquired resistance to vitamin D hypothesis has been suggested, based on the interaction between genetic susceptibility polymorphisms of the vitamin D system and an accumulation of environmental factors that alter vitamin D hormonal signaling. Treatment for vitamin D resistance is based

on a protocol of vitamin D doses up to approximately 1000 IU per kg of body weight, with dietary calcium restriction[16]. The role of vitamin D in multiple sclerosis is well-studied and known, and supplementation can be prioritized from the time of diagnosis.

The gut microbiome composition varies throughout life, influenced by factors such as diet, medications (especially antibiotics), and stress. Modulating the gut microbiota through diet can inhibit the growth of pathogenic microorganisms. Nutrients such as omega-3 polyunsaturated fatty acids, fiber, and vitamins influence the proliferation of microorganisms capable of producing anti-inflammatory substances for multiple sclerosis[17].

Patients with multiple sclerosis show taxonomic changes in the composition of their gut microbiome compared to the healthy population[18]. Therapeutic management of multiple sclerosis varies and shows individual responses for each case. Current bidirectional communication between the gut and the central nervous system has established fecal microbial transplantation as a new treatment target, seen as a way to improve neurological symptoms by normalizing intestinal permeability, and it may be considered in this case as well[19]. A study on three wheelchair-bound patients who received fecal microbiota transplantation for constipation showed dramatic improvements in neurological symptoms, with the recovery of the ability to walk unassisted[20]. Non-pharmacological treatment strategies are currently being studied to influence the gut microbiome, such as probiotics or fecal transplants[21].

Nutritional interventions can be a useful tool to improve the course of multiple sclerosis by increasing the diversity of the gut microbiota, which can alter the host's immune system[22]. Neurorehabilitation programs can have a positive influence on the gut microbiome of patients with multiple sclerosis, potentially improving disease-related inflammation levels[23].

The rehabilitation process for people with multiple sclerosis may lead to low motivation and treatment compliance due to the long periods involved. The Bobath concept is based on inhibiting pathological tonic reflexes to achieve active movement and appropriate muscle tone and is used in patients with higher EDSS scores. Hydrotherapy at temperatures between 34 and 36 degrees decreases gamma neuron activity and limits afferent impulses, leading to relaxing, analgesic, anti-spasticity effects, and improvements in depressive symptoms. Hot baths are not allowed to avoid the occurrence of the Uhthoff phenomenon[24].

Cryotherapy, applied in various forms (ice bath, ice massage, frozen silicone gel packs), can be applied systemically to achieve analgesic and fatigue-reducing effects.

Transcutaneous electrical nerve stimulation (TENS) can be used for pain treatment by placing electrodes in painful areas or along nerves. Hufschmidt current is used for spasticity in multiple sclerosis to normalize muscle tension by achieving functional balance between agonist and antagonist muscles. Repetitive transcranial magnetic stimulation applied to patients with multiple sclerosis reduces lower limb spasticity and neurogenic bladder dysfunction[25].

Neurological rehabilitation is an approach that can improve activity limitation, social participation restriction, and quality of life, even if it does not directly influence disease progression[26, 27].

4. Conclusions

Multiple sclerosis is a complex, multifactorial disease that requires an interdisciplinary approach associated with a personalized neurorehabilitation program, nutritional interventions, occupational therapy, and cognitive-behavioral therapy[28-30].

The therapeutic approach to modifying the course of the disease consists of therapies aimed at reducing relapse rates, slowing disease progression, and delaying the onset of disability.

Interventions on modifiable risk factors, neurorehabilitation, and influencing the composition of the gut microbiome can modulate the immune system and, consequently, the course of the disease.

Author Contributions: Conceptualization, C.M.L. and M.G.I.; methodology, C.M.L. and D.O.; software, C.M.L. and L.E.S.; validation, M.G.I., formal analysis, D.O. and E.V.I.; investigation, C.M.L. and B.G.; resources, C.M.L.; data curation, C.M.L.; writing—original draft preparation, C.M.L; writing—review and editing, C.M.L. and M.G.I.; visualization, D.O. and L.E.S.; supervision, M.G.I and D.O..; project administration, M.G.I. All authors contributed equally in this paper.
Funding: This research received no external funding.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. The patient(s) has obtained written informed consent to publish this paper.
Data Availability Statement: All information in this review is documented by relevant references.
Acknowledgments: The research was conducted with the support of the Research Nucleus of Balneal Sanatorium of Techirghiol, Romania
Conflicts of Interest: The authors declare no conflict of interest.

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