

# Successful Application of Magnetite Nanoparticles in The Comprehensive Therapy of Multiple Sclerosis: A Clinical Case

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## Abstract

Multiple sclerosis (MS) is a serious neurological disorder due to its widespread prevalence, chronic nature, frequent progression to disability, and tendency to affect young people. The pathogenesis of MS is based on the immunopathogenesis hypothesis. Biocompatible magnetite nanoparticles, which exhibit selective sorption activity towards cell membrane surface proteins, circulating immune complexes, lymphocytotoxic antibodies, and the complement system, as well as enhance phagocytic activity and the completion index of leukocyte phagocytosis, can be effectively used for immunocorrection. The main goal of the study is to slow the progression of MS, improve the neurological status and overall condition of the patient, and reduce the dynamics of the spread of demyelinating lesions in the brain. Materials and methods: A patient diagnosed with multiple sclerosis, secondary progressive type, cerebrospinal form, at the clinical aggravation stage was included in the study. Neurological status and disability were assessed using the EDSS scale, and brain MRI with contrast enhancement was performed. The nanodevice Micromage-B was administered orally as an immunosorbent and immunomodulator. The regimen and dosage of Micromage-B were personalized. Assessments of general condition and neurological status were conducted every 7 days for 6 months, with contrast-enhanced brain MRI performed in the 5th month. Results: The use of Micromage-B in MS treatment led to an objective improvement in neurological status, with reduced stiffness and fatigue in the lower extremities. Gait and coordination improved, hand tremors decreased, depression and concentration disorders subsided, appetite was restored, and speech improved. Throughout the treatment period, positive dynamics in the normalization of neurological status were observed. After 6 months, the total score on the EDSS scale decreased from 210 to 45.

The most significant improvements were observed in the evaluation of the pyramidal system and coordination, with the EDSS Disability Scale score decreasing from 6.0 to 5.0. For the first time, contrast-enhanced brain MRI showed a reduction in the number of new demyelination foci by the 4th month of Micromage-B administration. The positive changes in neurological status correlated with the MRI results. The recovery of central nervous system activity in MS is likely not only due to the immunosuppressive properties of magnetite nanoparticles but also due to the activation of remyelination mechanisms and oligodendrocyte differentiation through enzymatic methylation. Conclusion: The use of biocompatible nanodevices in the complex treatment of MS is promising. Further improvement and study of the regimen and method of using biocompatible magnetite nanoparticles to enhance MS treatment effectiveness are required.

**Keywords:** Multiple Sclerosis; Treatment; Nanodevice; Micromage-B; Neurological status assessment; Remyelination; MRI, Central nervous system; Antigens; Antibodies; Complete Immunosuppression; Migration; B-lymphocytes; Immunopathogenesis; Cerebellar ataxia

## Introduction

Multiple sclerosis (MS) is a significant neurological issue due to its widespread prevalence, chronic nature, frequent progression to disability, and tendency to affect young people, with an average onset age of 30 years. The primary hypothesis of MS immunopathogenesis suggests that immunological tolerance

is disrupted, leading to the active penetration of autoreactive cells sensitized to nervous tissue antigens through the blood-brain barrier into brain tissue. B-lymphocytes recognize myelin and signal T cells to initiate an immune attack [1-7]. T- and B-cells secrete chemicals that attract other immune cells, causing

inflammation [8,9]. Plasma cells produce antibodies that attack myelin and recruit other immune cells [10,11]. T- and B-cells establish a persistent presence in the central nervous system (CNS) and continue their attack [12,13]. There are two main hypotheses for MS pathogenesis: the outside-in hypothesis, which posits that immunocompetent cells activated in the periphery penetrate brain tissue, and the inside-out hypothesis, which suggests primary damage to nervous tissue leads to the expression of damage receptors from the DAMPs (Danger-associated Molecular Patterns) family, resulting in immune activation and loss of tolerance to myelin antigens [14]. Antibodies produced by plasma cells actively destroy the protective covering of nerve cells, causing inflammation. Over time, this tissue becomes scarred, disrupting conduction. Consequently, impulses from the brain fail to reach the limbs and organs, leading to a loss of body control [15]. Common initial clinical symptoms include weakness and impaired sensation in one or more limbs, decreased vision, urinary disturbances, and cerebellar ataxia.

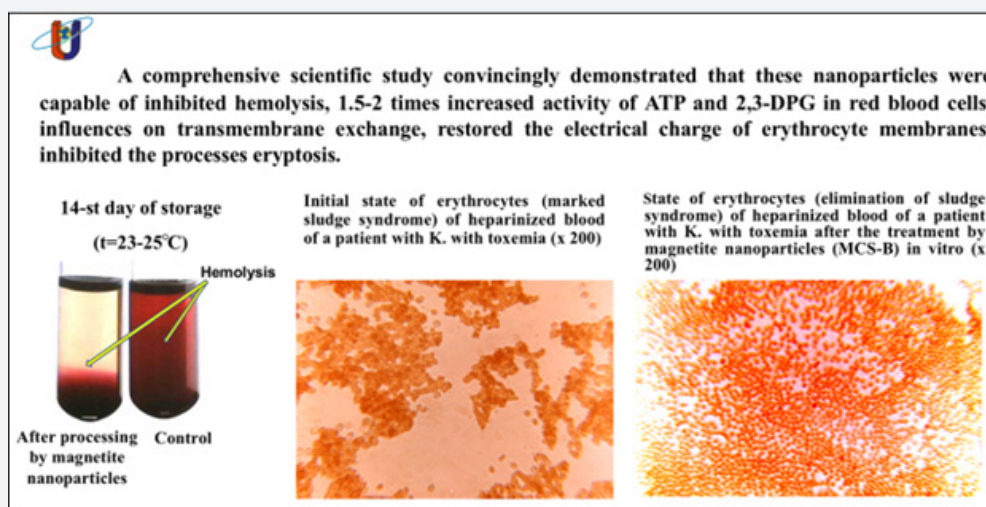
Currently, immunomodulatory and immunosuppressive drugs that alter the course of MS form the cornerstone of pathogenetic treatment. Their mechanisms of action involve: 1) selective immunosuppression, 2) complete immunosuppression, 3) prevention of the migration of activated cells from lymph nodes or into brain tissue, or 4) a combination of immunoregulatory, anti-inflammatory, antioxidant, and potentially neurotrophic actions. Future directions for new MS treatments include selective local immunocorrection, remyelination and neuroprotection, enhancement of neuroplasticity and functional relocalization, evaluation of the efficacy and safety of cell therapy, and individualized therapy selection based on predictions of pathological process variants and potential treatment responses derived from the molecular and cellular biology of MS [16-22]. The development of inflammation and demyelination in MS is driven by an impaired immune response, imbalance between regulatory and effector T cells, activation of B-cell immunity, and microglia. All drugs that impact the course of MS either deplete T- or B-cells or modify the signaling pathways involved in immune response

formation [23]. Recently, significant attention has been given to the role of B-cells in chronic CNS inflammation, evidenced by their involvement in autoantibody formation, antigen presentation, and continuous T-cell activation in the brain parenchyma. Anti-B-cell therapies (Rituximab, Ocrelizumab, Ofatumumab) have shown effectiveness in both remitting and progressive MS. Stimulating remyelination in MS is associated with the development of new monoclonal antibody preparations, such as anti-LINGO and human immunoglobulin M (IgM), which promote remyelination and the differentiation of oligodendrocytes and their precursors [24]. One of the key mechanisms of axonal degeneration is mitochondrial dysfunction. Some drugs, such as Dimethylfumarate, Idefenone, and Biotin, show promise in addressing this issue [25]. Additionally, the use of drugs that affect the redistribution of ion channels in demyelinated axons (Lamotrigine, Amiloride, Fampridine) can help reduce the energy deficit in axons and neurons [26].

Recently, biocompatible nanotechnological preparations have seen increasing use in medicine. Since 1998, Ukrainian clinics have been officially using nanodevices developed by Belousov's Applied Nanotechnology Laboratory, including the Micromage-B, MCS-B, and ICNB brands (Figure 1) [27]. These nanodevices are based on biocompatible magnetite nanoparticles, whose unique physical and chemical characteristics enable a wide range of applications. They influence the quantitative and qualitative composition of bodily fluids, metabolic and biochemical processes, and the energy balance of cells. Their selective sorption activity against surface proteins of cell membranes, circulating immune complexes, lymphocytotoxic antibodies, and the complement system, as well as their ability to enhance phagocytic activity and leukocyte phagocytosis completion index [28], allow these nanodevices to be effectively used for immunocorrection. Moreover, these nano preparations impact glycolysis processes, cell membrane ion channel activity, normalize erythrocyte function, improve microcirculation, and reduce the platelet aggregation index (Figure 2) [29-31]. They also activate the system of antiradical enzymes and inhibit lipid peroxidation processes [32,33].



Figure 1: New official nanomedical devices based on biocompatible magnetite nanoparticles.



**Figure 2:** Effect of biocompatible magnetite nanoparticles on functional status of erythrocytes and hemorheology.

Figure 2. Effect of biocompatible magnetite nanoparticles on functional status of erythrocytes and hemorheology. The results of these studies lay the foundation for developing innovative techniques for the effective and safe use of biocompatible magnetite nanoparticles in treating severe autoimmune diseases, including multiple sclerosis. The primary objective of the study is to slow the progression of MS, improve the neurological status and overall condition of the patient, and reduce the spread of demyelinating foci in the brain.

### Materials and Methods

Patient K. was diagnosed with multiple sclerosis, secondary progressive type, cerebrospinal form, at the clinical aggravation stage. The patient presented with pronounced spastic tetraparesis, more severe in the lower extremities, leading to walking impairment, pronounced urinary-ataxic syndrome, and sphincter and sensory disorders. MRI revealed signs of multifocal diffuse brain lesions (more than 30) of a demyelinating nature, indicating the active phase of the disease, and a diffuse atrophic process in the cerebral cortex. The average number of relapses in the year before study inclusion was 1.0, and the EDSS disability score was 6.0. The disease had progressed for 24 years since the onset of the first symptoms. For 14 years, the patient received regular treatment with vascular and metabolic drugs in combination with hormonal therapy. In the 6th year, despite active treatment, the disease progressed to a secondary progressive course, leading to the addition of the immunosuppressive drug Teriflunomide to the therapy regimen. However, despite all treatment efforts, the patient's general condition progressively worsened, and the neurological status did not stabilize. MRI examinations over the last four years showed a continuous increase in the number of new demyelinating foci in the brain. Given the above, the therapy regimen was supplemented with the prescription of Micromage-B

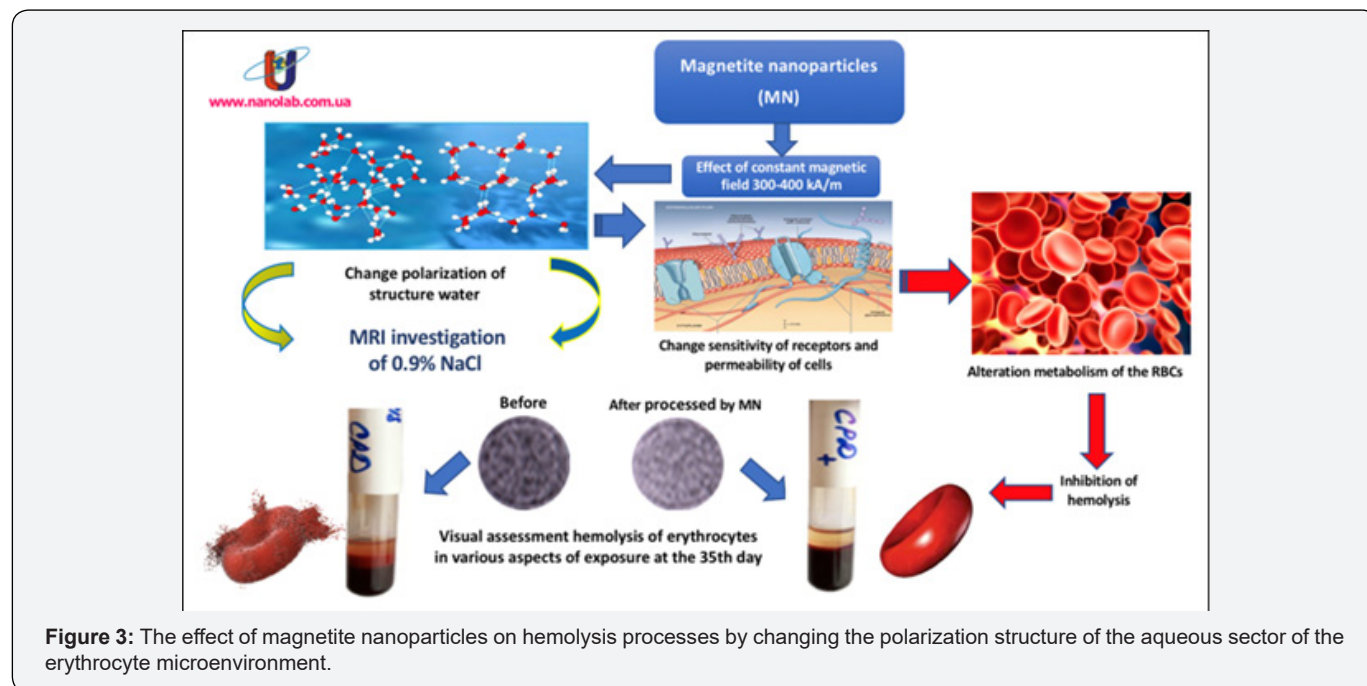
[34]. Before starting the study, the patient's formal consent to the use of Micromage-B was obtained. This fact was recorded in the medical history, and the plan of treatment and subsequent study was agreed with the attending physician. Micromage-B is an oral nanodevice officially registered by the Ministry of Health of Ukraine. It is a powder form of magnetite ( $\text{Fe}_3\text{O}_4$ ) nanoparticles designed for the prevention and treatment of various diseases and to enhance the body's resistance to adverse environmental factors.

As a nanotechnology device, Micromage-B features magnetite nanoparticles sized between 6 and 12 nm. The therapeutic effect of Micromage-B is based on the mechanism of sorption and the action of a constant magnetic field on cellular and subcellular structures induced by the magnetite nanoparticles. The nanoparticles have a sorption surface area of 800 to 1200  $\text{m}^2/\text{g}$  and an induced magnetic field strength of 300-400 kA/m. The target of Micromage-B is the microenvironment of the cell's aqueous spaces and surface membrane proteins. Through selective sorption, the magnetite nanoparticles alter the quantitative and qualitative composition of cell surface proteins, and the constant magnetic field changes the mobility and orientation of hydrogen protons in the cell's aqueous microenvironment (Figure 3).

Figure 3. The effect of magnetite nanoparticles on hemolysis processes by changing the polarization structure of the aqueous sector of the erythrocyte microenvironment. This leads to the activation of hydrolysis of the phosphate residue ATP, ultimately modifying the cell's transmembrane exchange and metabolism, and altering its susceptibility. The nanodevice enhances adaptive mechanisms and the potential of cell organelles, accelerates reparative processes at the membrane and macromolecule levels, significantly increases the level of synthetic intracellular reactions. Additionally, Micromage-B nanoparticles adsorb toxic

substances and circulating immune complexes, significantly enhancing the treatment efficacy of various allergic diseases, autoimmune processes (such as rheumatoid arthritis, acute and chronic polyarthritis, eczema, etc.), and acute poisoning. Micromage-B regulates the activity of antioxidant enzymes, absorbs lipid peroxidation products, and rebalances antiradical

and pro-radical product levels [35,36]. The dosing regimen for Micromage-B entails 500 mg daily for the first month, 500 mg every other day for the second month, and subsequently, 500 mg once every three days. The selection of Micromage-B dosage and regimen is tailored individually, considering the patient's rate of improvement and neurological recovery.



**Figure 3:** The effect of magnetite nanoparticles on hemolysis processes by changing the polarization structure of the aqueous sector of the erythrocyte microenvironment.

The study monitored changes in neurological status using a modified version of the Multiple Sclerosis Patient Assessment Scale [37,38], which evaluates the severity of motor impairments alongside other nervous system damage indicators. Disability was quantitatively assessed using Kurtzke's online EDSS calculator [39]. Manifestations of cerebral demyelination foci were examined through contrast-enhanced MRI. The patient's overall condition and neurological status were assessed every 7 days over a 6-month period. As per the protocol, a contrast-enhanced MRI of the brain was conducted annually, aligning with the 5th month of Micromage-B usage.

## Results

The progression of neurological changes was assessed using a modified scale. One week following the administration of Micromage-B, a marked enhancement in the patient's neurological condition was evident. The patient reported a notable reduction in

lower limb stiffness and rapid fatigue. Objectively, improvements were observed in gait and coordination, reduction in hand tremors, complete alleviation of depression and concentration issues, restoration of appetite, and enhancement in speech. Positive trends in normalizing neurological status persisted throughout the entire duration of Micromage-B treatment. Table 1 illustrates the evaluation of a multiple sclerosis patient's neurological status before and after 6 months of Micromage-B administration. Estimated scores of the neurological status before and after using the Micromage-B. The data presented in Table 1 illustrate a positive trend in normalizing neurological status following 6 months of Micromage-B usage. Initially, the total points amounted to 210, which decreased to 45 after the 6-month period, indicating a reduction of 165 points. The most significant improvement was observed in the assessment of the pyramidal system and coordination. Additionally, the EDSS disability scale score decreased from 6.0 to 5.0.

Table

1. Movements (pyramidal system)				
Input data		Six months after application Micromage-B		Clinical manifestations
Arm	Leg	Arm	Leg	
0	0	0	0	Norma
5	10	5*	10*	Absence of loss symptoms, revival of tendon reflexes, enlargement of reflexogenic zones, clonus, presence of pathological signs, anisoreflexia, (absence of paresis)
10	20	10	20	Raises a limb independently, full volume of active movements, signs of pyramidal lesion, overcomes not only the gravity of his own limb, but also an additional obstacle of moderate strength, positive Barre-Rusetsky's symptom
15	40	15	40	Raises a limb independently, the volume of active movements is full, cannot hold a limb in a given position for a long time, and cannot overcome an additional obstacle.
20*	60*	20	60	Can pull a limb off the plane, the amount of active movement is limited, cannot hold a limb in a given position.
40	80	40	80	Cannot detach a limb from the plane, active movements in the joints of the fingers, ankle and wrist, elbow, knee joints are possible only on the plane.
50	100	50	100	Complete absence of movement (paralysis)
2. Sensitivity				
Before	After		(a) superficial sensitivity	
0	0*		Norma	
5	0		Paresthesias, burning sensation, numbness, coldness of a limb (no objective disorders)	
10*	10		Hyperesthesia or hypoesthesia	
15	15		Anesthesia phenomena	
b) deep sensitivity				
0*	0*		Norma	
10	10		Disorder of joint and muscle feeling in small joints	
20	20		Disorder of joint and muscle feeling up to the level of the middle joints (wrist, ankle)	
40	40		Disorder of joint and muscle feeling up to the level of large joints (elbow, shoulder, knee, hip)	
3. Coordination				
0	0		Norma	
10	10*		Unsteadiness, swaying in the sensitized Romberg's test while standing on one leg, mild intensional trembling (in the complicated test), slight ataxia in the heel-knee test, deviation when walking with eyes closed.	
40*	10		Unsteadiness in simple Romberg's pose, atactic gait with open eyes and legs spread wide apart, "drunkenness," moderately pronounced intensional tremor and ataxia in the heel-knee test.	
100	100		Because of ataxia, the patient cannot move without assistance, sharp hypotonia of muscles, intensional shaking of the head, trunk, coarse - upper extremities, coarse ataxia during heel-knee test, trembling of upper extremities when trying to perform purposeful movement, chanted speech.	
4. Psycho-emotional sphere				
0	0*		Norma	
10	10		Mild impairment of the intellect in combination with euphoria, rapid change of mood, neurasthenic syndrome.	
20*	0		Euphoria, depression, decreased criticism of one's condition, decreased memory.	
100	100		Severe mental disorder, complete intellectual disintegration, Korsak's syndrome, etc.	
5. Nystagmus				
0	0*		Norma	

5	5	Nystagmus is detected only in the extreme leads (degree 1)
<b>10*</b>	10	Nystagmus when looking straight ahead (degree 2)
15	15	Sharp beating nystagmus, nystagmus in both directions, even toward the slow component (3rd degree)
6. State of the sphincters		
0	<b>0*</b>	Norma
<b>10*</b>	10	Impulsive urges, inability to hold urine for a long time, difficulty urinating
20	20	Urinary incontinence, urinary retention, intermittent urination disorders, persistent constipation
7. Sexual function		
0	<b>0*</b>	Norma
<b>5*</b>	5	Decreased sexual activity in men (intermittent impotence), sexual coldness in women
10	10	Total impotence, menstrual disorders in women
8. The ocular fundus		
0	0	Norma
5	5	Disturbance of vascular pattern, narrowing of arteries, dilation of veins, changes on fluorescence ophthalmoscopy
<b>10*</b>	<b>10*</b>	Partial optic atrophy (bitemporal pallor), optic neuritis
15	15	Complete atrophy of the optic nerve
9. Visual acuity		
0	0	Norma (vision within 1.0 or myopia)
5	5	Occasional blurring of vision, rapid fatigue when reading and performing work without impaired visual acuity
<b>10*</b>	<b>10*</b>	Visual acuity from 0.9 to 0.7
15	15	Visual acuity from 0.6 to 0.4
20	20	Visual acuity from 0.3 to 0.1
25	25	Visual acuity 0.1 and below
100	100	Blindness in one or both eyes
10. Oculomotor nerves		
0	<b>0*</b>	Norma (absence of subjective and objective symptoms)
<b>5*</b>	0	Concealed insufficiency, without visible dysfunction of one of the oculomotor nerves, internuclear ophthalmoplegia syndrome
10	10	Mild visible impairment, visible insufficiency of one or more nerves, diplopia, ptosis, anisocoria
15	15	Convergent or divergent strabismus
20	20	Complete ophthalmoplegia (in one or both eyes)
11. The trigeminal nerve		
<b>0*</b>	<b>0*</b>	Norma (absence of subjective and objective symptoms)
5	5	Subjective sensations in the form of pain, numbness, sense of "creeping chills", oppression in the face.
10	10	Objective signs of lesions, hypoesthesia, loss or decrease in the corneal reflex.
20	20	Severe anomalies with loss of trigeminal nervous functions, with or without neuralgic disorders.
12. The facial nerve		
0	<b>0*</b>	Norma
<b>5*</b>	0	Moderate weakness of facial muscles (eye closes completely, but cannot actively close it), asymmetry of frontal and nasolabial folds

10	10	Moderate weakness of mimic muscles (lagophthalmus, positive Bell's symptom, facial asymmetry in grinning), with preservation, to some extent, of mimic movements
20	20	Complete paralysis of facial muscles
13. Bulbar group of cranial nerves (nerves 9,10,11,12)		
0	0*	Norma
5*	5	Mildly pronounced bulbar phenomena (gagging when taking liquid food, change in speech, without gross organic symptoms of prolapse)
10	10	Severe dysphagia, dysarthria, decreased soft palate and posterior pharyngeal wall reflexes
100	100	Complete bulbar paralysis
14. Auditory nerve		
0*	0*	Norma
5	5	Conversational speech at a distance of 4 to 6 m, whispered speech at a distance of 1 to 3 m.
10	10	Speech - from 2 to 4 m, whisper - from 0.5 to 1 m.
15	15	Spoken speech 2 m or less, whispered speech 0 to 0.5 m
20	20	Complete deafness in one or both ears
Total:	Total:	
<b>210*</b>	<b>45*</b>	

A contrast-enhanced MRI of the brain conducted after 4 months of Micromage-B usage revealed a decrease in the number of new demyelination foci in the brain for the first time. The favorable progression of neurological status correlated with the brain MRI findings. Upon analyzing the collected data, particular attention should be given to the observed positive clinical effects attributed to immunosorption and the active contribution of Micromage-B's magnetite nanoparticles to neurological status restoration. This effect may be attributed to remyelination processes and oligodendrocyte differentiation. Oligodendrocytes, a type of neuroglial cell, form the myelin sheath around neurons in the central nervous system (CNS). The molecular mechanisms underlying cell differentiation and specialization remain complex and poorly understood, presenting a challenging area in cell and developmental biology. The development and maturation of various cell types continue to pose significant research challenges. However, it is now understood that one mechanism underlying oligodendrocyte maturation involves enzymatic methylation, specifically the addition of a methyl group (-CH<sub>3</sub>) to the N6 nitrogen atom in adenosine's nitrogenous base, referred to as m6A-methylation. Despite its seemingly minor nature, this modification can significantly impact subsequent stages of protein biosynthesis. The role of m6A-methylation has been demonstrated in numerous processes associated with oligodendrocyte maturation [40]. The body's universal methyl group donor is S-adenosylmethionine, generated through the interaction between the amino acid methionine and ATP. Given that Micromag-B activates glycolysis, it significantly increases the production of the macroergic compound ATP [41,42], and promotes the formation of the reduced form of the coenzyme NADPH<sub>2</sub>, facilitating the conversion of oxidized glutathione to its reduced form [43]. These conditions are conducive to initiating enzymatic methylation processes, which likely enhance the

mechanism of action of magnetite nanoparticles (Micromag-B). This, in turn, supports the differentiation of oligodendrocytes and the remyelination process. Additionally, it should be noted that these nanoparticles polarize the aqueous environment of the cellular microenvironment [44], leading to the activation of ATP hydrolysis, energy release, and the formation of ADP. For a detailed understanding of how biocompatible magnetite nanoparticles (Micromag-B) influence remyelination processes, refer to Figure 4.

Given the positive neurological status dynamics, it was deemed appropriate to continue Micromage-B nano preparation administration at the prescribed dosage. Therapy was augmented with a regimen of rehabilitative exercises aimed at expediting the restoration of physical, cognitive, and psychosocial functions in patients with MS. Considering the positive progression in neurological status, it was decided to continue the administration of the nano preparation Micromage-B at the prescribed dosage. Additionally, the therapy was augmented with a comprehensive rehabilitation exercise program designed to expedite the recovery of physical, cognitive, and psychosocial functions in a patient with MS.

### Conclusion

The study's results broadened the clinical effectiveness of biocompatible magnetic nanoparticles in treating severe autoimmune diseases [45-48]. The use of the Micromage-B nano preparation in treating multiple sclerosis (MS) demonstrated a significant positive clinical effect. Positive trends in normalizing the neurological state were observed throughout the application period of Micromage-B. After six months of treatment, the overall score decreased from 210 to 45. The most notable improvement was seen in the assessment of the pyramidal system

and coordination. The EDSS Disability Scale score decreased from 6.0 to 5.0. For the first time, contrast-enhanced MRI of the brain recorded a reduction in the number of new demyelination foci by the fourth month of Micromage-B administration. The normalized neurological condition correlated with positive brain

MRI results. The restoration of central nervous system activity in MS is attributed not only to the immunosuppressive properties of magnetite nanoparticles but also likely to the activation of remyelination mechanisms and oligodendrocyte differentiation through enzymatic methylation.

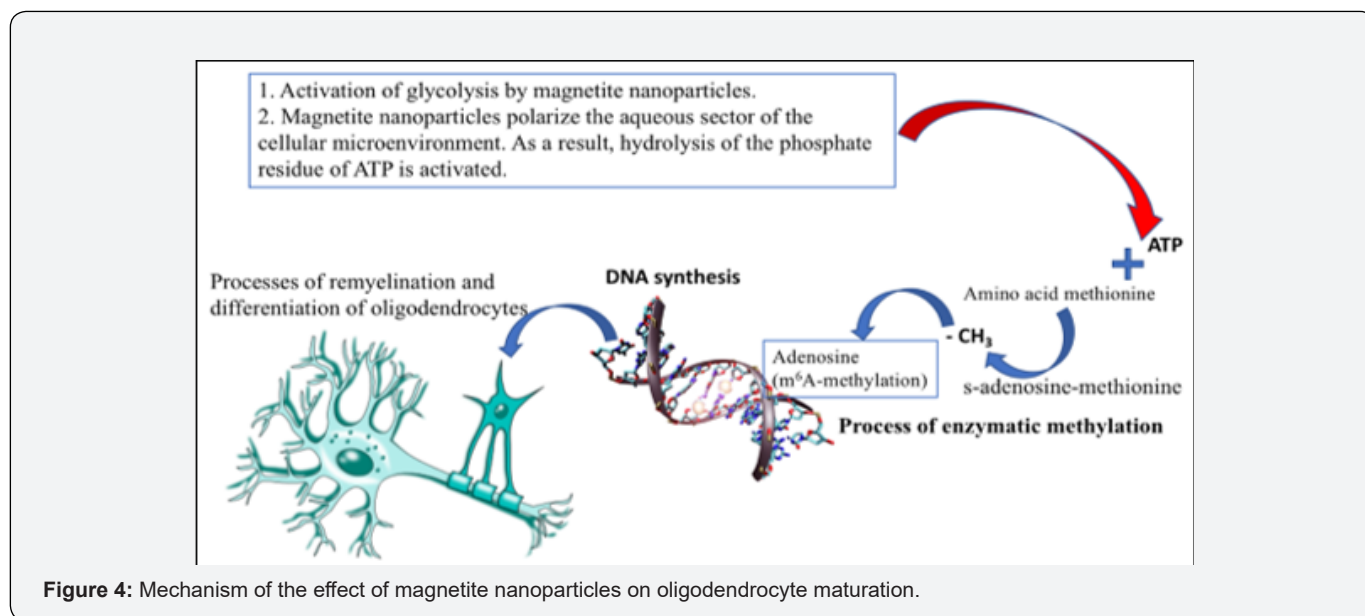


Figure 4: Mechanism of the effect of magnetite nanoparticles on oligodendrocyte maturation.

The design and method of using biocompatible magnetite nanoparticles to enhance MS treatment efficiency require further refinement and research. The use of biocompatible nanodevices in the comprehensive treatment of MS is a promising innovation [49-51]. Micromage-B is a biologically active form of a nanodevice officially approved by the Ministry of Health of Ukraine and authorized for clinical use since 1998. To date, no side effects or contraindications to its use have been identified. Given the key properties of bio-compatible magnetite nanoparticles, their clinical applications continue to expand. Recent studies have deepened our understanding of the mechanisms regulating cellular metabolism, microcirculation, erythropoiesis, as well as the mechanisms of action of antibacterial agents and other processes. To substantiate the necessity of further utilizing magnetite nanoparticles in larger clinical trials, it is crucial first to identify relevant biochemical markers. These markers should not only objectively reflect the severity of multiple sclerosis from a pathogenetic perspective but also provide a high-probability prognosis of disease outcomes.

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