Study of the Level of Matrix Metalloproteinase-9 as an Indicator of Activity of Inflammatory Process Among Patients Suffering from Multiple Sclerosis

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Received: March 31, 2025
Published: April 30, 2025

Abstract. Multiple Sclerosis progresses in Ukraine as a cause of disability of young people in conditions of martial law. The role of matrix metalloprotease-9 in the development of the inflammatory process in different types of multiple sclerosis is considered. A study of the level of matrix metalloprotease-9 was conducted in 135 patients with multiple sclerosis with different types of course and at different stages of activity of the pathological process. Higher levels of matrix metalloprotease-9 were found in patients with the remitting type of the disease at the stage of exacerbation, while in patients with the primary-progressive type of the disease this indicator was the lowest. The study of the level of matrix metalloprotease-9 allows us to judge the degree of severity of the inflammatory process and serves as a means of monitoring the effectiveness of multiple sclerosis therapy. It requires a pharmacoeconomic study of the stages of clinical monitoring of patients using a complex of pharmacotherapeutic measures and drugs. The data of the World Health Organization on additions to the Essential Medicines List and the Essential Medicines List for Children with innovative drugs for the treatment of multiple sclerosis, improving the health of the population worldwide, WHO Recommendations and ICD-11 require the development of the issue for the publication of the monograph "Medicines for neurologists, psychiatrists and narcologists" in a new edition.

Keywords: multiple sclerosis, diagnosis, matrix metalloproteinase-9, remitting course, progressive course, pharmacotherapy.

Introduction. Multiple Sclerosis is progressing in Ukraine as a cause of disability of young people in conditions of martial law. Due to constant stress, the number of patients with multiple sclerosis at the age of 20-30 is increasing [1-3]. As of 2023, the number of patients with Multiple

Sclerosis in Ukraine was 28,500 citizens, and by 2024 their number had increased to 30 thousand patients. If we consider the latency of the disease and the complexity of diagnosis, the number of patients with Multiple Sclerosis can be up to 70-100 thousand people. As Berezivska S. notes, among the problematic issues associated with Multiple Sclerosis [4]:

- treatment is expensive and almost inaccessible for independent purchases of medicines by patients;
- the initial cost of one drug is from 50 thousand hryvnias;
- drugs are ordered by the state and issued to patients free of charge by prescription in accordance with the Orders of the Ministry of Health of Ukraine dated January 13, 2025. No. 86 and dated January 13, 2025 No. 76 [5, 6];
- provision of patients with multiple sclerosis in the city of Kyiv is carried out in accordance with the order of the Department of Health of the executive body of the Kyiv City Council (Kyiv City State Administration) dated December 19, 2024 No. 1193 “On the distribution of medicines for the treatment of patients with multiple sclerosis, purchased from the budget of Kyiv for 2024” and is assigned to the head of the municipal non-profit enterprise “Kyiv City Clinical Hospital No. 4” [7].

Therefore, the task of the healthcare sector is to ensure timely access of citizens to the level of doctors (paramedic and obstetrician point, general practice family medicine outpatient clinics) for the diagnosis of the health disorder for signs of Multiple Sclerosis at an early stage of the disease development. The mechanisms underlying the pathogenesis of multiple sclerosis, as Ciccarelli O., Barkhof F., Bodini B., De Stefano N., Golay X., Nicolay K. believe, cause changes that cause relapses and progressive disability of the patient. The mechanisms of the disease can be studied in preclinical models, in patients with multiple sclerosis using molecular and metabolic imaging methods. Thanks to such imaging studies, an understanding of the problems has been gained [8]:

- persistent inflammation in the absence of a damaged blood-brain barrier;
- activated microglia inside and outside the lesions;
- enhanced mitochondrial activity after acute lesions;
- increased sodium concentration in the brain;
- increased glutamate in acute lesions and normal white matter;
- different degrees of demyelination in different patients and lesions;
- early neuronal damage in the gray matter;
- early astrocytic proliferation and activation in lesions and white matter.

That is, the clinical translation of molecular and metabolic imaging and the expansion of these methods will allow us to assess the mechanisms of action of modern drugs. Pharmacotherapeutic action is directed at the mechanisms of the disease. It will have the potential to improve health outcomes through stratification of patients for the quality, effectiveness, and safety of treatment.

Multidisciplinary research in the system of legal relations "doctor-patient-pharmacist" made it possible [9-17]:

- obtain data using immunological, morphological and neuroimaging research methods;
- prove significant changes in the traditional understanding of the treatment of multiple sclerosis;
- clinically prove that Multiple Sclerosis, as a disease of the central nervous system, causes the destruction of myelin [18] of the conductors of the brain and spinal cord [19-21];
- to reveal that the pathological process continues even in the phase of clinical remission, axons are damaged from the initial stage of the disease; in addition to the white matter of the central nervous system, the gray matter of the cortex and subcortex is damaged.

However, several issues remain unresolved. The different clinical course of Multiple Sclerosis, the heterogeneity of its clinical manifestations, the different effect of immunomodulatory therapy in the same clinical forms indicate different pathogenetic mechanisms of damage to the central nervous system in Multiple Sclerosis.

The scientific and practical goal of the study of Multiple Sclerosis is [19]:

- ❖ to study the mechanisms of development of neurodegenerative processes, to assess the relationship between inflammatory, immunopathological and degenerative processes;
- ❖ to establish informative immunobiochemical markers that would allow to control the activity of the pathological process in different courses of multiple sclerosis by assessing the activity of the process and prognosis;
- ❖ elucidation of the mechanisms that cause exacerbation and remission;
- ❖ the applicability of immunological and biochemical markers to assess the effectiveness of immunocorrective and anti-inflammatory therapy is controversial.

Fig. 1 shows that in multiple sclerosis, the immune system attacks the nerve sheaths of the brain and spinal cord (myelin), which disrupts their ability to send signals [18].

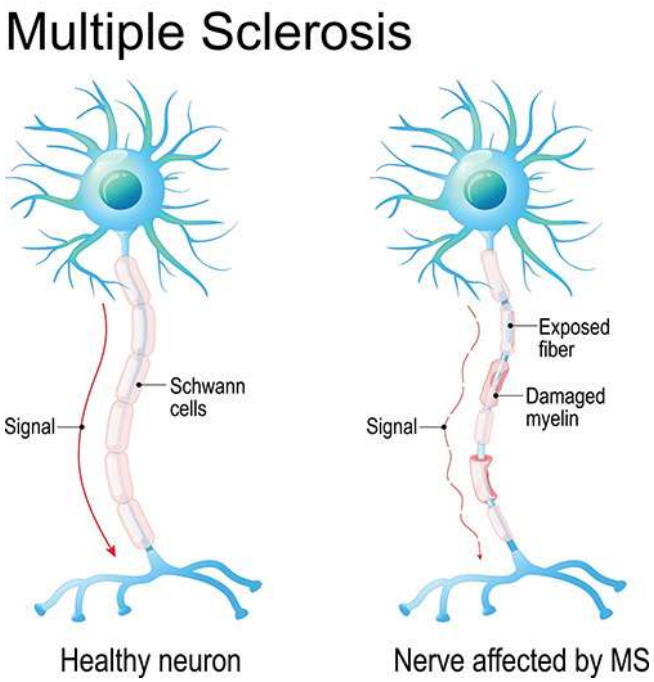

Fig. 1. Multiple Sclerosis: the immune system attacks the nerve sheaths of the brain and spinal cord (myelin) [18].

The proposed methods are complex, laborious, and economically expensive. Therefore, the search for informative and widely available markers suitable for monitoring and predicting the pathological process is relevant.

At the same time, in modern conditions, multidisciplinary research is being conducted aimed at finding new, more effective methods of treating Multiple Sclerosis, which are closely related to the in-depth study of the links in the pathogenesis of the disease, many aspects of which have not yet been clarified. In particular, the role of matrix metalloproteinase is not well understood. Normally, it is a physiological mediator in the pathogenesis of Multiple Sclerosis. Most of the research is based on animal experiments and studies of matrix metalloproteinase in vitro [22, 23].

One of the main pathogenetic links of Multiple Sclerosis is the disruption of the blood-brain barrier and the migration of plasma proteins to the brain parenchyma of matrix metalloproteinase. Matrix metalloproteinase forms a series of enzymes. The main activity is the remodeling of the extracellular matrix. Matrix metalloproteinase-9 (or gelatinase B) is the most complex in terms of domain structure and regulation of activity. The activity of matrix metalloproteinase-9 is strictly regulated at different levels: regulation of genetic transcription by cytokines and various cellular interactions; regulation of proenzyme activation by a cascade of enzymes, including serine proteases and other matrix metalloproteinases; regulation by specific tissue matrix metalloproteinase inhibitors (TIMP- tissue matrix metalloproteinase inhibitors) or nonspecific inhibitors. The main function of matrix metalloproteinase is the degradation of extracellular matrix components [24].

Matrix metalloproteinases are involved in many processes (Table 1).

Table 1. Role of matrix metalloproteinase in extracellular matrix (ECM) remodeling [24].

Physiological processes	Pathological processes
Ovulation	Growth / metastatic dissemination of tumors
Trophoblast and blastocyst implantation	Rheumatoid arthritis, osteoarthritis
Embryogenesis	Periodontium disease
Morphogenesis of salivary glands	Pulmonary fibrosis
Development/involution of mammary glands	Liver cirrhosis
Dilatation of cervix uteri	Gastric and stercoral ulcer
Uterine involution	Dilatational cardiomyopathy
Development/alteration of bones	Atherosclerosis
Healing of wounds/fractures	Arterial aneurism
Angiogenesis	Glomerulonephritis
Functioning of macrophages/ neutrophils	Encephalomyelitis

Clinicians attach great importance to the study of the role of matrix metalloproteinase in the detection of inflammation. An in-depth retrospective analysis of scientific sources since 1995 shows that [25]:

- most cells involved in immune reactions and inflammation (T lymphocytes, macrophages, eosinophils, and neutrophils) produce some matrix metalloproteinase;
- production of the role of matrix metalloproteinase depends on various inflammatory mediators;
- synthesis of matrix metalloproteinase in macrophages is induced by contact with collagen and is additionally intensified by T-lymphocyte membrane determinants;
- damage of matrix metalloproteinase prepares the vascular wall for adhesion of immune cells, promotes migration of cells, proteins, antibodies through the basement membrane to tissues [26-28];
- according to the publications of Luiz G., Gottschall P.E., Deb S., the role of matrix metalloproteinase is very important for the development and differentiation of the central nervous system and can be produced by neurons [29, 30];
- through the remodeling of the ECM (extracellular matrix) there is an impact on various functions of the nervous tissue, growth factor concentration, formation, and stabilization of synapses and subsequent interneuronal and neuroglial interaction.

Published studies conducted by Kaur K.K., Allahbadia G., Singh M. and Behl T., Kaur G., Sehgal A., are devoted to the role of matrix metalloproteinase in metastatic dissemination of tumors of the central nervous system, stroke, neurodegenerative and demyelinating diseases [31, 32].

Some studies are devoted to the study of the activity and intensity of matrix metalloproteinase in infectious diseases of the central nervous system. Particular attention is paid to the role of matrix metalloproteinase in bacterial meningitis. The main pathogenetic mechanism of secondary damage in demyelinating diseases is the disruption of the blood-brain barrier. Inflammatory mediators play a certain role in the disruption of the blood-brain barrier [33-35]. However, the mechanisms of the disruption of the blood-brain barrier have not yet been comprehensively studied.

Thus, matrix metalloproteinase is a physiological mediator important for the growth, development and functioning of the central nervous system, affects proteolytic enzymes that actively interact with cellular and humoral factors of the immune system and trigger pathological processes.

The purpose of the study was to improve the level of diagnostics of the stages of the pathological process in Multiple Sclerosis and further optimize the process of pharmacotherapy depending on the activity of the inflammatory process in the patient.

Materials and methods. 137 patients were examined: 55 men (40.1%) and 82 women (59.9%) from 18 to 67 years old with Multiple Sclerosis (diagnosed according to the McDonald criteria, 2007) of various courses and at different stages of activity of the pathological process. Quantitative determination of the concentration of matrix metalloproteinase-9 was performed in

blood serum using an enzyme-linked immunosorbent assay kit (Human MMP-9 ELISA, Bio Tech Lab-S).

ANOVA (analysis of variance) analysis was performed. Immunological, morphological, neuroimaging, graphical, mathematical, and comparative methods were used.

Symptoms of Multiple Sclerosis were established (Fig. 2).

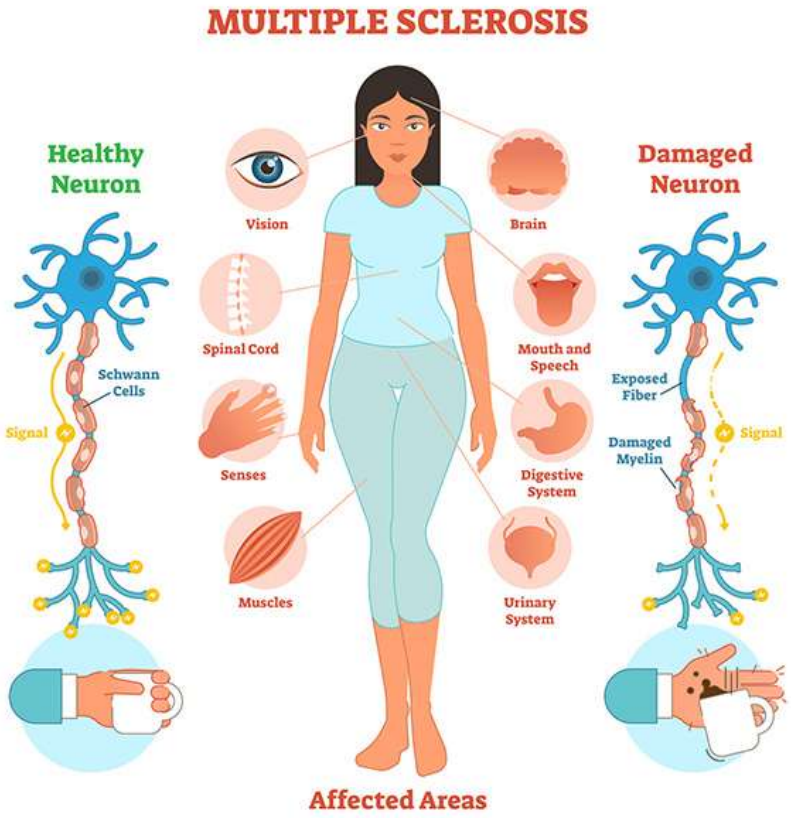

Fig. 2. Multiple Sclerosis affects the nervous system, which sends signals throughout the body, and symptoms can be diverse [18].

Multiple Sclerosis can cause many symptoms that may come and go. Medical and pharmaceutical care provides diagnosis and pharmacotherapy [18, 36].

Common signs of Multiple Sclerosis include:

- ✓ pain of various origins (sometimes constant);
- ✓ feeling of stiffness and involuntary muscle spasms;
- ✓ marked excessive fatigue without association with depression or muscle weakness;
- ✓ fatigue (sometimes increased);
- ✓ depression;
- ✓ dizziness or vertigo;
- ✓ emotional reactions, including irritability or uncontrollable laughter or crying
- ✓ muscle weakness in the arms and legs;
- ✓ unpleasant tingling sensations in the back from top to bottom, sometimes with a transition to the limbs or when tilting the head forward (Lhermitte's symptom);
- ✓ numbness or tingling in the face, body, arms, and legs;
- ✓ vision problems (often the first sign of the disease), double vision, worsening or loss of vision in one eye, accompanied by pain when moving the eyeball; problems with walking;
- ✓ problems with balance and coordination, unsteadiness, or clumsiness;
- ✓ progressive sensory disorders and/or weakness of the limbs;
- ✓ problems with the bladder and bowel;

- ✓ sexual dysfunction;
- ✓ stress.

Less common symptoms:

- ✓ hearing loss;
- ✓ slurred speech or loss of volume;
- ✓ problems with swallowing;
- ✓ problems with breathing;
- ✓ itching;
- ✓ seizures;
- ✓ tremor.

Secondary symptoms (some conditions are not caused by nerve fiber problems, but are complications of other symptoms, they may include:

- ✓ loss of muscle tone from inactivity;
- ✓ urinary tract infections due to bladder problems.

The research of the article is a fragment of research works of P.V. Voloshyn Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine on the topic of "Study of mechanisms of inheritance of multiple sclerosis in persons born from parents with this disease" (state registration number 0121U111900, implementation period 2022-2024).

Results and discussion. In difficult conditions associated with martial law in Ukraine [37], research fellows-doctors of the Department of Autoimmune and Degenerative Diseases of the Nervous System (Second Neurological Department) of the State Institution P.V. Voloshyn Institute of Neurology, Psychiatry and Narcology National Academy of Sciences of Ukraine specializes in the diagnosis of diseases of the central, peripheral, nervous systems. The department is the All-Ukrainian center for the treatment of Multiple Sclerosis in adults and children, myasthenia gravis, extrapyramidal and neurodegenerative diseases [38].

The scientific staff of the Department of Autoimmune and Degenerative Diseases of the Nervous System agree with the conclusions of Filippi M., Bar-Or A., Piehl F. that Multiple Sclerosis is the most common chronic inflammatory, demyelinating, and neurodegenerative disease of the central nervous system in young people [39]. This disorder is a heterogeneous, multifactorial, immune-mediated disease, which is influenced by both genetic and environmental factors. In most patients, reversible episodes of neurological dysfunction lasting several days or weeks characterize the initial stages of the disease (i.e., clinically isolated syndrome and relapsing-remitting Multiple Sclerosis). Over time, irreversible clinical and cognitive impairments develop. In a minority of patients, the disease progresses from the beginning. The pathological hallmark of multiple sclerosis is the formation of demyelinating lesions in the brain and spinal cord, which may be associated with damage to neuroaxons. It is believed that focal lesions are caused by infiltration of immune cells, including T cells, B cells and myeloid cells, into the parenchyma of the central nervous system with associated damage. Multiple Sclerosis is associated with a significant burden on society due to the high cost of available treatments and poorer employment prospects and job retention for patients and citizens (relatives, social workers, health workers, etc.) who care for them.

In order to improve the level of diagnostics of the stages of the pathological process in Multiple Sclerosis and optimize the process of pharmacotherapy in the Department of Autoimmune and Degenerative Diseases of the Nervous System, 137 patients were examined in recent years: 55 men (40.1%) and 82 women (59.9%) of different ages (from 18 to 68 years) with Multiple Sclerosis (diagnosed according to the McDonald criteria, 2007) of different courses and at different stages of activity of the pathological process of the disease (Fig. 3).

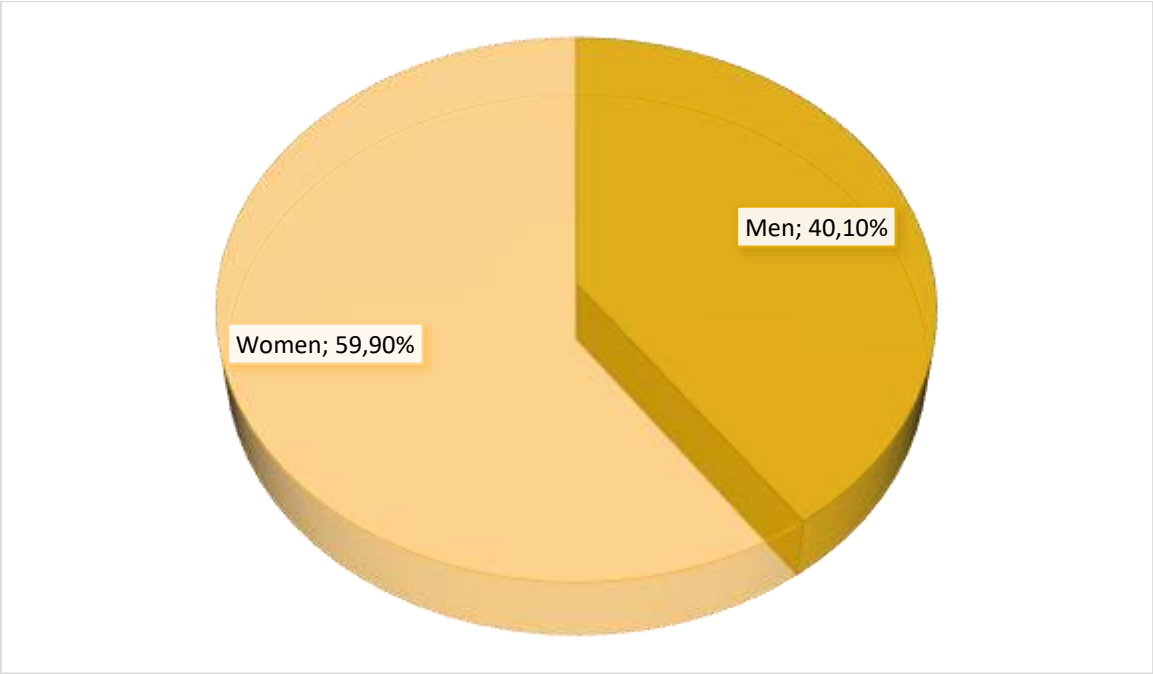

Fig. 3. Quantitative ratio (%) of male and female patients with Multiple Sclerosis who participated in the survey.

During the study, it was found that the highest index of matrix metalloproteinase-9 was observed in patients with relapsing-remitting Multiple Sclerosis (mean index of matrix metalloproteinase-9av = 212.37 ± 17.51).

The lowest index was in patients with primary progressive Multiple Sclerosis (of matrix metalloproteinase-9av = 135.33 ± 6.87).

The average index was in patients with secondary progressive (of matrix metalloproteinase-9av = 252.19 ± 10.36). The obtained coefficient F = 5.238; its statistical significance $p < 0.01$.

To determine the relationship between the type of clinical course and the frequency of matrix metalloproteinase-9, we used ANOVA analysis of variance (Fig. 4).

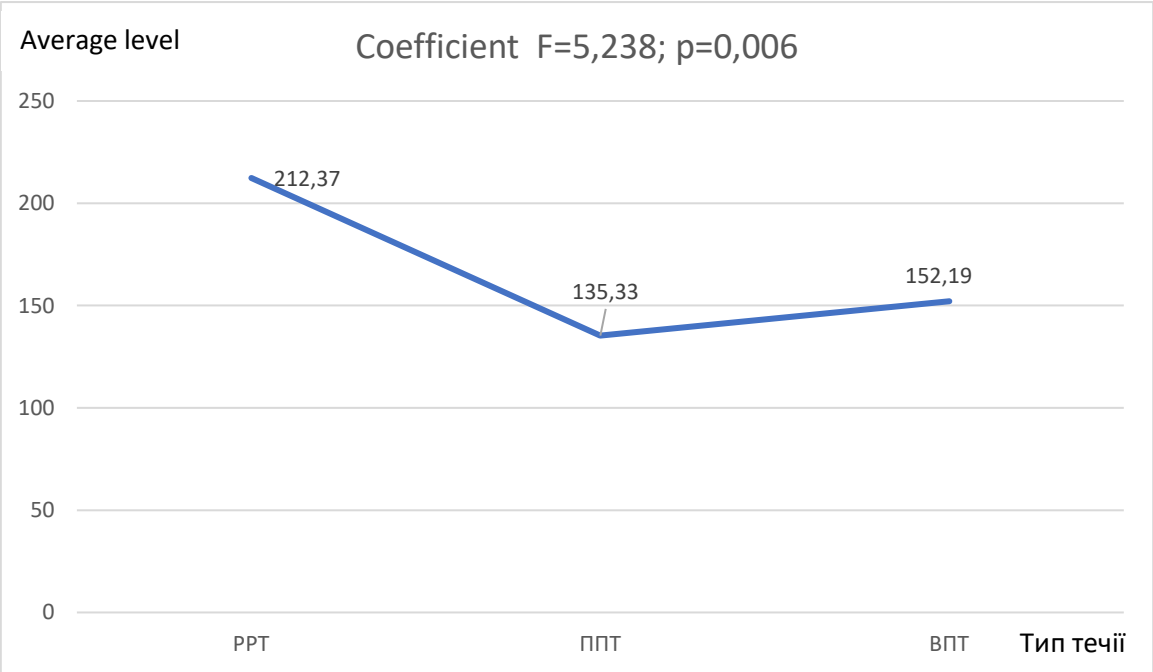

Fig. 4. Dependence of the frequency of matrix metalloproteinase-9 on the type of clinical course.

In addition, the level of matrix metalloproteinase was analyzed at different stages of the activity of the pathological process (exacerbation and remission in relapsing multiple sclerosis, progression, and stabilization in progressive types of the course).

The average values of matrix metalloproteinase-9 for the studied groups were: in relapsing remitting multiple sclerosis in the remission stage – 122.05±7.82, in the exacerbation stage – 378.68±21.54. In progressive types of the course: in the progression stage – 164.73±12.21, in the stabilization stage – 114.64±8.43 (Fig. 5).

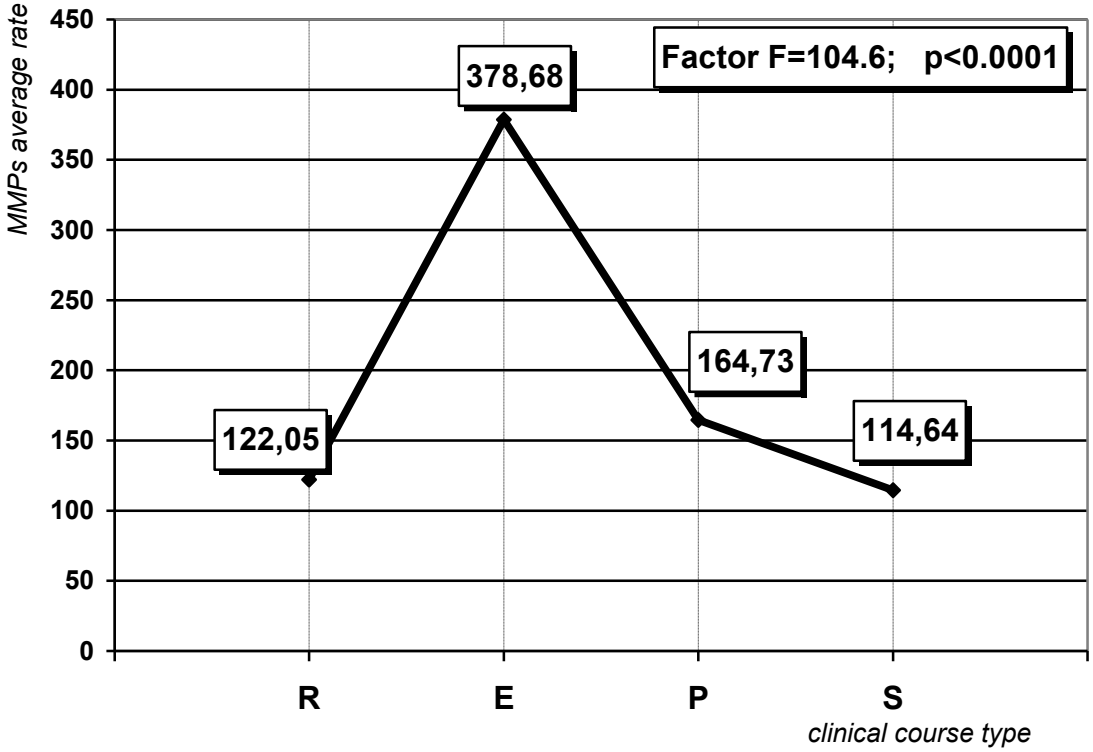

Fig. 5. Dependence of the frequency of matrix metalloproteinase-9 on the type of clinical course in Multiple Sclerosis.

The value of the factor F is so large that the probability of error is practically zero ($p<0.0001$). The graph shows that:

- ✓ the highest indicators of matrix metalloproteinase-9 were observed at the stages of exacerbation and progression of the pathological process;
- ✓ at the stages of remission and stabilization, the indicators of matrix metalloproteinase-9 were within normal limits;
- ✓ thus, the dependence of the average indicator of matrix metalloproteinase-9 on the stage of the disease was proven with high reliability.

The level of matrix metalloproteinase-9 is influenced by all factors together, but not separately. Therefore, the types of clinical course and stages of the disease as factors that most affect the frequency of matrix metalloproteinase-9 were analyzed using multivariate analysis of variance. The results obtained are given in Table. 2.

Table 2. Norma Matrix metalloproteinase-9 rate depending on the course type and stage of disease Multiple Sclerosis.

Course type	Stage of disease	Number of patients	MMP-9 rate
RRMS	Exacerbation	26	381.54 ± 22.19
	Remission	45	122.05 ± 7.82
SPMS	Progression	28	169.98 ± 15.64
	Stabilization	21	114.64 ± 8.43

PPMS	Progression	8	147.03 ± 6.78
	Stabilization	7	121.96 ± 10.90

According to the data presented in Table 2, the highest levels of matrix metalloproteinase-9 were observed in the group of relapsing-remitting multiple sclerosis at the stage of exacerbation of the disease (381.54±22.19).

The level of matrix metalloproteinase-9 was within normal limits at the stage of remission and reached 122.05±7.82.

The levels of matrix metalloproteinase-9 were high at the active stage in secondary progressive multiple sclerosis and primary progressive multiple sclerosis: 169.98±15.64 and 147.03±6.78, respectively.

The generalized results when comparing them proved that inflammatory reactions in secondary progressive multiple sclerosis are more pronounced than in primary progressive multiple sclerosis, when neurodegenerative processes are of primary importance.

However, unexpectedly, the levels of matrix metalloproteinase-9 at the stabilization stage were higher in relapsing-remitting multiple sclerosis (121.96±10.90) than in secondary progressive multiple sclerosis (114.64±8.43). This is explained by the significant difference between the number of patients in the respective groups – in the primary progressive multiple sclerosis group at the stabilization stage there were three times fewer patients than in the secondary progressive multiple sclerosis group at the same stage (Fig. 6).

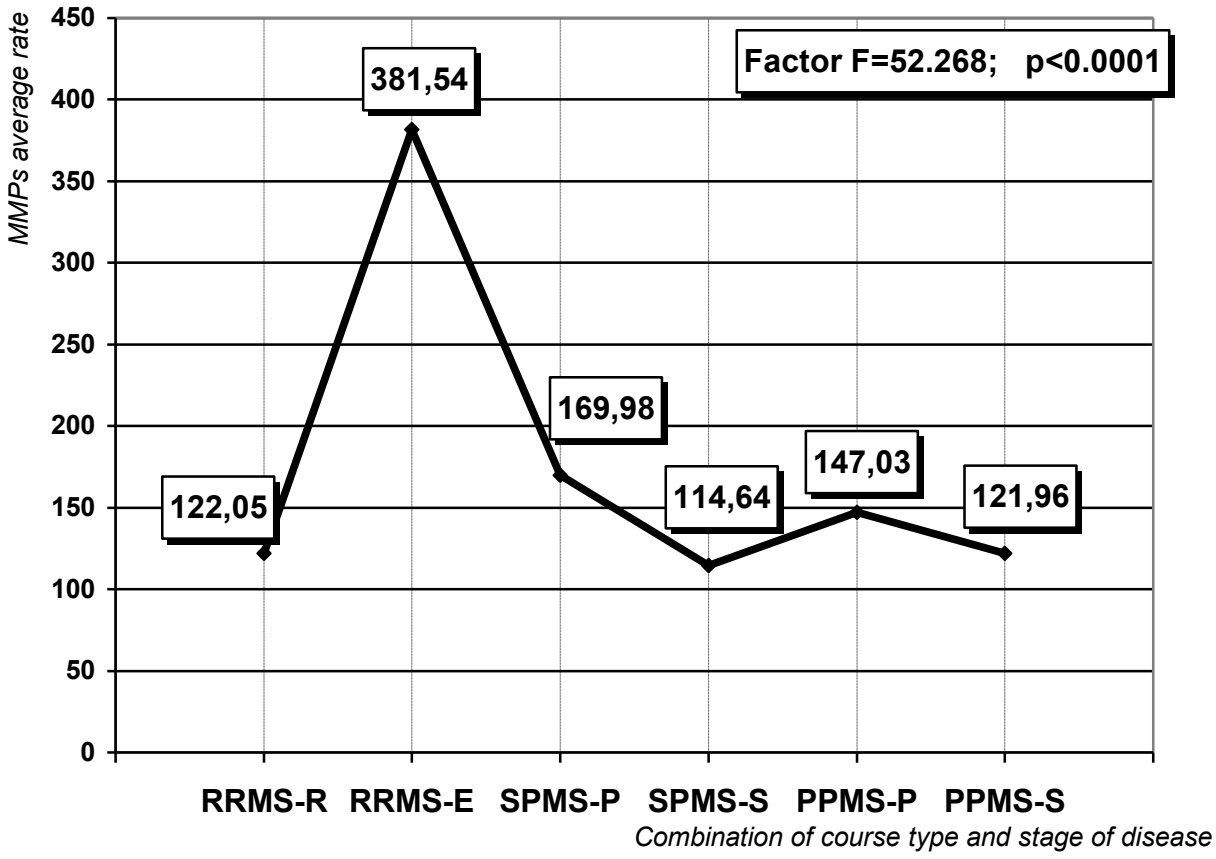

Fig. 6. Dependence of matrix metalloproteinase -9 rate on the course type and stage of disease.

According to experts from the International Federation of Multiple Sclerosis and Medinfo, there are about 2.8 million citizens living with Multiple Sclerosis in the world, which is [40, 41]:

- with an incidence rate of approximately 35.9 cases per 100,000 population;
- the highest rate is in Northern Europe, North America, and Australia, for example, in Scandinavian countries the incidence can reach 100-150 cases per 100,000 population; in

Asian and African countries the prevalence is much lower and can be less than 5 cases per 100,000 population;

- in 2021, doctors in Ukraine identified approximately 21 thousand patients, the dynamics show that over the years the number of new cases is increasing, which corresponds to the global trend towards an increase in the incidence of Multiple Sclerosis;
- the highest incidence rates in Ukraine are observed in the western and northern regions, while in the southern and eastern regions they are somewhat lower. The highest incidence rate is recorded in Kyiv, Kyiv region, Lviv, and Kharkiv regions (50-60 cases per 100,000 population; in other regions – the average level and is 40 patients per 100,000 population);
- women in Ukraine suffer from Multiple Sclerosis approximately 2 times more often than men, which corresponds to world statistics;
- the disease is most often diagnosed in the most able-bodied part of the population of Ukraine (age from 20 to 40 years), but cases are possible both at a younger and older age, and the average age of onset of the disease is about 20-30 years;
- Multiple Sclerosis significantly affects the quality of life, ability to work and social activity of patients;
- 10-15 years after diagnosis, about 50% of patients require social assistance in moving or transfer to a wheelchair.

An important point is that the World Health Organization experts, considering ICD-11 to improve the quality and duration of life, protect working capacity and promote social activity of citizens and patients, presented for use in the daily work of doctors and pharmacists [42- 44]:

- the latest editions of the Essential Medicines List (EML) and the Essential Medicines List for Children (EMLc), which include the most important innovative drugs for the treatment of Multiple Sclerosis;
- the updated model lists include revolutionary drugs for the treatment of Multiple Sclerosis;
- the purpose of this inclusion is to expand the availability of innovative drugs that have obvious clinical advantages worldwide;
- additions to the list can significantly improve the health of the population worldwide, while preserving the financial resources of low- and middle-income countries.

The WHO and ICD-11 recommendations require further elaboration and publication of the monograph “Medicines for neurologists, psychiatrists and narcologists” in a new edition [45].

Conclusions. Proven that Multiple Sclerosis progresses in Ukraine as a cause of disability of young people in conditions of martial law. The improvement of the level of diagnostics of the stages of the pathological process in Multiple Sclerosis and further optimization of the pharmacotherapy process depending on the activity of the inflammatory process in the patient are studied. It is noted that one of the main pathogenetic links of Multiple Sclerosis is the violation of the blood-brain barrier and the migration of plasma proteins to the brain parenchyma of matrix metalloproteinase. Matrix metalloproteinase-9 can be considered as a marker of the activity of the inflammatory process, an indicator of the state of the blood-brain barrier in Multiple Sclerosis. It is determined that the level of matrix metalloproteinase-9 can contribute to monitoring the effectiveness of pharmacotherapy of patients suffering from Multiple Sclerosis at different stages of the disease. A method for determining the norm of matrix metalloproteinase-9 for implementation in clinical practice of healthcare institutions within the framework of diagnostic examination of patients suffering from Multiple Sclerosis is proposed. Requires further pharmacoeconomic research of the stages of clinical monitoring of patients from diagnosis and modern research, to outpatient or inpatient treatment using a complex of pharmacotherapeutic measures. WHO and ICD-11 recommendations require further development and publication of the monograph "Medicines for neurologists, psychiatrists and narcologists" in a new edition.

Declaration of conflict interest. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors confirm that they are the authors of this work and have approved it for publication. The authors also certify that the obtained clinical data and research were conducted in compliance with the requirements of moral and

ethical principles based on medical and pharmaceutical law, and in the absence of any commercial or financial relationships that could be interpreted as potential conflict of interest.

Funding. The authors state, that this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical approval. Ethical clearance was obtained from the administration of the P.V. Voloshyn Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine. Permission statement for conducting the experiments was received from the administration of the P.V. Voloshyn Institute of Neurology, Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine. Before any data collection, the main purpose of the study was clearly explained to each department (concerned personnel).

Acknowledgements. The authors of the article express their gratitude to the scientists-doctors of the Department of Autoimmune and Degenerative Diseases of the Nervous System – All-Ukrainian Center for Multiple Sclerosis of the State Institution "P.V. Voloshyn Institute of Neurology, Psychiatry and Narcology of the National Academy of Sciences of Ukraine" for their support and valuable comments and suggestions aimed at improving the results of the research and writing of the article.

Data availability statement. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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