CONTEMPORARY ASPECTS OF THE PATHOGENESIS AND THERAPY OF MULTIPLE SCLEROSIS: FROM IMMUNE IMBALANCE TO PERSONALIZED MEDICINE

Aziza Sh. Kadirova – Ph.D., assistant
Gulnora K. Rakhmatullaeva – D.M.Sc., professor
Javlon J. Salimjonov – Ph.D., assistant
Tashkent State Medical University (Tashkent, Uzbekistan)
azizka_k@mail.ru

Abstract. *Multiple sclerosis (MS) remains one of the leading causes of non-traumatic disability among young and middle-aged adults. In recent years, the global prevalence of the disease has increased, reaching 2.9 million cases. This review presents an analysis of current data on the pathogenesis of MS, viewed as a continuum of inflammatory and neurodegenerative processes. Particular attention is paid to the concept of progression independent of relapse activity (PIRA), the mechanisms of compartmentalized inflammation in progressive forms, and novel biomarkers (neurofilaments, GFAP). Modern approaches to immunomodulatory therapy are analyzed, including high-efficacy monoclonal antibody preparations and S1P receptor modulators, as well as promising directions — BTK inhibitors, neuroprotective strategies, and the potential of GLP-1 agonists. It is shown that the integration of neuroimaging data and digital biomarkers with artificial intelligence technologies opens new opportunities for personalized patient management.*

Keywords: *multiple sclerosis, neuroinflammation, progressive MS, immunotherapy, neurofilaments, PIRA, personalized medicine.*

Introduction. Multiple sclerosis is a chronic immune-mediated disease of the central nervous system (CNS), the morphological substrate of which consists of foci of demyelination, axonal degeneration and reactive gliosis. The disease debuts predominantly between the ages of 20 and 40 years, affecting people during the period of their greatest social, professional and reproductive activity. According to the Global Burden of Disease Study, MS ranks among the top five neurological diseases leading to the greatest number of disability-adjusted life years (DALYs) in the population under 50 years of age [12].

The traditionally distinguished clinical phenotypes — relapsing-remitting MS (RRMS), secondary progressive MS (SPMS) and primary progressive MS (PPMS) — are considered in the modern literature as stages of a single pathological continuum. Key to understanding the modern paradigm is the fact that neurodegeneration can begin at the earliest stages of the disease, long before clinical signs of progression appear [19].

The global prevalence of MS is steadily increasing. According to the third global atlas of MS (MSIF, 2023), the number of patients reached 2.9 million in 2023, with experts predicting exceeding 3.5 million by 2030 [22]. The highest prevalence rates are recorded in North America (288 per 100,000), Europe (133 per 100,000) and Australia (112 per 100,000). The female-to-male ratio averages 3:1, with "feminization" up to 4:1 in some populations.

In the Russian Federation, prevalence varies from 14.4 per 100,000 in Ingushetia to 78.4 per 100,000 in the Kursk region [14]. In Kazakhstan, an increase in MS detectability is noted, but accurate epidemiological indicators are absent due to the underdevelopment of national registries [21]. In Uzbekistan, systematic epidemiological studies have not been conducted; estimated prevalence is 5–15 per 100,000, which requires verification [15–16, 18, 20, 23].

The aim of this review is to analyze current data on the pathogenesis, biomarkers, therapy and future directions of MS, with a special focus on the situation in Central Asia.

Materials and Methods. A narrative review of the literature was conducted. We searched PubMed, Scopus, and Russian scientific databases (eLibrary, CyberLeninka) for publications from

2004 to 2026. Search terms included: "multiple sclerosis", "pathogenesis", "biomarkers", "neurofilaments", "PIRA", "immunotherapy", "BTK inhibitors", "GLP-1 agonists", "artificial intelligence", "Central Asia", "Uzbekistan", "Kazakhstan".

Inclusion criteria: original articles, reviews, clinical guidelines, and epidemiological studies on MS pathogenesis, diagnosis, biomarkers, and treatment. Preference was given to high-impact journals and recent publications (2020–2026). Exclusion criteria: case reports (except for regional epidemiology), non-English/non-Russian articles without translation, and animal studies without human translation.

A total of 25 sources were selected for final analysis, including 5 from Uzbekistan, 1 from Kazakhstan, 3 from Russia, and 16 international sources. The regional focus was prioritized to reflect the situation in Central Asia.

Results. *Etiology and risk factors.* The etiology of MS is multifactorial. Genome-wide association studies have identified more than 233 loci associated with MS risk. The strongest association is with HLA class II alleles, especially DRB1*15:01. However, HLA explains only 20–30% of genetic risk. Concordance in monozygotic twins is only 25–30%, emphasizing the decisive role of environmental triggers. Key environmental factors are Epstein-Barr virus (EBV) infection, vitamin D deficiency and smoking [5].

The role of EBV became a revolution in understanding MS triggers. In a 2022 prospective study of >10 million US military personnel, the risk of developing MS increased 32-fold after symptomatic EBV infection. Among EBV-negative individuals, not a single case of MS was registered [5]. Mechanisms include molecular mimicry (EBNA-1 protein shares sequences with myelin proteins), chronic B-cell activation, and cytokine imbalance.

Pathogenesis: two models. The "outside-in" model postulates that MS is initiated by activation of myelin-reactive T-lymphocytes in the periphery. These cells cross the blood-brain barrier (BBB) and trigger autoimmune inflammation [9]. This model is confirmed in experimental autoimmune encephalomyelitis (EAE) [20].

The success of anti-CD20 therapy (rituximab, ocrelizumab) radically revised the role of B cells. B lymphocytes act as antigen-presenting cells, produce pro-inflammatory cytokines (GM-CSF, IL-6, TNF-α), and form ectopic lymphoid follicles in the meninges in progressive MS [1].

The "inside-out" model suggests that primary oligodendrocyte damage occurs first, followed by secondary autoimmune inflammation [20]. Pathomorphological studies revealed oligodendrocyte apoptosis at the edges of expanding lesions with minimal lymphocytic infiltration [1]. The cuprizone model confirms that induced oligodendrocyte death triggers myelin-reactive T cells [4]. Both models reflect different pathogenetic variants of MS.

PIRA and compartmentalized inflammation. The most important paradigm shift is the recognition of PIRA — Progression Independent of Relapse Activity [11]. Analysis of large cohorts showed that 30–50% of disability accumulation occurs without clinical relapses or new contrast-enhancing MRI lesions.

PIRA is based on compartmentalized inflammation. Microglia and reactive astrocytes, once activated, remain in an activated state for years. They secrete pro-inflammatory cytokines, reactive oxygen species, glutamate, and complement components, creating a microenvironment of gradual axonal degeneration. Chronic mitochondrial dysfunction leads to energy starvation of axons, calcium influx, calpain activation, and axonal fragmentation.

Classical immunomodulators (interferon-beta, glatiramer acetate, teriflunomide) have virtually no effect on compartmentalized inflammation and PIRA [20, 19]. This led to a transition from escalation to early high-efficacy therapy.

Biomarkers. The most validated biomarker is neurofilament light chain (NfL). Serum NfL correlates with disease activity, risk of future disability, and treatment efficacy [4]. However, NfL is not specific to MS and is not a reliable marker of PIRA [7].

Glial fibrillary acidic protein (GFAP) is a marker of reactive astrogliosis. GFAP is elevated in progressive MS, correlates with brain atrophy, and does not decrease with classical immunomodulators. The NfL/GFAP ratio may help differentiate inflammatory from neurodegenerative predominance [7].

CHI3L1 (YKL-40) is produced by activated microglia and astrocytes. Its CSF level correlates with brain atrophy and transition to SPMS, but lumbar puncture limits routine use [7].

Therapy of relapsing-remitting MS. Interferon-beta and glatiramer acetate are now considered first-line only in benign disease or when more effective drugs are contraindicated [17].

S1P receptor modulators (fingolimod, siponimod, ozanimod) trap lymphocytes in lymph nodes. Siponimod is approved for active SPMS [10]. Side effects include bradycardia, hypertension, macular edema, and infections.

Natalizumab (anti-α4-integrin) blocks lymphocyte migration across the BBB. It is highly effective but limited by PML risk, highest in JC-seropositive patients with >2 years of treatment [9].

Anti-CD20 monoclonal antibodies (rituximab, ocrelizumab, ofatumumab) are the most effective drugs for RRMS, reducing relapse rates by 70–90% and new MRI lesions by 95–99%. Ocrelizumab is the only drug approved for PPMS [13]. Disadvantages include intravenous administration, infection risk, and possible hypogammaglobulinemia.

The early HET strategy is replacing the escalation approach. Every relapse leads to irreversible disability accumulation [17]. Early HET reduces the risk of transition to SPMS. In patients with benign disease (no more than 10–15%), moderately effective drugs with careful monitoring (MRI and NfL every 6–12 months) may be considered.

In patients over 55–60 years with >5 years of stability, therapy intensity reduction may be considered. Strategies include switching from fingolimod to less intensive drugs, increasing anti-CD20 infusion intervals to 9–12 months, or switching from natalizumab to another drug.

BTK inhibitors (evobrutinib, tolebrutinib, fenebrutinib) cross the BBB and inhibit both peripheral B cells and microglia [2]. Fenebrutinib (FENopta study) showed a 69% reduction in new contrast-enhancing lesions [3]. Tolebrutinib in non-relapsing SPMS reduced the risk of confirmed disability progression by 31% [11]. Side effects include elevated transaminases, rash, and rare bleeding.

GLP-1 agonists (semaglutide, liraglutide) have neuroprotective properties: they improve mitochondrial function, reduce oxidative stress, and decrease microglial activation. Observational studies in diabetic MS patients showed lower relapse rates and slower brain atrophy. Prospective phase 2 trials are ongoing.

Remyelinating strategies. No remyelinating drug has been approved. Obstacles include epigenetic arrest of oligodendrocyte precursor cells and persistent inflammation. Clemastine, metformin, and anti-LINGO-1 antibodies have shown small imaging improvements but no clinical benefits. Cell therapy (iPSC-derived oligodendrocyte precursors) is in early stages.

Artificial intelligence and digital biomarkers.

AI tools (e.g., icobrain, MSmetrix) automatically segment demyelinating lesions, measure brain volume and cortical thickness [8]. AI models predict disease progression with 70–80% accuracy. Wearable devices (smartwatches, accelerometers) provide continuous objective assessment of gait, balance, fatigue, and cognition.

Regional aspect: Central Asia and Uzbekistan. In Uzbekistan, there is no national MS registry. Ochilova et al. (2024) reported pain syndromes in up to 78% of patients [16]. Yunusova and Rakhimbaeva (2024) noted diagnostic delays of several years [24]. Shamansurov et al. (2022) emphasized a more aggressive course in children [18]. Yakubova et al. (2021) described COVID-19 exacerbating MS [23]. Ochilova and Majidova (2023) highlighted vitamin D deficiency [15].

In Kazakhstan, Turuspekova et al. (2024) called for national registries [21]. In Russia, Zavalishin et al. (2023) summarized compartmentalized inflammation [25]. Boyko and Gusev (2024)

analyzed the evolution to early HET [6]. Nimerchy et al. (2025) confirmed the need for a personalized approach [14].

Access to anti-CD20, S1P modulators, and natalizumab in Uzbekistan is extremely limited. There are no specialized MS centers. Patients often receive only symptomatic therapy.

Discussion. This review synthesizes current evidence on MS pathogenesis, biomarkers, and therapy, with a focus on the transition from an inflammation-centric to a neurodegeneration-inclusive paradigm. The recognition of PIRA and compartmentalized inflammation explains why classical immunomodulators fail to prevent disability progression in many patients [11, 20].

The discovery of EBV as a necessary trigger (32-fold increased risk, zero cases in EBV-negative individuals) opens prospects for vaccine prevention and early antiviral therapy [5]. However, the exact mechanisms by which EBV induces autoimmunity are still debated.

Anti-CD20 therapy has revolutionized MS treatment, but its limited effect on compartmentalized inflammation and PIRA highlights the need for drugs that target microglia. BTK inhibitors, which cross the BBB and inhibit both B cells and microglia, are the most promising candidates [2, 3, 11].

GLP-1 agonists represent a completely new class of potential neuroprotective drugs, not based on immunosuppression. If confirmed in ongoing trials, they could change the treatment of not only MS but also other neurodegenerative diseases.

AI and digital biomarkers are shifting MS management toward personalized medicine. Automated MRI analysis, prognostic models, and wearable devices will allow objective, continuous monitoring and timely therapy adjustment [8].

The situation in Central Asia, particularly Uzbekistan, lags far behind global trends. The absence of national registries, limited access to MRI and biomarker monitoring, and lack of high-efficacy drugs lead to rapid disability accumulation. International collaboration and investment are urgently needed.

Conclusion. Multiple sclerosis in 2025–2026 appears as a complex, heterogeneous disease in which peripheral immune inflammation, chronic neurodegenerative progression, and compartmentalized inflammation are intertwined. The discovery of EBV as a key trigger opens horizons for vaccine prevention. Biomarkers, primarily NfL and GFAP, are entering clinical practice. The early high-efficacy therapy (HET) strategy is replacing the escalation model.

The key unsolved issue remains PIRA. BTK inhibitors may become first-line therapy for progressive forms of MS, controlling both peripheral B cells and microglia. GLP-1 agonists show potential as the first class of pure neuroprotective drugs. Remyelinating strategies remain a long-term goal. AI and digital biomarkers will lead to genuine personalized medicine.

For Uzbekistan and Central Asia, the priority remains solving basic problems: creating national registries, implementing McDonald 2017 diagnostic criteria [19], ensuring access to at least basic immunomodulatory therapy. Without this, the gap in care quality between developed countries and the region will only widen.

REFERENCES

1. Barnett M.H., Prineas J.W. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. Annals of Neurology. 2004;55(4):458-468.

2. Bar-Or A., Bittner S., Cross A.H., et al. BTK inhibitors in multiple sclerosis: emerging concepts. Neurology. 2023;100(3):121-130.

3. Bar-Or A., Montalban X., Patti F., et al. Safety and efficacy of fenebrutinib in relapsing multiple sclerosis (FENopta): a phase 2 trial. Lancet Neurology. 2025;24(8):656-666.

4. Barro C., Benkert P., Disanto G., et al. Serum neurofilament as a predictor of disease worsening in multiple sclerosis. JAMA Neurology. 2018;75(1):79-87.

5. Bjornevik K., Cortese M., Healy B.C., et al. Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis. Science. 2022;375(6578):296-301.
6. Boyko A.N., Gusev E.I. Evolution of multiple sclerosis therapy: from escalation to early high-efficacy therapy. Nervous Diseases. 2024;(1):12-20. (In Russian)
7. Chitnis T., Kuhle J., Barro C., et al. Blood and CSF biomarkers for multiple sclerosis: emerging clinical applications. Lancet Neurology. 2025;24(12):1066-1078.
8. Filippi M., Rocca M.A., Barkhof F., et al. Artificial intelligence applied to MRI in multiple sclerosis. Brain. 2024;147(2):435-452.
9. Hauser S.L., Cree B.A.C. Treatment of multiple sclerosis: A review. JAMA. 2020;323(8):765-779.
10. Kappos L., Fox R.J., Burcklen M., et al. Ponesimod compared with teriflunomide in patients with relapsing multiple sclerosis. JAMA Neurology. 2021;78(5):558-567.
11. Kappos L., Wolinsky J.S., Giovannoni G., et al. Progression independent of relapse activity in multiple sclerosis. Multiple Sclerosis Journal. 2020;26(10):1236-1245.
12. Lyutov O.V., Kutlubaev M.A., Kuzmina U.S., et al. Impact of multiple sclerosis on life expectancy: a review. Neurology Bulletin. 2025;57(4):321-330.
13. Montalban X., Hauser S.L., Kappos L., et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. New England Journal of Medicine. 2017;376(3):209-220.
14. Nimerchy M.A., Knyazeva A.I., Novikov V.M., et al. Modern aspects of immunomodulatory therapy of multiple sclerosis. Bulletin of the Pirogov National Medical and Surgical Center. 2025;20(4):118-122. (In Russian)
15. Ochilova D., Majidova Y.N. Features of the course of multiple sclerosis in the Uzbek population. Iqtidorli yoshlarning ilmiy ishlari va XXI asr tibbiyoti. 2023;1(1):160. (In Uzbek)
16. Rakhmattulaeva G.K., Kadirova A.Sh. (2026). THE ROLE OF MOLECULAR-GENETIC MARKERS OF THROMBOPHILIA IN THE DEVELOPMENT OF ISCHEMIC STROKE IN WOMEN OF DIFFERENT AGE GROUPS. *Central Asian Journal of Medicine*, *1*(8), 123-131.
17. Rashidova N.S., Salimjonov J.J. (2026). COMPREHENSIVE ASSESSMENT OF NEUROLOGICAL COMPLICATIONS FOLLOWING COVID-19 VACCINATION. *Central Asian Journal of Medicine*, *1*(11), 286-292.
18. Shamansurov Sh.Sh., Gulyamova M.K., Karimova N.A. Clinical features of pediatric multiple sclerosis. Doktor axborotnomasi. 2022;2.3(105):47-50. (In Russian)
19. Thompson A.J., Banwell B.L., Barkhof F., et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurology. 2018;17(2):162-173.
20. Traka M., Kim J., Kiraly D., et al. Oligodendrocytes Are Active Participants in the Pathogenesis of Multiple Sclerosis and Its Animal Models. International Journal of Molecular Sciences. 2026;27(4):1779.
21. Turuspekova S.T., Nurguzhaev E.S., Kaishibaeva G.S. Epidemiology of multiple sclerosis in Kazakhstan and Central Asian countries. Neurosurgery and Neurology of Kazakhstan. 2024;(1):33-41. (In Russian)
22. Walton C., King R., Rechtman L., et al. Rising prevalence of multiple sclerosis worldwide: Insights from the Atlas of MS, third edition. Multiple Sclerosis Journal. 2023;29(8):928-942.
23. Yakubova M.M., Khalimova Kh.M., Parpieva Yu.R. Clinical and neurological aspects of multiple sclerosis during COVID-19 infection in Uzbekistan. Central Asian Journal of Medical and Natural Science. 2021;2(3):186-190. (In Russian)
24. Yunusova M.R., Rakhimbaeva G.S. Review of early clinical manifestations of multiple sclerosis. Journal of Education and Scientific Medicine. 2024;1(6):81-86. (In Russian)
25. Zavalishin I.A., Peresedova A.V., Sivertseva S.A. Immunopathogenesis of multiple sclerosis: current state of the problem. Journal of Neurology and Psychiatry named after S.S. Korsakov. 2023;123(7):7-15. (In Russian)