IJCNP, Volume 3, Issue 9, 2025 ISSN: 2995-536X
https://medicaljournals.eu/index.php/IJCNP

INTERNATIONAL JOURNAL OF COGNITIVE NEUROSCIENCE AND PSYCHOLOGY

CLINICAL MANIFESTATIONS OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY AND MODERN ANALYSIS OF RISK FACTORS IN PEDIATRIC PRACTICE

KHUDOYBERDIYEVA Dilovar Imomnazarovna
Samarkand State Medical University

NIYOZOV Shuxrat Toshtemirovich
Doctor of Medical Sciences, Associate Professor, Samarkand State Medical University

Abstract: Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by JC virus (JCV), mainly observed in immunodeficient conditions. This neuroinfection is considered a severe pathology with a high probability of leading to death.

Key words: progressive multifocal leukoencephalopathy, children, JC virus, immunodeficiency, neurodemelination, clinical features, risk factors, pediatric neurology, neuroinfection, modern diagnostics.

RELEVANCE. Progressive multifocal leukoencephalitis (PML) is a severe demyelinating disease caused by JC virus (John Cunningham virus), mainly developing in immunodeficient conditions, characterized by sudden onset of progressive focal neurological symptomatology, mental-psychological disorders, and cognitive degradation [1]. According to the World Health Organization, the incidence of PML in the general pediatric population is 0.1-0.3 cases per 1 million children annually, but this indicator is 100-1000 times higher in children with immunodeficiency, especially against the background of HIV infection, oncohematological diseases, and immunosuppressive therapy [4].

PML was first described in 1958 by Karl Erik Åström in patients with chronic lymphocytic leukemia, and later in 1965, polyomavirus particles were identified by Gabriele Zu Rhein and Sylvia Chou using electron microscopy [3]. In 1971, JC virus was isolated by Billard and colleagues, and the etiological agent of the disease was identified. Epidemiological studies show that infection with JC virus in adults reaches 60-90% and mainly occurs during childhood. The virus usually enters the organism through the lungs and tonsils, then spreads to various organs via lymphohematogenous route and remains latent throughout life. The development of PML requires severe immune system weakening, especially impairment of T-cell immunity [2].

Progressive multifocal leukoencephalitis in children is recognized not only as a medical but also as a serious social and economic problem. This is because most children who have undergone this disease are forced to live with severe and irreversible disruption of vital functions. These changes include complete or partial loss of motor functions, progressive decline in cognitive abilities, severe speech function disorders, visual field limitations, epileptic seizures, and psychiatric symptoms [5]. As a result, such children require constant medical care and multisectoral social support, which constitutes a significant financial burden for families and society.

Progressive multifocal leukoencephalitis (PML) is considered a polyfactorial disease with complex multi-stage pathogenesis. JC virus (JCV) is a small double-stranded DNA virus belonging to the Polyomaviridae family, with a genome size of only 5130 nucleotide pairs [6]. The virus genome is divided into three main functional regions: early gene (encodes T-antigen), late gene (encodes capsid proteins), and control region (regulates replication and transcription).

Progressive multifocal leukoencephalitis (PML) is characterized by relatively rare occurrence in the pediatric population, but its severe clinical course and the severity of neurological consequences have made the disease one of the important problems of modern pediatrics and neurology. Epidemiological studies show that JC virus (John Cunningham virus) is present in latent form in 70-90% of the population, and its reactivation and PML development are organically linked to certain risk factors [7].

The annual incidence of PML worldwide is 0.1-0.3 cases per 100,000 children. However, this indicator is significantly higher in immunocompromised children groups, reaching 2-5 cases per 1000 children. Prospective studies conducted in European countries show that PML most commonly occurs in children aged 5-15 years, with no statistically significant difference observed between girls and boys [8].

The exact epidemiological indicators of PML in the Republic of Uzbekistan have not yet been fully studied. According to preliminary data obtained from local neurological centers, more than 45 PML cases have been registered throughout the republic during 2018-2023, of which 78% belong to the pediatric group. The geographical distribution of the disease is uneven, occurring 2.3 times more frequently in urban areas compared to rural areas [9].

The main risk factors for PML development are divided into two major groups: primary (related to immunodeficiency) and secondary (additional risk factors). Primary risk factors include HIV infection, congenital immunodeficiency syndromes, and children receiving immunosuppressive therapy (transplantation, oncohematological diseases). HIV infection is considered the strongest risk factor for PML, with the risk of PML development increasing 50-100 times in children with CD4+ lymphocyte counts below 200 cells/μl. PML is also frequently observed in children with congenital immunodeficiency syndromes, including SCID (Severe Combined Immunodeficiency), Wiskott-Aldrich syndrome, and DiGeorge syndrome [10].

Children receiving immunosuppressive therapy deserve special attention. Specifically, long-term use of drugs such as natalizumab, rituximab, and fingolimod has been found to increase PML risk by 10-15 times. In children who have undergone transplantation, the PML risk is highest during the first 2 years of the post-transplantation period, requiring special monitoring during this time.

Secondary risk factors include genetic predisposition, environmental factors, and age characteristics. Carriers of HLA-DRB104:01 and HLA-DQB103:02 alleles have been found to have increased susceptibility to PML. Among environmental factors, ultraviolet radiation, stress factors, and nutritional status are of significant importance [11].

From an age perspective, PML most commonly occurs in children aged 8-12 years, when immune system immaturity and high probability of initial encounter with JC virus coincide. PML is very rare in children under 3 years of age, which is explained by the protective effect of maternal antibodies [12].

Among somatic diseases, diabetes, kidney failure, liver diseases, and chronic inflammatory diseases have been observed to increase PML risk. Particularly, in children with chronic kidney failure, PML risk increases 5-7 times due to the immunosuppressive effect of uremia.

Among pharmacotherapeutic factors, chemotherapy drugs, high doses of corticosteroids, and immunomodulators are of particular importance. Long-term use of drugs such as methotrexate, cyclophosphamide, and mycophenolate mofetil has been found to significantly reduce CD4+ lymphocyte counts and increase PML risk.

Among infectious factors, diseases such as EBV, CMV, HSV infections, tuberculosis, and pneumocystosis can disrupt immune status differently and contribute to PML development. Specifically, EBV infection can lead to JC virus reactivation by transforming B-lymphocytes and disrupting immune control.

Among stress factors, psychoemotional strain, separation from parents, and school adaptation difficulties play a certain role in increasing PML risk. These factors affect through disrupting

hypothalamic-pituitary-adrenal axis activity, increasing cortisol levels, and weakening immune functions.

Nutritional status is also considered an important risk factor. In children suffering from protein-energy deficiency and those with vitamin D, B12, and folic acid deficiencies, PML risk has been observed to increase 2-3 times.

The epidemiological landscape of PML in children differs significantly from that observed in adults. Although the overall incidence remains relatively low at 0.1-0.3 cases per million children annually in the general pediatric population, this figure increases dramatically to 2-5 cases per 1,000 children in immunocompromised cohorts. The disease predominantly affects children aged 5-15 years, with no significant gender predilection, and carries a mortality rate exceeding 50% within the first year of diagnosis, making it one of the most feared complications in pediatric immunocompromised patients.

The pathophysiology of PML involves the reactivation of latent JC virus, a ubiquitous polyomavirus that establishes persistent infection in 70-90% of the population during childhood. Under normal circumstances, the virus remains dormant in various tissues, including the kidneys, bone marrow, and potentially the central nervous system. However, when cellular immunity becomes severely compromised, particularly T-cell mediated responses, JCV undergoes reactivation and gains neurotropism, specifically targeting oligodendrocytes and astrocytes in the white matter of the brain.

The clinical presentation of PML in children often differs from adult manifestations, presenting unique diagnostic challenges. Pediatric patients may exhibit subtle or atypical neurological symptoms that can be easily mistaken for other conditions. The classical triad of cognitive decline, motor weakness, and visual disturbances may not always be present simultaneously, and children may initially present with behavioral changes, academic difficulties, or non-specific neurological complaints that progress insidiously over weeks to months.

Risk stratification in pediatric PML has become increasingly sophisticated, incorporating both traditional immunodeficiency-related factors and emerging risk markers. Primary risk factors include HIV infection with CD4+ T-cell counts below 200 cells/μL, primary immunodeficiency syndromes such as severe combined immunodeficiency (SCID), and iatrogenic immunosuppression from treatments for autoimmune diseases, malignancies, or organ transplantation. The advent of newer biological therapies, particularly natalizumab, rituximab, and other monoclonal antibodies, has introduced novel risk categories that require careful monitoring and risk-benefit assessment.

Secondary risk factors encompass genetic predisposition, with certain HLA allotypes (HLA-DRB1*04:01 and HLA-DQB1*03:02) conferring increased susceptibility, environmental factors including ultraviolet radiation exposure and psychosocial stressors, and nutritional deficiencies that may compromise immune function. The interplay between these various risk factors creates a complex web of vulnerability that clinicians must navigate when caring for at-risk pediatric populations.

Diagnostic advances have revolutionized the approach to PML in children. The development of highly sensitive polymerase chain reaction (PCR) assays for detecting JCV DNA in cerebrospinal fluid has largely replaced the need for brain biopsy in most cases. Magnetic resonance imaging (MRI) has become the cornerstone of neuroimaging diagnosis, with characteristic findings including asymmetric, subcortical white matter lesions that are hyperintense on T2-weighted and FLAIR sequences, typically showing no enhancement or only minimal peripheral enhancement. Advanced MRI techniques, including diffusion-weighted imaging, perfusion studies, and magnetic resonance spectroscopy, have further refined diagnostic accuracy and helped differentiate PML from other demyelinating conditions.

The therapeutic landscape for pediatric PML remains challenging, with no specific antiviral therapy currently approved. Treatment strategies focus primarily on immune reconstitution, when possible, through optimization of antiretroviral therapy in HIV-positive patients, reduction or modification of immunosuppressive regimens, and supportive care measures. Experimental approaches, including immune checkpoint inhibitors, therapeutic vaccination, and adoptive T-cell therapy, are being investigated in clinical trials, offering hope for future therapeutic interventions.

The prognosis of pediatric PML has shown some improvement over recent decades, largely attributed to earlier recognition, better supportive care, and more effective immune reconstitution strategies. However, the disease continues to carry significant morbidity and mortality, with survivors often experiencing persistent neurological deficits that impact quality of life and require long-term rehabilitation and support services.

From a public health perspective, PML in children represents not only a medical challenge but also a significant socioeconomic burden. The complex care requirements of affected children, including specialized medical management, rehabilitation services, and family support systems, place considerable strain on healthcare resources and family structures. Understanding the full spectrum of risk factors and implementing appropriate preventive strategies are crucial for reducing disease incidence and improving outcomes.

The purpose of this comprehensive review is to examine the current understanding of clinical manifestations and risk factors associated with progressive multifocal leukoencephalopathy in pediatric practice. We aim to synthesize contemporary research findings, analyze epidemiological trends, evaluate diagnostic approaches, and discuss therapeutic strategies while highlighting areas requiring future investigation. This analysis seeks to provide clinicians, researchers, and public health professionals with an evidence-based framework for understanding, diagnosing, and managing this complex condition in children.

Through systematic examination of recent literature and analysis of clinical data, this review will address key questions regarding optimal risk stratification strategies, early diagnostic markers, therapeutic interventions, and long-term outcome predictors in pediatric PML. Additionally, we will explore the implications of emerging risk factors, including novel immunosuppressive agents and changing epidemiological patterns, for clinical practice and public health policy.

The increasing recognition of PML in pediatric populations, coupled with advances in diagnostic technology and therapeutic approaches, necessitates a contemporary reassessment of this condition. This review aims to contribute to the growing body of knowledge surrounding pediatric PML and ultimately improve outcomes for affected children through enhanced clinical awareness, improved diagnostic strategies, and evidence-based management approaches.

CONCLUSION. Thus, thorough knowledge of epidemiological aspects and risk factors of PML development is of significant importance in early disease detection, developing preventive measures, and effective treatment of patients. Progressive multifocal leukoencephalopathy in pediatric practice represents a complex and multifaceted clinical challenge that demands comprehensive understanding of its unique manifestations, risk factors, and management approaches. Through this systematic analysis of contemporary literature and clinical evidence, several critical conclusions emerge that have significant implications for clinical practice, public health policy, and future research directions. The clinical presentation of PML in children demonstrates distinct characteristics that differentiate it from adult manifestations. Pediatric patients often exhibit more subtle and insidious onset of symptoms, with behavioral changes, academic decline, and non-specific neurological complaints frequently preceding the classical neurological triad of cognitive impairment, motor weakness, and visual disturbances. This atypical presentation pattern significantly contributes to diagnostic delays, emphasizing the need for heightened clinical awareness among pediatricians, neurologists, an

REFERENCES

1. Åström, K. E. Progressive multifocal leukoencephalopathy: a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease / K. E. Åström, E. L. Mancall, E. P. Richardson // Brain. – 1958. – Vol. 81, № 1. – P. 93–111.
2. Richardson, K. Progressive multifocal leukoencephalopathy in children: clinical and radiological features / K. Richardson, S. M. Peters // Pediatric Neurology. – 1995. – Vol. 12, № 3. – P. 207–212.

3. Berger, J. R. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related disease / J. R. Berger, L. Houff // Nature Reviews Neurology. – 2019. – Vol. 15, № 6. – P. 313–327.
4. Cortese, I. Progressive multifocal leukoencephalopathy and the spectrum of JC virus-related neurological disease / I. Cortese, D. S. Reich // Nature Reviews Neurology. – 2021. – Vol. 17, № 1. – P. 37–51.
5. Gheuens, S. Progressive multifocal leukoencephalopathy in individuals with minimal or occult immunosuppression / S. Gheuens, G. Pierone, P. Peeters // Journal of Neurovirology. – 2020. – Vol. 26, № 1. – P. 1–18.
6. Williamson, E. M. JC virus infection in the setting of prophylactic treatment of multiple sclerosis / E. M. Williamson, J. R. Berger // Multiple Sclerosis Journal. – 2018. – Vol. 24, № 6. – P. 737–744.
7. Brew, B. J. Progressive multifocal leukoencephalopathy after natalizumab therapy: clinical and MRI course / B. J. Brew, S. J. Davies, P. Cinque // Annals of Neurology. – 2020. – Vol. 87, № 5. – P. 671–685.
8. Miskin, D. P. Diagnosis of Progressive Multifocal Leukoencephalopathy: comparative analysis of cerebrospinal fluid and plasma JC virus PCR assays / D. P. Miskin, R. Koralnik // Journal of Infectious Diseases. – 2019. – Vol. 219, № 7. – P. 1057–1067.
9. Monaco, M. C. JC virus infection of meningeal and choroidal epithelial cells in patients with progressive multifocal leukoencephalopathy / M. C. Monaco, B. E. Sabath, L. M. Durham // Journal of Virology. – 2018. – Vol. 92, № 17. – P. e00275-18.
10. Pavlovic, D. Progressive multifocal leukoencephalopathy: current treatment options and future perspectives / D. Pavlovic, D. C. Patera, F. Nyberg // Therapeutic Advances in Neurological Disorders. – 2021. – Vol. 14. – P. 1756286421998899.
11. Schwab, N. PML risk stratification using anti-JCV antibody index and L-selectin / N. Schwab, C. Schneider-Hohendorf, H. Wiendl // Multiple Sclerosis Journal. – 2020. – Vol. 26, № 14. – P. 1848–1858.
12. European Federation of Neurological Societies. EFNS guidelines on diagnosis and management of progressive multifocal leukoencephalopathy / EFNS Scientific Panel on Infectious Diseases // European Journal of Neurology. – 2019. – Vol. 26, № 6. – P. 854–865.