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CLINICAL–NEUROVISUALIZATION CHARACTERISTICS AND EARLY DIAGNOSIS OF PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) IN CHILDREN

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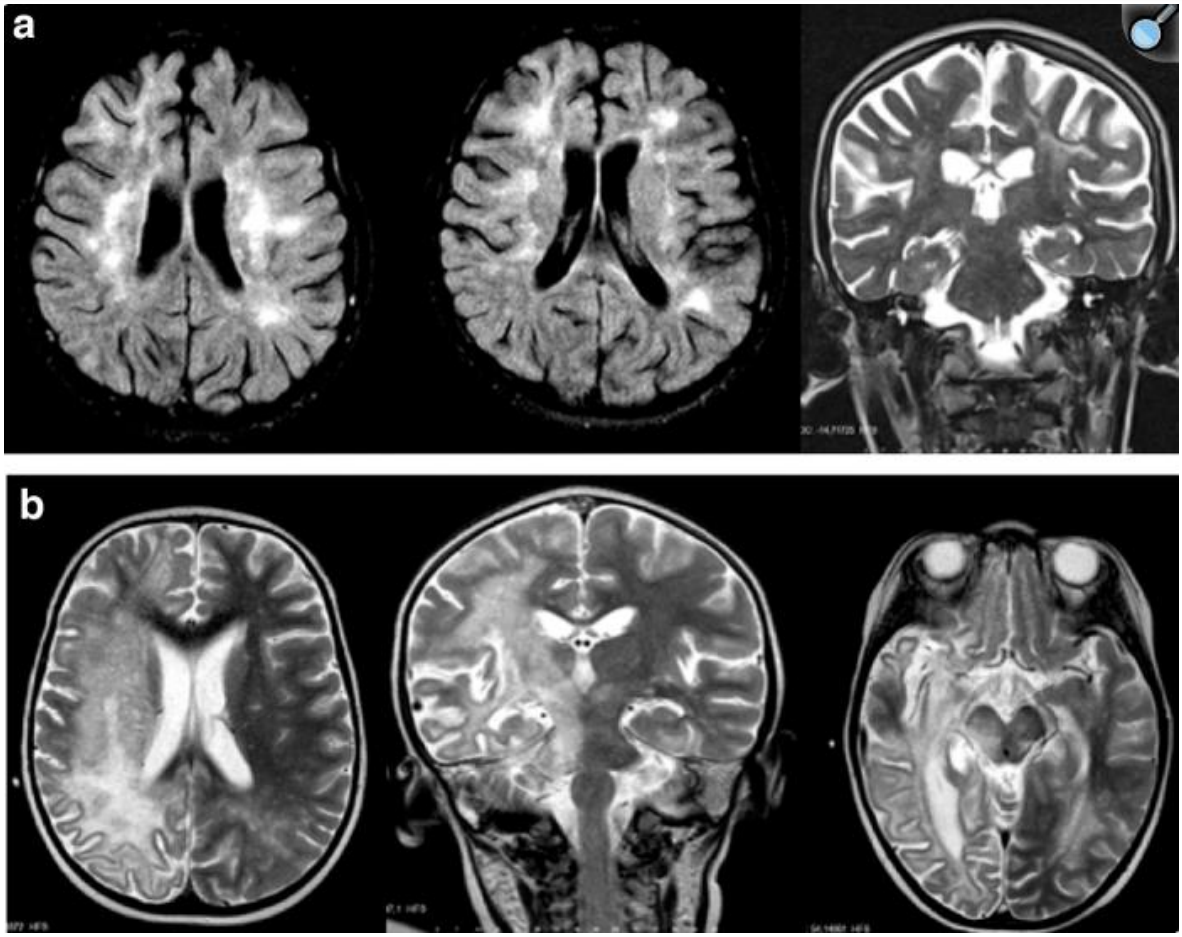
Abstract. Progressive multifocal leukoencephalopathy (PML) is an opportunistic demyelinating disease of the central nervous system caused by reactivation of the JC virus in immunocompromised patients. Although rare in childhood, the disease represents a serious clinical problem due to its rapid progression and severe neurological outcomes. Early diagnosis remains difficult because the initial clinical manifestations are often nonspecific and may mimic other demyelinating or autoimmune disorders such as acute disseminated encephalomyelitis and autoimmune encephalitis. The aim of this study was to analyze the clinical manifestations and neuroimaging characteristics of leukoencephalitis in children and to determine diagnostic criteria for early detection of the disease. Clinical data, neurological examination results, and magnetic resonance imaging (MRI) findings were analyzed in pediatric patients with suspected demyelinating pathology.The results demonstrated that the early stages of the disease are characterized by behavioral changes, cognitive decline, attention deficits, sleep disturbances, and speech impairment. Neuroimaging revealed multifocal demyelinating lesions in the cerebral white matter, involvement of subcortical and periventricular regions, and diffuse damage of the brainstem and cerebellum. MRI proved to be the most informative diagnostic method for detecting early demyelinating changes and differentiating PML from other pediatric white matter disorders. The study confirms that the integration of clinical assessment and neuroimaging findings significantly improves early diagnosis and helps prevent the development of irreversible neurological deficits in children.

Keywords: Progressive multifocal leukoencephalopathy, children, demyelinating diseases, neuroimaging, MRI diagnostics, JC virus, leukoencephalitis, early diagnosis.

Relevance. Progressive multifocal leukoencephalopathy is an opportunistic demyelinating infection of the central nervous system caused by reactivation of the JC virus in immunocompromised patients. In childhood the disease remains insufficiently studied and is frequently misdiagnosed at the early stage due to clinical similarity with inflammatory demyelinating disorders, primarily acute disseminated encephalomyelitis and autoimmune encephalitis. Because neurological manifestations may initially be nonspecific, neuroimaging becomes the key diagnostic tool allowing detection of the disease before irreversible neurological deficit develops.[6] Leukoencephalitis is an unusual and rapidly progressive disease of the central nervous system in children, the accurate diagnosis of which at an early stage is of great importance for effective treatment and reduction of complications. [1,2] According to international data, leukoencephalitis in children is rare, but in recent years the number of viral and immunopathological forms has been increasing. The number of cases associated with PML (progressive multifocal leukoencephalitis) and HIV may be around 1–5%, depending on the composition observed in the population and clinical practice. Therefore, the analysis and systematization of early diagnosis options based on clinical and neuroimaging (MRI) criteria is one of the urgent scientific and practical problems in this area [4,5]

Introduction. Leukoencephalitis belongs to the group of neuroinfectious and neuroimmune diseases accompanied by demyelinating processes in children. Viral infections (measles, herpes viruses, enteroviruses, polyomaviruses), autoimmune reactions and immune disorders play an important role in its etiology. [3,7] In particular, subacute sclerosing panencephalitis, which develops as a result of prolonged persistence of the measles virus in the central nervous system, is one of the severe forms of leukoencephalitis in children. In recent years, scientific achievements in the field of neuroimaging and neuroimmunology have allowed us to understand the pathogenesis of leukoencephalitis more deeply. However, a comprehensive study of the correlation between clinical symptoms and MRI signs still remains an urgent scientific problem. In pediatric patients, PML is extremely rare, accounting for less than 5% of reported cases; however, it represents a severe clinical challenge due to rapid neurological deterioration and limited therapeutic options [7,10]. Most pediatric cases are associated with congenital or acquired immunodeficiency, including primary immune deficiencies, HIV infection, and immunosuppressive therapy. [7,10] Magnetic resonance imaging demonstrates characteristic involvement of subcortical and juxtacortical white matter without significant mass-effect, which reflects primary destruction of oligodendrocytes rather than inflammatory edema. Lesions typically appear hyperintense on T2-weighted and FLAIR images and hypointense on T1-weighted sequences, while contrast enhancement is absent or minimal during early stages. A distinctive feature is asymmetric distribution along U-fibers with gradual extension to parieto-occipital regions and sometimes cerebellum and brainstem in pediatric patients.[6] The most distinctive neurovisualization feature of progressive multifocal leukoencephalopathy is the discrepancy between extensive white matter destruction and minimal inflammatory reaction. Unlike acute disseminated encephalomyelitis, lesions do not produce significant edema or mass effect despite large size, indicating primary viral cytolysis rather than immune-mediated injury. The presence of a peripheral diffusion restriction rim surrounding a central area of increased diffusion represents ongoing demyelination at the lesion border, which is considered a radiological marker of active disease progression. Therefore, the combination of asymmetric subcortical lesions, absence of mass effect, and diffusion mismatch forms a specific imaging pattern allowing early differentiation of progressive multifocal leukoencephalopathy from other pediatric demyelinating disorders.[9] Diffusion-weighted imaging significantly improves early detection because the advancing edge of demyelination shows restricted diffusion even before conventional MRI changes become clearly visible. This finding corresponds to active viral replication and ongoing myelin breakdown. Magnetic resonance spectroscopy additionally reveals metabolic alterations including decreased N-acetylaspartate reflecting neuronal damage and increased choline indicating membrane destruction, which together form a metabolic pattern of progressive demyelination.In children inflammatory response may be more pronounced than in adults, occasionally producing contrast enhancement and leading to diagnostic confusion with acquired demyelinating syndromes. Therefore, recognition of specific clinical-neurovisualization correlations is essential for early diagnosis and timely initiation of therapy. Identification of reliable neuroimaging markers may improve differentiation of progressive multifocal leukoencephalopathy from other pediatric white matter disorders and reduce delay in diagnosis.[6] Pediatric progressive multifocal leukoencephalopathy demonstrates several neuroimaging differences compared with adult cases. More frequent involvement of the cerebellum and brainstem as well as occasional contrast enhancement related to a stronger inflammatory response in children. Lesions may initially mimic acute disseminated encephalomyelitis; however, the absence of significant edema and progressive asymmetric expansion along white matter tracts favors PML. Recognition of these imaging characteristics improves diagnostic accuracy in pediatric patients **[10]**

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Radiological findings. **(a)** Findings of cranial MRI lesions of a 13-year-old male with primary immune deficiency. Patch lesions in the subcortical deep white matter in both frontoparietal lobes. There are also T2WI flair hyperintense lesions in the right half of the pons, both cerebellar hemispheres. **(b)** A 6-year-old patient with HIV encephalopathy and progressive multifocal leukoencephalopathy; brain MRI from a patient with PML, showing on FLAIR-weighted images and T2-weighted MRI sequences, we can see PV area and subcortical–cortical involvement of the left frontoparietal lobe adjacent to the WM lesion. FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging; PML, progressive multifocal leukoencephalopathy; PV, periventricular; T2WI, weighted imagine; WM, white matter [7].

Research Aim. Comprehensive analysis of clinical signs and neuroimaging characteristics of leukoencephalitis in children, determination of interrelationships between them, and development of clinical and MRI criteria for early diagnosis of the disease.

Materials and methods. The study analyzed cases of leukoencephalitis in children. Patients underwent: clinical neurological examination, anamnesis data, MRI examinations, EEG, serological and immunological analyses. The obtained clinical data were compared with the results of neuroimaging and pathogenetic analysis was performed.

Fergana city multidisciplinary clinic for children we examined 8 patients admitted to the neurology department. The age of sick children is from 3 to 7 years to the age of 4.7 years on average. 6 of them were boys (75%) and 2 were girls (25%). Among the research methods, a special blood serum to confirm that measles has passed Anti-Measles Virus IgG, which detects antibodies to measles (normal range 0-0.12 IU/ml) laboratory examination was carried out.

Results. The results of the analysis showed that leukoencephalitis in children often develops after viral infections at an early age. In the initial stage of the disease, the following symptoms prevailed: behavioral changes, cognitive decline, decreased attention, sleep disorders, and changes in speech activity. In the later stages of the disease: myoclonic and epileptic seizures, hyperkinesis, pyramidal and extrapyramidal syndromes, movement coordination disorders, development of

progressive neurological deficit were noted. In the results of MRT: multifocal demyelination in the white matter of the brain, pathological changes in the subcortical and periventricular areas, foci of gliosis, signs of diffuse damage in the cerebral hemispheres and brain stem were revealed. In the pathogenesis of the disease, MRI of the central nervous system revealed: multifocal demyelination in the white matter of the brain, pathological changes in the subcortical and periventricular areas, foci of gliosis, signs of diffuse damage in the cerebral hemispheres and brain stem. The persistence of the virus in the central nervous system, autoimmune reactions, cytokine imbalance, and damage to neurons and oligodendrocytes were assessed as the main mechanisms in the pathogenesis of the disease. The results obtained confirm the progressive nature of the clinical course of leukoencephalitis in children. The nonspecificity of the initial clinical signs leads to a late diagnosis of the disease. Recent scientific studies show that MRI is the “gold standard” for diagnostics of demyelinating diseases in children. At the same time, the development of early diagnostic algorithms based on the integration of clinical symptoms and neuroimaging data remains an urgent scientific task. In particular, the decline in measles vaccination coverage is considered an important epidemiological factor that increases the risk of developing PSPE and some forms of leukoencephalitis.

Conclusion. Leukoencephalitis in children is a complex neuroinfectious disease with an integral relationship between clinical and neuroimaging symptoms. Comprehensive assessment of clinical symptoms, MRI signs and immunological indicators is necessary for early diagnosis of the disease. In children, the main difficulty in early detection of progressive multifocal leukoencephalopathy is that clinically the disease mimics other demyelinating conditions. In practice, physicians often suspect ADEM or autoimmune encephalitis, since neurological symptoms are nonspecific and rapidly change. Therefore, the decisive stage of diagnosis becomes not the clinical presentation but neuroimaging. When analyzing MRI scans, attention should be focused on extensive white-matter damage that does not correspond to the degree of inflammation. In other words, the lesion is large but without edema — suggesting that this is not a typical inflammatory demyelination. Restricted diffusion indicates that the process is still actively progressing. When these features are assessed together, PML can be suspected at an early stage. Thus, in clinical practice, correct diagnosis often depends not on laboratory results but on the physician’s ability to correctly interpret MRI patterns. Combining neuroimaging with clinical reasoning reduces diagnostic delay and helps prevent the development of irreversible neurological deficits in the child.The obtained results serve to improve strategies for early detection and treatment of leukoencephalitis in children.

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