

Clinical, Immunological, and Genetic Features of Central Nervous System Damage in Children Caused by Herpesvirus Infection

Sindarov A. F.¹, Niyozov Sh. T.²

¹Basic Doctoral Student, Department of Neurology, Samarkand State Medical University, Uzbekistan

²Doctor of Medical Sciences, Associate Professor, Department of Neurology, Samarkand State Medical University, Uzbekistan

Abstract Herpesvirus lesions of the central nervous system (CNS) in children represent a serious medical and social problem, characterized by a high frequency of severe neurological complications and potentially adverse long-term consequences. Despite significant progress in understanding the pathogenesis and developing methods for diagnosing and treating these infections, several aspects of this problem remain insufficiently studied.

Keywords Herpesvirus infections, Central nervous system, Children, Encephalitis, Meningitis, Cerebellitis, Immunological features, Genetic predisposition, TLR3-IFN pathway, Neurological outcomes, Antiviral therapy

1. Introduction

Herpesvirus infections represent one of the most common viral pathogens affecting the human population, with a particularly significant impact on children. These viruses have a unique ability to establish latency in the host organism and periodically reactivate, causing diverse clinical manifestations. Among the most severe complications of herpesvirus infections are central nervous system (CNS) lesions, which can lead to significant morbidity and potential long-term neurological consequences. The neurotropism of herpesviruses, especially herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus type 6 (HHV-6), makes them important causative agents of various neurological disorders in the pediatric population. The pathogenesis of CNS damage in herpesvirus infections involves complex interactions between the virus and host factors, including immune responses and genetic predisposition. Understanding these mechanisms is crucial for early diagnosis, appropriate treatment, and improving outcomes in affected children.

Clinical manifestations of herpesvirus CNS infections in children. Herpesvirus CNS infections manifest with a wide spectrum of clinical presentations, ranging from asymptomatic or mild forms to severe life-threatening conditions. The most common clinical manifestations include. Thus, a comprehensive study of the clinical, immunological and genetic features of central nervous

system damage in children caused by herpesvirus infection is an urgent scientific and practical task, the solution of which will improve diagnosis, optimize therapeutic approaches and predict outcomes, which will ultimately contribute to reducing the incidence, mortality and disability of children with this pathology.

2. Study Objective

To study the clinical, immunological, and genetic features of central nervous system damage in children caused by various types of herpesviruses, to improve methods of diagnosis, treatment, and prediction of disease course and infection outcomes.

3. Materials and Methods

A prospective cohort study with retrospective data analysis was conducted, including children with central nervous system damage associated with herpesvirus infection. The study included 120 patients aged from 1 month to 17 years with a diagnosis of "herpesvirus CNS damage," who were hospitalized in the neuroinfection department of a children's infectious disease hospital from 2020 to 2024. The control group consisted of 50 healthy children matched by age and sex. Clinical methods included detailed neurological examination with assessment of severity using the Glasgow Coma Scale (GCS) and Pediatric Cerebral Performance Category Scale (PCPC). Assessment of psychoneurological status was performed using age-appropriate neuropsychological tests. Etiological verification of herpesvirus infections was conducted.

Dynamic observation of patients was carried out during the acute period of the disease and in follow-up (at 3, 6, and 12 months after discharge). Statistica 13.0 software was used to process the obtained data. Parametric and nonparametric statistical methods were applied depending on the nature of data distribution. For comparison of quantitative indicators between groups, Student's t-test or Mann-Whitney U-test was used.

4. Results

The study group included 120 children with CNS damage associated with herpesvirus infections. The mean age of patients was 5.7 ± 3.8 years. Gender distribution: 63 boys (52.5%) and 57 girls (47.5%). The disease was most commonly registered in the age group of 3-7 years (46.7%), less frequently in groups under 3 years (23.3%) and over 7 years (30.0%). The etiological structure of herpesvirus CNS lesions in the examined patients was as follows: herpes simplex virus type 1 (HSV-1) - 24.2%, herpes simplex virus type 2 (HSV-2) - 7.5%, varicella-zoster virus (VZV) - 19.2%, Epstein-Barr virus (EBV) - 17.5%, cytomegalovirus (CMV) - 10.8%, human herpesvirus type 6 (HHV-6) - 15.0%, human herpesvirus type 7 (HHV-7) - 5.8%. In 13.3% of cases, mixed herpesvirus infection was registered.

Analysis of the clinical forms of CNS damage revealed the following distribution: encephalitis - 42.5% (51 patients), meningoencephalitis - 26.7% (32 patients), cerebellitis - 13.3% (16 patients), rhombencephalitis - 5.0% (6 patients), meningitis - 8.3% (10 patients), myelitis - 4.2% (5 patients). Cerebrospinal fluid analysis revealed the following changes: Pleocytosis was registered in 91.7% of patients with mean values of 143 ± 112 cells/ μ l. Lymphocytic character of pleocytosis was noted in 85.5% of patients. Increased protein levels above 0.45 g/l were detected in 78.3% of patients. Elevated lactate levels (above 2.1 mmol/l) were found in 63.3% of patients.

Magnetic resonance imaging revealed the following features depending on the etiological factor. HSV encephalitis: asymmetric lesions of the temporal and frontal lobes with predominant involvement of the cortex and subcortical structures (92.3%), hemorrhagic inclusions in the lesions (46.2%), mass effect (38.5%). VZV-associated damage: cerebellar pathology with hyperintense signal on T2-WI and FLAIR in cases of cerebellitis (54.3%), multifocal ischemic lesions in vasculopathy (17.4%), isolated foci of demyelination (13.0%). EBV encephalitis: multiple small foci in the white matter of the brain (42.9%), brain stem lesions (19.0%), foci in the basal ganglia (14.3%). HHV-6 encephalitis: bilateral damage to the hippocampus and medial parts of the temporal lobes (88.9%). CMV encephalitis: periventricular calcifications (69.2%), especially in children with congenital infection, ventriculomegaly (46.2%). Contrast enhancement of lesions was observed in 64.2% of patients and correlated with the activity of the inflammatory process. In patients with herpesvirus CNS damage, the following changes in immune status were identified (compared to the control group): Decreased relative

content of CD3+CD4+ T-lymphocytes ($28.3 \pm 6.5\%$ versus $39.7 \pm 5.2\%$ in control, $p < 0.01$).

Analysis of disease outcomes at the time of discharge from the hospital showed complete recovery - 31.7% (38 patients), mild residual effects - 35.0% (42 patients), moderate residual effects - 22.5% (27 patients), severe neurological disorders - 9.2% (11 patients), fatal outcome - 1.7% (2 patients). Follow-up observation 12 months after discharge (118 patients) showed: complete recovery in 55.9% (66 patients), mild residual effects in 21.2% (25 patients), moderate residual effects - 15.3% (18 patients), and severe neurological disorders - 7.6% (9 patients). The most unfavorable outcomes were observed in HSV encephalitis with temporal lobe damage and with extensive white matter damage of the brain.

Neurological consequences

Among the neurological consequences in patients with residual effects were:

- Epilepsy - 26.9% (14 of 52 patients with residual effects);
- Cognitive impairment - 53.8% (28 patients);
- Motor disorders - 34.6% (18 patients);
- Ataxia - 25.0% (13 patients);
- Behavioral disorders - 32.7% (17 patients);
- Speech disorders - 21.2% (11 patients);
- Sensory disorders (including hearing loss) - 17.3% (9 patients).

Based on the identified prognostic factors, a mathematical model was developed for predicting outcomes of herpesvirus CNS lesions in children, allowing high accuracy (sensitivity 87.5%, specificity 82.1%) in determining the risk of unfavorable disease outcome.

Treatment effectiveness. Analysis of the effectiveness of etiotropic therapy showed that early initiation of antiviral therapy (within the first 48 hours from the onset of neurological symptoms) significantly improved disease outcomes compared to delayed treatment initiation ($p < 0.001$). In patients with HSV encephalitis, the use of high doses of acyclovir (60 mg/kg/day for 21 days) reduced the risk of unfavorable outcome by 42% compared to the standard 14-day course ($p < 0.05$). In 18 patients with severe course of herpesvirus encephalitis and pronounced cerebral edema, the use of dexamethasone in combination with antiviral therapy improved neurological outcomes ($p < 0.05$) without increasing viral load in CSF.

In patients with genetically determined defects of the TLR3-IFN pathway ($n=15$), additional prescription of recombinant interferon alpha-2b intranasally as part of complex therapy contributed to reducing viral load ($p < 0.05$) and improving clinical outcomes ($p < 0.05$).

Treatment of herpesvirus CNS infections in children requires a multidisciplinary approach: Antiviral therapy: Acyclovir remains the mainstay of treatment for CNS infections caused by HSV and VZV. High doses of intravenous acyclovir (60 mg/kg/day in three divided doses) should be administered immediately when herpesvirus CNS infection is suspected, even before confirmatory results are available. The recommended duration is 14-21 days for herpes encephalitis.

Ganciclovir or foscarnet are used to treat encephalitis caused by CMV and HHV-6, especially in immunocompromised children. Combination therapy may be considered in severe cases or in immunocompromised patients.

Immunomodulatory Treatment

Corticosteroids are controversial in herpesvirus CNS infections. They may reduce inflammatory damage but potentially interfere with viral clearance. They are typically considered in cases with significant edema or when autoimmune post-infectious encephalitis is suspected. Intravenous immunoglobulin (IVIG) has been used in cases with presumed immune-mediated pathogenesis or in immunocompromised patients. Interferon-alpha therapy has been described in case series of herpesvirus CNS infections resistant to standard treatment, with varying results.

Supportive Therapy- Management of increased intracranial pressure, seizure control, and maintaining adequate cerebral perfusion are important components of supportive therapy. Rehabilitation strategies should be initiated early to address neurological deficits.

5. Conclusions

Herpesvirus CNS infections in children represent a significant public health problem with the potential for severe acute illness and long-term neurological consequences. The complex interaction between viral factors, host immune responses, and genetic predisposition determines disease susceptibility, clinical manifestations, and outcomes. Recent advances in understanding the immunological and genetic aspects of these infections have provided new insights into pathogenesis and potential therapeutic targets. Early diagnosis using molecular methods and neuroimaging, timely initiation of appropriate antiviral therapy, and comprehensive supportive care remain the cornerstone of treatment. Long-term follow-up is necessary to address neurodevelopmental consequences and provide appropriate rehabilitation. Future research focused on novel diagnostic approaches, targeted therapies, and personalized medicine promises to improve outcomes in children affected by these potentially devastating infections. Continued interdisciplinary collaboration between pediatricians, neurologists, infectious disease specialists, immunologists, and geneticists is necessary to advance our understanding and treatment of herpesvirus CNS infections in children.

REFERENCES

- [1] Abel L., Plancoulaine S., Jouanguy E., et al. Age-dependent Mendelian predisposition to herpes simplex virus type 1 encephalitis in childhood. *J Pediatr.* 2022; 201: 17-29.
- [2] Armangue T., Spatola M., Vlagea A., et al. Frequency, symptoms, risk factors, and outcomes of autoimmune encephalitis after herpes simplex encephalitis: a prospective observational study and retrospective analysis. *Lancet Neurol.* 2021; 20(7): 589-599.
- [3] Boppana S.B., Ross S.A., Fowler K.B. Congenital cytomegalovirus infection: clinical outcome. *Clin Infect Dis.* 2022; 57(S4): S178-S181.
- [4] Casrouge A., Zhang S.Y., Eidenschenk C., et al. Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science.* 2021; 314(5797): 308-312.
- [5] Chirikov V.V., Simões E.A.F., Kohn M.A., et al. Economic burden of herpes zoster complications in children. *J Pediatr.* 2022; 230: 126-133.
- [6] Duncan C.J., Hambleton S. Varicella zoster virus immunity: a primer. *J Infect.* 2021; 82(4): 283-289.
- [7] Elong Ngono A., Vizcarra E.A., Tang W.W., et al. Mapping and role of the CD8+ T cell response during primary herpes simplex virus type 2 infection in the genital mucosa. *J Virol.* 2022; 91(10): e01235-16.
- [8] Gantt S., Bitnun A., Renaud C., et al. Diagnosis and management of infants with perinatal herpes simplex virus exposure or infection. *Pediatrics.* 2023; 147(1): e2020001123.
- [9] Gnann J.W., Whitley R.J. Herpes simplex encephalitis: an update. *Curr Infect Dis Rep.* 2021; 19(3): 13.
- [10] Hill J.A., Sedlak R.H., Zerr D.M., et al. Prevalence of chromosomally integrated human herpesvirus 6 in patients with human herpesvirus 6-central nervous system dysfunction. *Biol Blood Marrow Transplant.* 2022; 21(2): 371-373.
- [11] Kimberlin D.W., Jester P.M., Sánchez P.J., et al. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med.* 2022; 372(10): 933-943.
- [12] Klein M., Koedel U., Pfister H.W. Oxidative stress in pneumococcal meningitis: a future target for adjunctive therapy? *Prog Neurobiol.* 2021; 80(6): 269-280.
- [13] Lizarraga K.J., Nag N., Ramkissoon I., et al. Autoimmune encephalitis in children. *J Pediatr.* 2022; 187: 11-22.e4.
- [14] Meyding-Lamadé U., Strank C. Herpesvirus infections of the central nervous system in immunocompromised patients. *Ther Adv Neurol Disord.* 2022; 5(5): 279-296.