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ANTI-NMDA ENCEPHALITIS FOLLOWING HSV-1 WITH HHV-6 CO-INFECTION

Paediatrics

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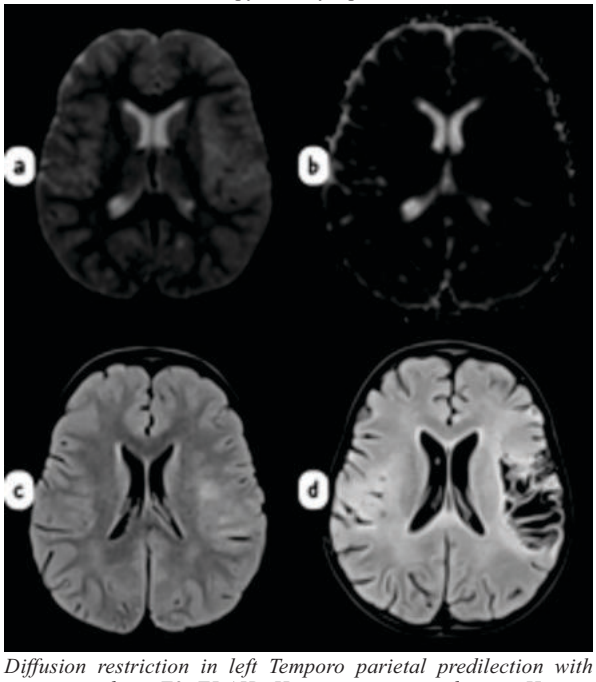
KEYWORDS

INTRODUCTION

Herpes Simplex Virus (HSV) encephalitis is a leading cause of viral encephalitis, with an incidence of 2–4 cases per million population[1]. Neurological relapses following HSV encephalitis can occur as autoimmune encephalitis (AIE), reported in 7%–25% of cases, particularly in children under 4 years of age. Such cases often result in poorer outcomes, including significant disability and high mortality rates[1-2]. Approximately 19% of autoimmune encephalitis cases show detectable HHV-6 in the cerebrospinal fluid (CSF), suggesting a potential contribution of co-infections to disease progression and outcomes [4,5].

Case Report

We report the case of a 3-year-old previously healthy and immunocompetent girl who presented with altered sensorium and refractory seizures. Cerebrospinal fluid (CSF) analysis via multiplex PCR detected *Herpes Simplex Virus-1* (HSV-1) and *Human Herpesvirus-6* (HHV-6). Anti-N-methyl-D-aspartate receptor (anti-NMDAR) antibodies were negative at the initial presentation. The patient was treated with intravenous acyclovir for three weeks and discharged. On Day 41, she returned with new-onset movement disorder and marked irritability.CSF analysis at this stage revealed the presence of anti-NMDAR antibodies with a 3+ titre, confirming the diagnosis of autoimmune encephalitis (AIE). The patient was initiated on treatment with high-dose intravenous methylprednisolone and intravenous immunoglobulin (IVIG), rituximab. By Day 72, she showed significant clinical improvement, though with residual expressive language disability. Repeat anti-NMDAR antibody titres were negative by Day 155. At her 6-month follow-up, the patient was stable on maintenance therapy with mycophenolate mofetil.



Diffusion restriction in left Temporo parietal predilection with corresponding T2 FLAIR Hyperintensities during Herpes Encephalitis phase (a,b,c)

Evolution to cystic changes during autoimmune encephalitis phase (d)

DISCUSSION

Herpes Simplex Virus (HSV) is the leading cause of fatal sporadic encephalitis in humans. Despite appropriate antiviral treatment, some patients experience relapse, with the most common cause being autoimmune encephalitis (AIE). Other members of the *Herpesviridae* family, including Varicella-Zoster Virus (VZV), Human Herpesvirus-6 (HHV-6), and Epstein-Barr Virus (EBV), may also cause similar clinical presentations, supporting a shared pathogenesis underlying post-infectious brain autoimmunity[4]. Proposed mechanisms for this phenomenon include molecular mimicry, bystander activation, epitope spreading, and genetic susceptibility[3].

Autoimmune encephalitis has been reported in approximately 27% of patients following HSV encephalitis, typically occurring within 2 months to 1 year after initial symptom onset[2]. Importantly, anti-NMDAR encephalitis secondary to HSV encephalitis has a worse prognosis compared to idiopathic anti-NMDAR encephalitis[1,2].

Human Herpesvirus-6 (HHV-6) infection presents with a wide clinical spectrum, ranging from self-limited febrile exanthematous illness to severe meningoencephalitis. Chromosomally integrated forms of HHV-6 are frequently detected; however, their clinical significance remains an area of ongoing investigation[5].

CONCLUSION

Although data explaining the interplay between genetic factors, co-infections, autoimmune responses in the pathogenesis and progression remain limited, this case illustrates a rare occurrence of post-HSV autoimmune encephalitis with a paradoxically favourable neurological outcome. It underscores the need for further research to better understand these multifactorial contributions and to develop effective treatment strategies, including potential prophylaxis during the acute phase of HSV encephalitis, to improve patient outcomes.

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