

# EBV-related hemophagocytic lymphohistiocytosis: a rare case of acute cerebral involvement

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**Background:** Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyperinflammatory syndrome resulting from uncontrolled immune activation. It is classified as either primary (genetic) or secondary, with viral infections—particularly Epstein-Barr virus (EBV)—being common triggers<sup>1</sup>. Central nervous system (CNS) involvement is rare but significantly increases mortality<sup>2</sup>.

**Case report:** We present the case of a 31-year-old male with Down syndrome and no prior comorbidities, initially admitted in February 2025 with acute acalculous cholecystitis complicated by septic shock and multi-organ failure. He was diagnosed with EBV-associated HLH. In April 2025, he was readmitted for suspected urinary tract infection and developed acute neurological symptoms, including anisocoria with fixed left mydriasis, left-sided ptosis, right hemiparesis, and left peripheral facial palsy. Brain MRI showed multiple lesions involving the brainstem, posterior limb of the left internal capsule, right amygdala, cerebellar cortex, and right inferior frontal gyrus, suggestive of inflammatory or lymphoproliferative pathology (*figure 1*). Cerebrospinal fluid (CSF) analysis was normal. Empirical high-dose intravenous methylprednisolone 1 g/day for 5 days, followed by IVIG 0.4 g/kg/day for 5 days, were administered, but neurological deterioration progressed, as confirmed by follow-up MRI (*figure 2*). EBV-DNA was detected in both serum and CSF. Stereotactic brain biopsy revealed interstitial and perivascular lymphoid infiltrate with aggregates of mature lymphocytes with plasmacytoid features and large blasts, features suggestive of CNS involvement by EBV-associated polymorphic lymphoproliferative disorder. Despite intensive immunosuppressive and immunomodulatory therapy (HLH-2004 protocol) based on intrathecal methotrexate 10 mg weekly, combined with dexamethasone, and then cyclophosphamide 1 g, the patient's neurological condition continued to worsen. Clinical stabilization was temporarily achieved only after salvage therapy with the JAK inhibitor ruxolitinib initiated at 5 mg twice daily and later increased to 10 mg twice daily. Unfortunately, after a couple of weeks, the patient definitely worsened and died of acute brainstem hemorrhage.

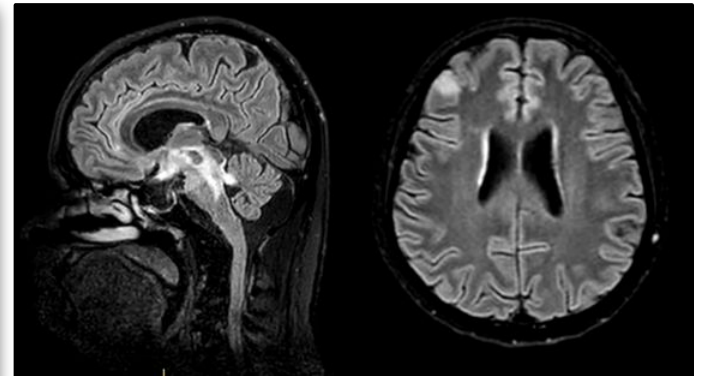


Figure 1: lesions involving the brainstem (left) and the right inferior frontal gyrus (right)

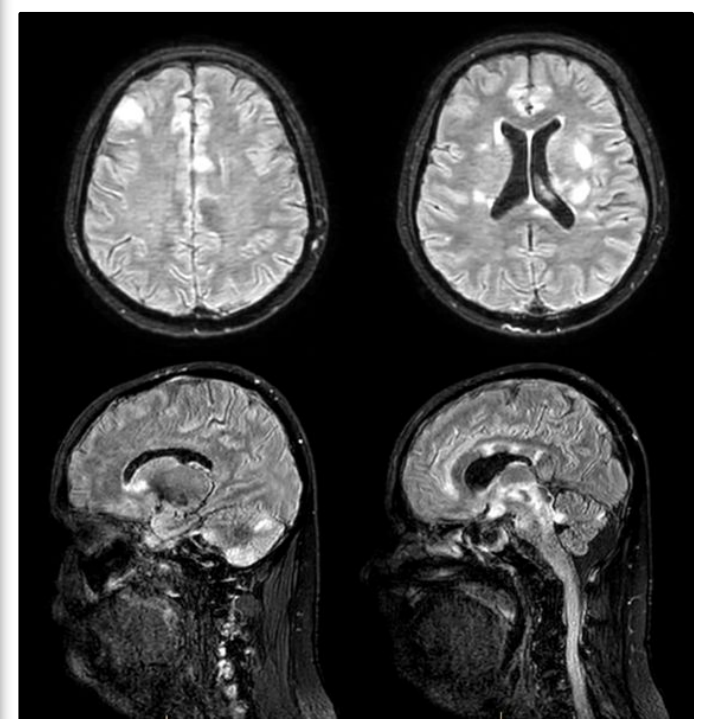


Figure 2: increase in known lesions and appearance of new lesions in the corpus callosum (bottom left), white matter (top right) and cerebellum (bottom right)

**Discussions:** The diagnosis of CNS involvement by EBV-related HLH was established based on prior HLH diagnosis (HLH 2004 diagnostic criteria criteria), detection of EBV-DNA in serum and CSF, characteristic MRI findings, and confirmatory histopathology. The clinical course was fulminant, with rapidly progressive neurological decline despite multimodal treatment, underscoring the severity of CNS-HLH.

**Conclusions:** EBV-associated HLH with CNS involvement is a rare and highly aggressive condition with limited treatment options and poor prognosis<sup>2,3</sup>. Early recognition and the use of targeted therapies such as JAK inhibitors may be critical for disease control in refractory cases.

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