RESIDENT & FELLOW SECTION

Child Neurology: Familial Hemophagocytic Lymphohistiocytosis Underlying Isolated CNS Inflammation

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Abstract

Encephalitis and encephalopathy in children represent a diagnostic challenge. We describe a patient with relapsing encephalitis in whom the differential diagnosis included acute disseminated encephalomyelitis, human herpesvirus 6 encephalitis, and hemophagocytic lymphohistiocytosis (HLH). Because of its rarity, HLH is often overlooked as a differential diagnosis in encephalitis, especially in the isolated CNS forms. As this case illustrates, inborn errors of immunity can underlie isolated encephalitis and should be included in the differential diagnosis of these presentations.

Background

Pediatric neuroinflammatory diseases represent a heterogeneous group of immune-mediated conditions affecting the CNS, including demyelinating diseases, autoimmune encephalopathies, autoinflammatory conditions, and neurodegenerative diseases.[1] Among these falls acute disseminated encephalomyelitis (ADEM), an inflammatory, demyelinating condition usually affecting children and young adults days to weeks after an acute infection or vaccination.[2] It is characterized by multifocal or diffuse gray and white matter damage and increased intensity lesions on T2/fluid-attenuated inversion recovery (FLAIR) MRI sequences.[1,2] The hypothesized pathogenesis is immune-mediated white matter damage triggered by an acute infection, followed by a secondary autoimmune response, with lymphocyte and macrophage infiltration of perivascular regions.[1,2] Viral encephalitis is one differential diagnosis in children presenting with symptoms compatible with ADEM. Human herpesvirus 6 (HHV-6) is a common cause of febrile seizures in children and can cause infectious encephalitis, more often in immunocompromised patients.[3] CNS manifestation of HHV-6 may or may not present with abnormal findings on MRI, and the imaging pattern is related to the immune status of the patient. Typical findings in the immunocompromised patient include hyperintense signal on the T2- and FLAIR-weighted sequences in the mesiotemporal regions, with or without diffusion restriction, and usually without enhancement. Nonimmunocompromised patients may present with a pattern of widespread T2 hyperintensities and areas of subcortical diffusion restriction.[3] Of interest, HHV-6 infection has been described in association with ADEM and other forms of autoimmune encephalitis.[4,5] CNS inflammation is also a common feature of hemophagocytic lymphohistiocytosis (HLH), a life-threatening systemic inflammatory disease due to a genetic (primary HLH) or acquired cause (secondary HLH), characterized by lymphocyte and macrophage activation and multiorgan infiltration.[6,7] We here describe the diagnostic process and clinical course of a child with HLH presenting with 2 episodes of encephalitis and HHV-6 infection to highlight the importance of searching for underlying inborn errors of immunity (IEIs) in children presenting with various forms of encephalitis.

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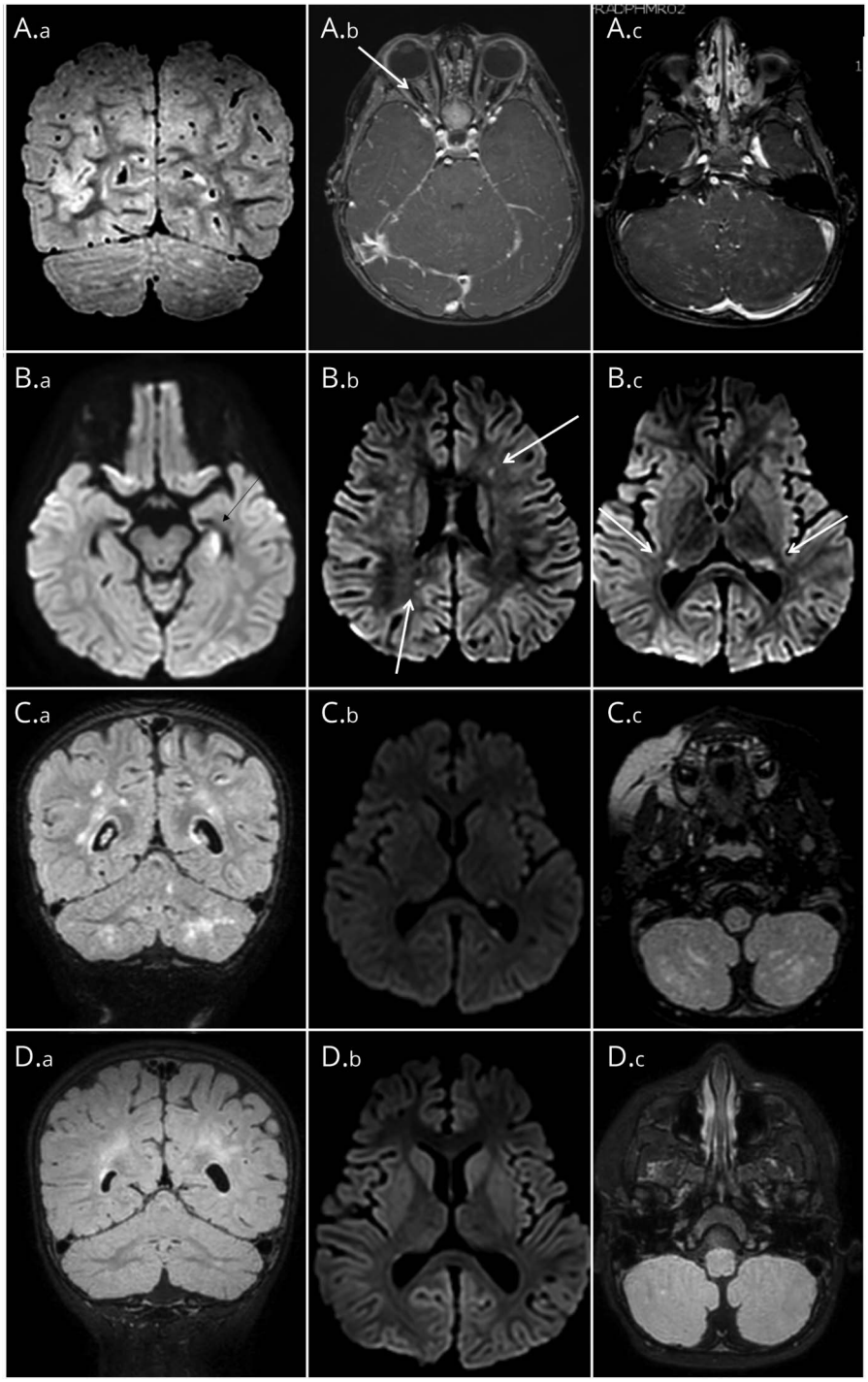
Figure Brain MRI at Different Stages of Disease



(A) Presentation with ataxia and encephalopathy. (A.a) Cortical right occipito-parietal hyperintensity on FLAIR. (A.b) Thickening and contrast enhancement of the right optic nerve on T1 sequences (arrow). (A.c) Cerebellitis with leptomeningeal and perivascular enhancement and cerebellar swelling, as well as subcortical patchy FLAIR hyperintensities. (B) Second episode of ataxia, 2 months after the first one. (B.a) Diffusion restriction and FLAIR hyperintensity in the left hippocampus. (B.b) Bilateral periventricular and subcortical white matter lesions with diffusion restriction (arrows). (B.c) Bilateral pulvinar nuclei lesions with diffusion restriction (arrows). (C) Evolution 4 months after the initial presentation. (C.a) Progressive multifocal white matter disease on FLAIR. (C.b and C.c) Signs of ependymal disease on DWI and leptomeningeal disease on FLAIR. (D) Evaluation 14 days after treatment with alemtuzumab and steroids: significant regression of the white matter lesions and regression of signs of leptomeningeal and ependymal disease. FLAIR = fluid-attenuated inversion recovery.

Case Report

The male patient was born from nonconsanguineous parents of Belgian descent. He was shortly hospitalized at age 4 months for *Salmonella* and influenza infection; he had Gianotti-Crosti syndrome at age 14–15 months and surgical correction of unilateral cryptorchidism at age 9 months. His growth and development were normal. At age 19 months, he was admitted with fever, diarrhea and vomiting, episodes of staring, refusal to stand or walk, jerking limb movements, and a preference for lying down and resting instead of playing. Blood tests were unremarkable, and x-rays of the legs and back were normal, as were a hip ultrasound and a bone scintigraphy. A complete neurologic examination highlighted truncal ataxia with impaired balance also when sitting, transient opsoclonus, and nystagmus. An abdominal ultrasound was negative for tumors,

and an ophthalmologic examination was normal. Brain CT scan was normal, but MRI revealed extensive signs of cerebellar inflammation with leptomeningeal and perivascular enhancement, focal FLAIR signal abnormalities, and cerebellar swelling, as well as supratentorial diffuse leptomeningeal enhancement, right parieto-occipital cortical FLAIR and DWI hyperintensity, FLAIR hyperintensity, thickening and contrast enhancement of the right optic nerve, enhancement of the optic chiasm and more subtle enhancement of the left optic nerve (main findings are shown in Figure, A). Radiologic differential diagnosis included infectious as well as inflammatory etiology, including neuromyelitis optica spectrum disorder (NMO-SD), myelin oligodendrocyte glycoprotein antibody disease (MOGAD), ADEM, and HLH. A lumbar puncture showed pleocytosis with 24 white blood cells/μL (100% mononuclear) and raised protein (975 mg/L) with normal glucose. Oligoclonal bands were absent. CSF culture and PCRs for herpes simplex, varicella-zoster, enterovirus, and HHV-6 were negative. Serology for cytomegalovirus, Epstein-Barr virus, and *Borrelia* was negative. A basic immunologic screening was normal, and he had no biochemical signs of inflammation, including normal ferritin. Based on these results, a working diagnosis of postinfectious ADEM was made, and the child was treated with high-dose pulse steroids (methylprednisolone 20 mg/kg/d) for 5 days with a marked improvement in atactic symptoms.

He was discharged, and steroids were tapered. After 1 month, the ataxia worsened, and he developed a febrile episode and was admitted for a second course of pulse steroids. Three days after admission, he developed a focal status epilepticus and was treated with valproic acid and levetiracetam. A lumbar puncture was normal. A new brain MRI showed regression of the previous cerebellar and parieto-occipital lesions but onset of new areas with T2/FLAIR hyperintensity and restricted diffusion involving the left hippocampal region, bilateral pulvinar nuclei, and bilateral periventricular and subcortical white matter (Figure, B). A broad panel of antineuronal autoantibodies was negative. HHV-6 was detected in blood by PCR (viral load between 8,000 and 17,000 copies/μL) but was not tested in CSF at this point. Suspecting an infectious encephalitis due to HHV-6, he was started on ganciclovir without effect on the viral load. His symptoms receded after 4 days of steroids. As part of the diagnostic workup for HLH, natural killer (NK) cell degranulation assays were performed and resulted impaired. Exome sequencing confirmed the presence of compound heterozygous variants in *UNC13D* (nonsense variant c.2695C>T, p.Arg899*; splice variant c.2092-1G>A), underlying familial HLH (MUNC-13 deficiency). In the absence of siblings, a donor search for allogeneic hematopoietic stem cell transplantation (HSCT) was started.

Three months after this second episode, the ataxia worsened, and a brain MRI showed extensive progression of the white matter disease with emergence of new lesions, focal ependymal disease, and cerebellar leptomeningeal enhancement (Figure, C). He was treated according to the C-HLH protocol (NCT02472054) with alemtuzumab (0.5 mg/kg D1, 1 mg/kg D2-3) and methylprednisolone (2 mg/kg) for 3 days, followed by gradual tapering of the steroids to reach 0.5 mg/kg on D14. MRI reevaluation on D14 showed a significant regression of the lesions (Figure, D), classified as a partial response to therapy. He received 1 maintenance dose of alemtuzumab (1 mg/kg) on D15 and was kept on methylprednisolone 0.5 mg/kg until the start of conditioning for HSCT, which he is currently undergoing.

Table Main Genetic Causes of Primary HLH

Primary HLH	Mutated genes
Familial HLH	*PRF1, UNC13D, STX11*, and *STXBP2*
Pigmentary disorders with HLH	*RAB27A, LYST, AP3B1*, and *PLDN*
X-linked lymphoproliferative syndromes 1 and 2	*SH2D1A* and *XIAP*
Autoinflammatory syndromes with HLH	*NLRC4* and *CDC42*
EBV susceptibility disorders	*MAGT1, ITK, CD27, CD70, CTPS1, RASGRP1*, and *GATA2*

Abbreviations: EBV = Epstein-Barr virus; HLH = hemophagocytic lymphohistiocytosis.

Discussion

In this article, we describe a patient presenting with encephalitis in whom we diagnosed familial HLH caused by compound heterozygous mutations in *UNC13D*. The differential diagnosis in this child included ADEM and HHV-6 viral encephalitis. HLH was suspected based on the radiologic presentation but was initially excluded because of the absence of systemic inflammation, hepatosplenomegaly and cytopenia, and normal ferritin. However, IEIs should also be considered in the differential diagnosis, as inflammatory or infectious CNS involvement is a common feature of familial HLH and many other primary immunodeficiencies.[6-8] Primary forms of HLH are defined by defective NK cell and cytotoxic $CD8^+$ T cell degranulation, which leads to sustained hyperinflammation, T-cell proliferation and activation, causing fever, hepatosplenomegaly, cytopenia, elevated ferritin, hypofibrinogemia, and hemophagocytosis.[6] They are caused by several genetic defects: 4 autosomal recessive familial HLH forms (*UNC13D*, *PRF1*, *STX11*, and *STXBP2*) and many more causing HLH in the context of other IEIs (Table).[9] CNS involvement in HLH can be isolated or accompany the systemic features and may evolve to severe neurologic symptoms (irritability, meningism, seizures, encephalopathy, and focal neurologic signs).[10] Pleocytosis and increased protein levels in the CSF are present in 10%–50% of cases.[7,10]

Imaging findings in CNS HLH range from normal findings, to nonspecific findings such as isolated cortical atrophy, to extensive parenchymal disease with multifocal white matter lesions with or without leptomeningeal and/or perivascular

enhancement, with frequent cerebellar involvement.[7,8,10,11] Tumefactive lesions, optic neuritis, and spinal cord lesions have also been described.[12] An imaging review study grouped imaging patterns into 2 main groups: (1) parenchymal disease and (2) normal or nonspecific findings, and subdivided the first group into (1.1) multifocal cerebral/cerebellar lesions, (1.2) brainstem predominant pattern (CLIPPERS-like pattern), and (1.3) diffuse cerebellar involvement/cerebellitis.[11] Our case mainly showed features of group 1.3 at presentation, with some features of 1.2 (a CLIPPERS-like enhancement pattern, although with relative sparing of the pons), and 1.1 (multifocal white matter lesions). These brain MRI findings are thus important to raise suspicion of HLH and perform further testing to exclude or confirm the diagnosis.

Unfortunately, because of its rarity, HLH is often overlooked as a differential diagnosis in encephalitis, especially in the isolated CNS forms of HLH.[8,10,13-15] A basic HLH screening, even in the absence of any systemic inflammation and hyperferritinemia, should include expression of perforin, SAP, and XIAP as well as NK cell and $CD8^+$ T-cell degranulation. It should be completed, also in the absence of abnormal results in the initial tests, by exhaustive genetic testing (preferentially genetic panel of HLH-related genes or exome sequencing, given the numerous possible genetic defects). The interpretation of these analyses requires expertise from a clinical immunologist and neuroradiologist. A prompt diagnosis of HLH is essential to provide disease-specific care to the patient and prevent irreversible brain damage leading to permanent invalidity due to untreated or insufficiently treated cerebral HLH.[8,10] Moreover, life-threatening systemic inflammation can occur at any moment, also in patients with isolated CNS involvement at presentation.[8] Steroids, often used in the suspect of ADEM or other forms of autoimmune encephalomyelitis, can offer a temporary relief from the symptoms, but their tapering often results in relapse of disease.[8] Specific therapy according to the current guidelines for primary HLH is necessary to guarantee survival and a favorable outcome. This includes targeted immune suppression with steroids, alemtuzumab (targeted antilymphocyte treatment) and cyclosporine A, associated with intrathecal steroids and methotrexate in selected cases, and is followed by HSCT to treat the underlying disease and prevent relapses. Finally, a definite diagnosis will allow prompt genetic counseling for the family.

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Disclosure

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Continued

Appendix *(continued)*

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