Child Neurology: Familial Hemophagocytic Lymphohistiocytosis Underlying Isolated Central Nervous System Inflammation

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Neurology® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.
Equal Author Contribution:

Contributions:
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Nele Willemyns: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
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Xavier Bossuyt: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
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Anniek Corveleyn: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data
Despina Moshou: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data
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Isabelle Meyts: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis or interpretation of data

Figure Count:
1

Table Count:
1

Search Terms:
[ 120 ] MRI, [ 131 ] All Immunology, [ 137 ] Encephalitis, [ 227 ] All Pediatric, hemophagocytic lymphohistiocytosis
Acknowledgment:

Study Funding:
This work was supported by ERN-RITA.

Disclosures:
I. Meyts holds the CSL Behring Chair in Primary Immunodeficiency in Children, paid to institution, is a Senior Clinical Investigator at the Research Foundation – Flanders, and is supported by a KU Leuven C1 Grant [grant number C16/18/007], by a VIB GC PID Grant; by the Research Foundation - Flanders (FWO) [grant numbers G0C8517N, G0B5120N and G0E8420N], by an European Research Council Starting Grant, and by the Jeffrey Modell Foundation. The other authors report no relevant disclosures.

Preprint DOI:

Received Date:
2022-03-18

Accepted Date:
2022-07-01

Handling Editor Statement:
Submitted and externally peer reviewed. The handling editor was Roy Strowd III, MD, Med, MS.
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 (ADEM), human herpesvirus 6 (HHV-6) encephalitis, and hemophagocytic lymphohistiocytosis (HLH). Because of its rarity, HLH is often overlooked as a differential diagnosis in encephalitis, especially in the isolated central nervous system (CNS) forms. As this case illustrates, inborn errors of immunity (IEIs) can underlie isolated encephalitis and should be included in the differential diagnosis of these presentations.

Introduction
Pediatric neuroinflammatory diseases represent a heterogeneous group of immune-mediated conditions affecting the central nervous system (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/FLAIR magnetic resonance imaging (MRI) sequences (1,2). The hypothesized pathogenesis is immune-mediated white matter damage triggered by an acute infection and 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 subjects (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. Non-immunocompromised patients may present with a pattern of widespread T2-hyperintensities and areas of subcortical diffusion restriction (3). Interestingly, HHV-6 infection is a known trigger for 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 multi-organ infiltration (6,7).
We here describe the diagnostic process and clinical course of a child with HLH presenting with two 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.

Case report
The male patient was born from non-consanguineous parents of Belgian descent. He was shortly hospitalized at the age of 4 months for *Salmonella* and influenza infection, he had Gianotti-Crosti syndrome at the age of 14-15 months, and surgical correction of unilateral cryptorchidism at the age of 9 months. His growth was regular on -1.5 standard deviations (SD) for his age, his 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, 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, and 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 right sided optic neuritis and signs of chiasmatic (main findings are shown in Figure 1A). Radiological 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 mononuclear 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 (HSV), varicella-zoster (VZV), enterovirus and HHV-6 were negative. Serology for cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Borrelia were negative. A basic immunological screening was normal, and he had no biochemical signs of inflammation, including normal ferritin. He was diagnosed with Based on these results, a working diagnosis of post-infectious ADEM was made and the child was treated with high-dose pulse steroids (methylprednisolone 20 mg/kg/day) for 5 days with a marked improvement on the atactic symptoms. He was discharged and steroids were tapered. After one month the ataxia worsened, 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 1B). A broad panel of anti-neuronal 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 work up for HLH, NK cell degranulation assays were performed and resulted impaired. Exome sequencing confirmed the presence of compound heterozygous mutations in UNC13D (nonsense mutation c.2695C>T, p.Arg899*; splice mutation 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 1C). 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 re-evaluation on D14 showed a significant regression of the lesions (Figure 1D), classified as a partial response to therapy. He received one 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.

**Discussion**

In this paper 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 radiological 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 isolated 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, 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 neurological symptoms (irritability, meningism, seizures, encephalopathy, and focal neurological signs) (10). Pleocytosis and increased protein levels in the cerebrospinal fluid (CSF) are present in 10-50% of cases (7,10).

Imaging findings regarding HLH in the central nervous system 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). Malik et al. grouped imaging patterns into two 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 in order 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, and it includes targeted immune suppression with steroids, alemtuzumab (targeted anti-lymphocyte treatment), cyclosporine A, associated with intrathecal steroids and methotrexate in selected cases and followed by HSCT to treat the underlying disease and prevent relapses. Finally, a definite diagnosis will allow prompt genetic counselling for the family.
References


Table. Main genetic causes of primary HLH

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<td>Familial HLH</td>
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EBV: Epstein-Barr virus; HLH: hemophagocytic lymphohistiocytosis.

Figure 1. Brain MRI at different stages of disease. A) Presentation with ataxia and encephalopathy:  a) Cortical right occipito-parietal hyperintensity on FLAIR. b) Thickening and contrast enhancement of the right optic nerve on T1 sequences. 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. a) Diffusion restriction and FLAIR hyperintensity in the left hippocampus. b) Bilateral periventricular and subcortical white matter lesions with diffusion restriction. 3) Bilateral pulvinar nuclei lesions with diffusion restriction. C) Evolution 4 months after the initial presentation: a) Progressive multifocal white matter disease on FLAIR. b-c) Signs of ependymal disease on DWI and leptomeningeal 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.
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Neurology published online August 10, 2022
DOI 10.1212/WNL.0000000000201124

This information is current as of August 10, 2022

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