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Case Study

Cerebellar swelling due to familial hemophagocytic lymphohistiocytosis: An unusual presentation

Shamshad G. Khan [a], *Mohammed Binmahfoodh* [a], *Muayad Alali* [b], *Mohammed Bayoumy* [b], *Youssef Al-Said* [a], *Husam R. Kayyali* [a,*]

[a] *Department of Neurosciences, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia*
[b] *Department of Hematology, King Faisal Specialist Hospital and Research Center, Jeddah, Saudi Arabia*

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ABSTRACT

Background: Cerebellar swelling with obstructive hydrocephalus is a rare but life threatening condition, associated with different etiologies, familial hemophagocytic lymphohistiocytosis (HLH) being rarely one of them.

Patient: 2-year-7-month old boy presented with irritability, cerebellar dysfunction, and somnolence. Brain MRI showed marked diffuse cerebellar swelling and obstructive hydrocephalus with mild tonsillar herniation. Laboratory testing revealed pancytopenia, elevated liver enzymes, elevated ferritin and triglycerides levels and decreased fibrinogen. The diagnosis of familial HLH was confirmed by the presence of homozygous missense mutation of Syntaxin 11 gene. The child was treated with HLH-2004 protocol of chemotherapy followed by allogenic stem cell transplantation. His neurological condition improved significantly after treating the underlying disease.

Conclusion: Cerebellar swelling is a rare manifestation of familial HLH. High degree of clinical suspicion may allow a timely diagnosis and appropriate therapy.

1. Introduction

Cerebellar swelling resulting in obstructive hydrocephalus and brainstem compression is a rare but life threatening condition.[1] This entity has gained much recognition in the recent years due to the wide spread use of magnetic resonance imaging (MRI). It might be misdiagnosed as a posterior fossa tumor; however, it typically occurs as a result of infection or post infectious autoimmune process. Other, rare etiologies include hypertensive encephalopathy,[2] lead and methadone intoxication.[3]

Familial hemophagocytic lymphohistiocytosis (HLH) is an autosomal recessive immune disorder that results from genetic defect in cytotoxic T-cell function which leads to hyperactivation, proliferation, and multi-organ infiltration of macrophages and T lymphocytes.[4] The typical clinical

* *Corresponding author*. Pediatric Neurology Section, Department of Neurosciences, King Faisal Specialist Hospital and Research Centre, PO Box 40047, Jeddah 21499, Saudi Arabia. Tel.: +966 505382029.
E-mail addresses: sshahrukh@kfshrc.edu.sa (S.G. Khan), binmahfoodh@kfshrc.edu.sa (M. Binmahfoodh), malali@kfshrc.edu.sa (M. Alali), mbayomi@kfshrc.edu.sa (M. Bayoumy), yalsaid@kfshrc.edu.sa (Y. Al-Said), kahusam@kfshrc.edu.sa (H.R. Kayyali).
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presentation consists of prolonged fever, hepatosplenomegaly, and cytopenias. Variable neurological manifestations may develop later in the course of the disease and can, occasionally, dominate the clinical picture.[5,6] Nevertheless, rapid progression of cerebellar swelling leading to life threatening obstructive hydrocephalus is a very unusual presentation of familial HLH. We aim to report this case to highlight the features that led to the diagnosis and treatment with bone marrow transplantation which is curative in this, otherwise, potentially fatal clinical problem.

2. Case study

A 2-year-7-months old Saudi boy presented with a 6 weeks history of progressive irritability, ataxic gait, and excessive somnolence. He also had low grade fever and vomiting on few occasions. There was no history of seizures, recent infection, or vaccination. Computed tomography (CT) of the brain at a local hospital showed signs of obstructive hydrocephalus, so a ventriculoperitoneal shunt was placed on urgent basis. Brain magnetic resonance imaging (MRI) was done subsequently and showed marked mass-like cerebellar swelling, so the child was referred to our neurosurgery center for further management of possible cerebellar neoplasm. He was the first child of his healthy first cousin parents. His weight was 10.5 kg, height 85 cm (both below 3rd percentile for age), and head circumference 47 cm (between 5th and 10th percentile), neonatal head circumference was just above the 10th percentile. At admission the child was somnolent, irritable, and pale child with marked head titubation and intention tremor. Muscle one was low particularly in the trunk. Reflexes were depressed with plantar response in flexion bilaterally. The child had horizontal nystagmus and bilateral dysmetria. He was unable to walk due to severe ataxia. Systemic examination showed hepatomegaly about 5 cm below subcostal margin, but no lymphadenopathy was detected. The remaining physical examination was unremarkable. Brain MRI showed diffuse enlargement of both cerebellar hemispheres with significant mass effect on the forth ventricle and brainstem and mild herniation of cerebellar tonsils (Fig. 1). T2-hyperintense diffuse lesions were seen in the periventricular cerebral and cerebellar white matter bilaterally. T1 with contrast images showed diffuse enhancement in the cerebellar white matter with few areas of nodular enhancement. MR spectroscopy showed high choline, reduced NAA, and lactate peak. Cerebrospinal fluid (CSF) analysis showed normal cell count, normal glucose and high protein. Other laboratory investigations showed anemia, thrombocytopenia, elevated liver enzymes, hyperbilirubinemia and prolonged PT and PTT (Table 1). Viral serology for Epstein–Barr virus (EBV), Cytomegalovirus (CMV), and herpes simplex were all negative. Blood and CSF cultures were negative.

Familial HLH was considered due to the presence of neurologic symptoms, hepatic dysfunction, and cytopenias. Further workup revealed markedly elevated ferritin and triglycerides levels and decreased fibrinogen. Bone marrow aspirate and biopsy was negative for hemophagocytosis. These laboratory derangements spontaneously normalized over next 2 weeks and clinically his neurological symptoms showed mild improvement so a presumed infectious/post infectious etiology was considered and the patient was discharged home with close follow up. After two weeks he was readmitted with complaints of persistent fever, body aches, and abdominal distension. His laboratory tests showed relapse of cytopenia, deranged hepatic profile, high ferritin and triglycerides levels, and prolonged PT and PTT (Table 1). CD25 level was elevated (5000, normal range < 2000). Repeated bone marrow biopsy again failed to show hemophagocytosis. Syntaxin-11 gene sequencing confirmed the diagnosis of familial HLH by revealing a homozygous missense mutation c.173T > C (p.L58P).

The patient was started on HLH-2004 protocol of chemotherapy (dexamethasone, etoposide and cyclosporine). He responded favorably, as his clinical symptoms gradually resolved and laboratory values showed steady improvement. On follow up MRI brain after 3 months, cerebellar swelling declined but gliotic changes were seen and the periventricular white matter changes were more prominent. The patient received allogenic stem cell transplantation from sibling-matched donor four months after the initial presentation. Fludarabine/melphalan/ATG-reduced intensity (RIC) regimen was used for conditioning. At nine months follow up visit, the patient is able to walk independently, cerebellar signs are absent. He can turn book pages one at a time. His speech is fluent and easily understood. He can tell his name and age and he is able to follow multistep commands.

3. Discussion

Cerebellar swelling is a notable entity with heterogenous etiopathology. A timely assessment and diagnosis of the underlying etiology is essential to improve the outcome of affected patients. The key clinical features that may suggest the diagnosis of familial HLH are fever, hepatosplenomegaly and lymphadenopathy. Supportive laboratory finding include pancytopenia, elevated liver enzymes, high ferritin and triglycerides, and hemophagocytes in bone marrow specimen. Although central nervous system (CNS) involvement in familial HLH is seen in (20–70%) of patients, the neurological manifestations are quite variable and nonspecific.[7] Previous reports described features of progressive encephalitis, seizures, ataxia, hemiparesis, and cranial nerve palsies.[8,9] Our patient presented with intriguing signs of cerebellar dysfunction, increased intracranial pressure and obstructive hydrocephalus which required immediate shunting. Our initial differential diagnosis included posterior reversible encephalopathy syndrome (PRES), acute disseminated encephalomyelitis (ADEM) and neoplastic lesions such as gliomatosis cerebri, medulloblastoma and primitive neuroectodermal tumor (PNET). All of these diagnoses were excluded due to the lack of characteristic imaging features. Despite established diagnostic criteria for familial HLH,[4] early diagnosis is often challenging on clinical grounds due to the remitting-relapsing pattern of clinical and laboratory abnormalities and the occasional absence of hemophagocytes in bone marrow biopsy, as in our patient. Brain MRI in familial HLH may show a combination of diffuse white matter signal abnormalities on T2/FLAIR sequences, necrotic areas and parenchymal volume