Case Report

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Hemophagocytic lymphohistiocytosis: A rare cause of recurrent encephalopathy

Raashda Ainuddin Sulaiman[1,2,*], Marwan Yassin Shaheen[3], Hamad Al-Zaidan[1,2], Zuhair Al-Hassnan[1,2], Moeenaldeen Al-Sayed[1,2], Zuhair Rahbeeni[1,2], Nasir Ahmed Bakshi[4], Namik Kaya[5], Mazhor Aldosary[5], Mohammed Al-Owain[1,2]

[1] *Department of Medical Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia;*
[2] *College of Medicine, Alfaisal University, Riyadh, Saudi Arabia;*
[3] *Department of Hematology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia;*
[4] *Department of Pathology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia;*
[5] *Department of Genetics, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.*

Summary **We report an unusual case of recurrent encephalopathy due to acquired hemophagocytic lymphohistiocytosis (HLH) in a patient with propionic acidemia (PA). PA is an inherited metabolic disorder in which patients often present with encephalopathy and pancytopenia during metabolic decompensation. However, these patients may rarely develop HLH with similar presentation. This case illustrates the need to distinguish HLH induced encephalopathy from the one secondary to metabolic decompensation in these patients, as early diagnosis and treatment of HLH improves prognosis. This case also highlights the importance of considering HLH in patients presenting with unexplained encephalopathy, as early diagnosis and treatment is lifesaving in this otherwise lethal condition. To our knowledge this is the first case report of acquired HLH presenting as recurrent encephalopathy followed by complete recovery, in a metabolically stable patient with PA.**

Keywords: Inherited metabolic disorders, propionic acidemia, pancytopenia

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a hyper-inflammatory condition caused by impaired function of natural killer cells (NKC) and cytotoxic T lymphocytes (CTL) leading to poor regulation of immune response. There is hypercytokinemia and abnormal proliferation of histiocytes and macrophages, which engulf hematopoietic cells (*1*). Diagnostic criteria for HLH includes fever, splenomegaly, pancytopenia, increased serum ferritin, triglycerides, soluble CD25, decreased fibrinogen levels and hemophagocytosis. HLH can be familial with genetic etiology or acquired, associated with infections, autoimmune disorders, immune suppression and malignancies. It has been increasingly reported in various inherited metabolic disorders. Herein, we report a patient with propionic acidemia (PA) who presented with recurrent episodes of encephalopathy and pancytopenia. The presentation of encephalopathy was initially attributed to the metabolic decompensation. However once the diagnosis of acquired HLH was established, it became evident that encephalopathy and pancytopenia were related to HLH presentation and responded well to treatment.

2. Case Report

A 16-year-old boy, a known case of PA and mild cognitive impairment, presented to the emergency room in May 2014 with three days history of fever, vomiting, diarrhea, lethargy and confusion. On examination, he was drowsy, and febrile (38.5°C). Spleen was palpable 4 cm below the costal margin.

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*Address correspondence to:
Dr. Raashda A Sulaiman, Department of Medical Genetics, MBC: 75 King Faisal Specialist Hospital and Research Centre, PO Box No: 3354, Riyadh, 11211, Saudi Arabia.
E-mail: rsulaiman@kfshrc.edu.sa

Table 1. Correlation of the level of consciousness with blood ammonia levels and HLH markers

Items	Level of consciousness	Ammonia µmol/L (*ref*: <50)	WBC (count × 10^9)	Platelet (count × 10^9)	Hemoglobin (g/L)	Ferritin mg/L (*ref*. 30-400)	CD25 pg/mL (*ref*. 458-1997)
First admission							
Day 1	Drowsy	66	1.4	123	83		
Day 3	Drowsy	77	2.0	14	72	1,845	> 5,000
Second admission							
Day 1	Alert	70	12.4	196	103		
Day 4	Drowsy	60	3.5	21	83	2,159	
Third admission							
Day 1	Alert	75	3.6	102	117		
Day 4	Drowsy	121	1.7	44	54	1,430	2,987
Day 26	Alert	134	4.28	271	78		

HLH, hemophagocytic lymphohistiocytosis; WBC, white blood cell.

He had pancytopenia and marginally raised plasma ammonia levels (Table 1). Blood tests including renal, liver function and venous blood gas (VBG) analysis were unremarkable. Computerized tomographic (CT) scan of brain did not show edema or intracranial bleeding. Clostridium difficile toxin was positive in stool. He received antibiotics and fluid resuscitation. His other medications were carnitine and sodium bicarbonate. On the third day of admission he had more marked pancytopenia and continued to be encephalopathic. However, his blood ammonia level was never high enough to account for the severity of the encephalopathy (Table 1), which raised suspicion of another underlying disorder like HLH causing reduced consciousness. He was found to have raised serum ferritin and soluble CD 25 levels (Table 1). A bone marrow aspiration showed active erythropoiesis, granulopoiesis and normal looking megakaryocytes. Histiocytes were significantly increased in number and many of them demonstrated hemophagocytosis (Figure 1B). No clonal chromosomal abnormality was detected by interphase fluorescence *in vitro* hybridization (FISH) DNA probes. Sequencing of the known familial HLH genes (*PRF1*, *MUNC13-4*, *STX11*, and *STXBP2*) was negative. This fulfilled the HLH 2004 diagnostic criteria (fever, pancytopenia, splenomegaly, low plasma fibrinogen, high serum ferritin, soluble CD25 levels and hemophagocytosis). He was treated according to the HLH 2004 protocol with methylprednisolone, vinblastine and gamma globulins. The patient recovered with complete resolution of encephalopathy and was discharged to home after 5 weeks.

He was readmitted three months later, with sepsis secondary to Port-a-Cath infection. He was alert on admission in spite of severe metabolic acidosis (VBG: pH 7.2; base excess -16.9 and bicarbonate 9 mmol/L). He had leukocytosis and blood ammonia level was 70 µmol/L (Table 1). Blood culture grew *Escherichia coli*. He was treated with intravenous antibiotics and sodium bicarbonate. His metabolic acidosis resolved. On day 4 of admission, he became drowsy. A relapse of HLH was suspected as evident by pancytopenia and raised serum ferritin concentrations (Table 1). He responded promptly to methylprednisolone with full recovery and was discharged in two weeks.

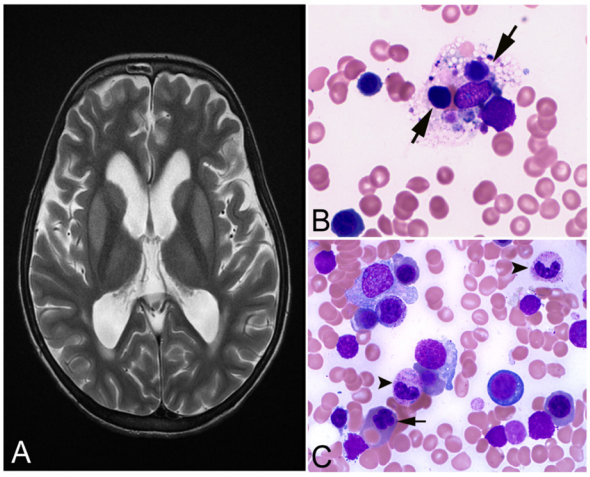

Figure 1. Radiological and hematological abnormalities. (A), Brain MRI showing T2 hyperintensity with edema of putamen; **(B)** Bone marrow aspirate showing a phagocytic histiocyte with ingested hematopoietic cells: a nucleated red cell precursor and a lymphocyte, highlighted by black arrows; **(C)** Bone marrow aspirate showing two dysplastic neutrophils, black arrow heads and one dysplastic erythroid precursor, black arrow. Wright-Giemsa staining ×500.

His third admission was with community acquired pneumonia in June 2015. He was fully conscious and metabolically stable on admission. Sputum culture grew *Streptococcus pneumoniae*. He received parenteral antibiotics. On day 4, he became confused, disoriented with severe pancytopenia (Table 1). He was treated with methylprednisolone. He remained encephalopathic requiring ventilator support over the next two weeks. A magnetic resonance imaging (MRI) of the brain showed edema of putamen and cerebellum (Figure 1A). An electroencephalogram revealed continuous generalized slow activity. Cerebrospinal fluid examination was unremarkable. In view of persistent pancytopenia, a bone marrow biopsy was performed. It showed morphological changes in all three cell lines consistent with myelodysplastic syndrome (MDS) with ring

sideroblasts and residual HLH (Figure 1C). No MDS related chromosomal anamoly was detected. He also received intermittent treatment with granulocyte colony-stimulating factor (G-CSF). He gradually recovered with no neurological sequelae and was discharged to home after seven weeks of hospitalization. His brain MRI scan repeated after eight weeks of discharge, showed complete resolution of the edema of putamen and cerebellum. His hemoglobin level was stable 114 g/L, white cell count 4.41 × 10^9/L, platelet count was 295 × 10^9/L.

3. Discussion

PA (OMIM 606054) is an inherited metabolic disorder caused by the deficiency of enzyme propionyl-CoA carboxylase. During acute metabolic decompensation which is mostly triggered by infections, these patients often develop encephalopathy due to hyperammonemia and or severe metabolic acidosis. Such patients also develop bone marrow suppression causing pancytopenia which is a common complication, seen not only during acute metabolic decompensation but is also observed during a metabolically stable state (*2*).

Although seen in patients with PA during metabolic decompensation, the encephalopathy in our patient was due to HLH. Central nervous system (CNS) involvement in HLH has been reported in 73% of cases at the time of diagnosis (*3*). It may also develop later during the course of the disease and is associated with poor prognosis (*3-5*). Neuropathological studies have shown perivascular infiltration of meninges and brain parenchyma by activated lymphocytes and macrophages with hemophagocytosis and active inflammation. This may progress to multifocal necrosis and astrogliosis (*6*). The neurological manifestations of HLH include varying degrees of encephalopathy, seizures, meningitis, hemiparesis, ataxia and cranial nerve palsy (*3-5*). CSF analysis may show raised proteins and or hemophagocytic cells. The role of cytokines in CSF remains to be elucidated.

Neuro-imaging in HLH shows a wide spectrum of abnormalities including periventricular T2 weighted hyperintensity, nodular parenchymal enhancement, leptomeningeal enhancement, hemorrhage and restricted diffusion. Gratton *et al.* in 2015 reported basal ganglia involvement in 4 out of 7 (57%) adult patients with acquired HLH (*4*). Interestingly, it is common for organic acidemias to involve basal ganglia as well. Indeed the MRI brain of our patient showed edema of putamen and cerebellum, which in the absence of other HLH features, could have been attributed to his primary metabolic disorder. Basal ganglia involvement in both disorders suggests that they may share a common mechanism of mitochondrial involvement leading to compromised aerobic respiration. Further research is required to explain the underlying mechanism.

CNS involvement in HLH is associated with poor prognosis (*3-5*), however, our patient responded well to the HLH treatment and recovered fully after each episode. During his third admission he had a prolonged period of encephalopathy when he had developed transient MDS, in addition to HLH. Although Sipahi *et al*. have previously reported isolated MDS in a patient with PA (*7*), our patient had a combination of HLH and MDS during his last admission.

The pathogenesis of acquired HLH in inherited metabolic diseases, remains unclear. It is hypothesized that the trigger, either a severe infection or accumulation of toxic metabolites would suppress the function of NKC and CTL, producing HLH. Inflammasome activation by oxidative stress may also cause hyperinflammation (*1*). Moreover, these patients might have genetic mutations that have not yet been identified as related to HLH such as those controlling inflammation and regulating cytokine function (*8*). Recently whole exome sequencing of DNA from secondary HLH patients found variants in familial HLH related genes as well as new candidate genes (*9*).

Acquired HLH in PA has been reported earlier in younger children during metabolic crisis, with no evidence of infection (*10,11*). However, relapsing HLH has not been reported in organic acidemias, for example PA. In our patient, all three episodes of HLH with encephalopathy were triggered by severe systemic bacterial infection. He was metabolically stable as his plasma ammonia levels were not significantly raised and he did not have metabolic acidosis. To our knowledge this is the first case report of repeated episodes of acquired HLH secondary to systemic infection presenting as recurrent encephalopathy in a metabolically stable patient with PA, who showed remarkable responsiveness to the treatment. Acquired HLH has been reported in an increasing number of inherited metabolic disorders and other systemic illnesses. Awareness of this complication and its neurological manifestations should prompt early diagnosis, and timely treatment with a better disease outcome in this otherwise potentially lethal condition.

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