Hemophagocytic lymphohistiocytosis - A fatal cause of persistent fever in neonates: A case series

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ABSTRACT

Primary hemophagocytic lymphohistiocytosis (HLH) is a rare fulminant genetic disease with uncontrolled immune activation and multiorgan involvement. It is quite rare in neonates but a high index of suspicion is needed as the condition will present like sepsis and is associated with high mortality. Persistent fever is a prominent clinical feature. Genetic diagnosis is essential as the condition is autosomal recessive in familial types. Here, we report four cases of HLH diagnosed in the newborn period. We got an uncommon homozygous genetic mutation in STXBP2 involving exon 19, which has been reported only in very few cases. HLH should be considered as a differential diagnosis in any sick neonate who presents with prolonged fever with an unusual clinical course.

Key words: Fever, Hemophagocytic lymphohistiocytosis, Neonate

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome of pathologic immune activation with the accumulation of macrophages and histiocytes within phagocytosed cells. The disease is extremely rare in newborns with reported incidence ranging from one in 50,000 to 150,000. The incidence varies based on ethnicity, particularly in populations in which consanguinity is common. HLH is associated with a high fatality rate and poor prognosis, making it important to recognize and diagnose it early. It can be primary (familial or sporadic) or secondary. Familial HLH is a genetic disorder, mostly autosomal recessive due to biallelic pathogenic variants in one of the four genes that regulate granule-dependent cytotoxicities such as PRF-1(Perforin 1 deficiency), UNC13D(Munc13–4 deficiency), STX 11 (Syntaxin 11 deficiency), and STXBP2(Munc 18–2 deficiency) [1]. Secondary causes of hemophagocytosis in neonates include infections (EBV, Parvo B19, CMV, Dengue, bacterial, fungal, parasitic, etc), malignancies, maternal autoimmune diseases, prolonged TPN, and metabolic diseases. About 70–80% of primary cases manifest before 1 year of age but 90% are asymptomatic in the 1st month [1]. Outcome data in neonates are limited and variable. Here, we are discussing four cases of neonatal HLH including one pair of siblings. Two of them turned out to have a rare autosomal recessive STX-BP2 mutation previously reported in very few cases around the world.

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CASE 1

A term 4.3 kg male baby born to a primi mother out of non-consanguineous marriage got referred to our outborn unit on postnatal day 12 in view of persisting fever from day 8 of life. Antenatal history was uneventful. The baby developed fever with abdominal distension on day 1 of life which subsided on treatment with oral antibiotics. At admission, he had a fever of 101° F with moderate activity, mild tachypnoea with a palpable liver, and spleen both 3 cm below the costal margins. There was no encephalopathy, shock, jaundice, or bleeding manifestations at admission. Other systems were within normal limits. The clinical profile is discussed in Table 1. With a provisional diagnosis of late-onset sepsis, antibiotics were started as per unit protocol and upgraded as the baby developed shock with bilious gastric aspirate later. The investigations are shown in Table 2. In spite of broad-spectrum antibiotics, high-grade fever persisted. As serial blood routine showed bicytopenia and all possible first and second-line investigations did not reach a diagnosis, HLH was suspected. Bone marrow study showed scattered histiocytes with hemophagocytosis. Criteria for HLH as shown in Table 3 were satisfied. Possible causes of secondary HLH were evaluated.

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Table 1: Clinical profile and initial presentations of the four HLH cases

Clinical details	Case 1	Case 2	Case 3	Case 4
Postnatal day of illness	1	8	50	1
Day of admission	12	12	55	1
Main clinical features	Fever, abdominal distension	Fever, rash, respiratory distress.	Fever, upper respiratory tract infection.	Fever Respiratory distress
Day of death	28	20	75	14
Gender	Male	Male	Female	Female
Consanguinity	No	No	No	No
Family history	No	No	Yes	No

Table 2: Investigation results of the four HLH cases

Investigations	Case 1	Case 2	Case 3	Case 4
Hb (g/dl)	10,8.7,6.1	6.7	6.3	8.6
ANC (cells/mm3)	1500,928	1000	990	700
Platelet count (counts/mm3)	45000	50000	35000	18000
Peripheral smear	No features of malignancy in anyone.			
CRP	Positive	Positive	Positive	Positive
Blood culture	Sterile	Sterile	Sterile	Pseudomonas
CSF	Not done as all babies were sick and had persistent thrombocytopenia.			
Chest and long bone X-ray	Nil significant and no features of osteopetrosis.			
TORCH screen	Negative	Negative	Negative	Negative
SGOT/SGPT (IU/L)	287/176	707/378	1761/873	673/950
FERRITIN ng/ml	6263	18600	1473	3080
Fibrinogen (mg/dl)	118	57	60	66
Triglyceride mg/dl	283	196	647	151
Bone marrow	Hemophagocytosis	No hemophagocytosis	Hemophagocytosis	Hemophagocytosis
Genetic study	Not done	Not done	STX-BP2 mutation	STX-BP2 mutation
Maternal ANA status	Negative	Negative	Negative	Negative
Neonatal dengue work up	Negative	Negative	Negative	Negative

Table 3: Demonstrating HLH-2004 diagnostic criteria satisfied by individual cases

Criteria for diagnosis	Case 1	Case 2	Case 3	Case 4
Genetic confirmation of molecular diagnosis consistent with HLHS or			+	+
5/8 criteria	√	√	√	√
1) fever >38.5 C,	√	√	√	√
2) splenomegaly	√	√	√	√
3) cytopenia (affecting >2 of 3 lineages in peripheral blood) Hemoglobin <9 g/dl, Platelets <1 lakh/mm3, Neutrophils <1.0 × 10 9/L	√	√	√	√
4) Hypertriglyceridemia and/or hypofibrinogenemia: fasting triglyceride >265 mg/dl or fibrinogen <150 mg/dl	√	√	√	√
5) Serum ferritin >500 microg/L	√	√	√	√
6) Hemophagocytosis in bone marrow, spleen, liver, lymph nodes, or other tissues.	√		√	
7) Low or absent NK cell activity	Not done			
8) Soluble IL-2 receptor >2400 U/ml.				

Pediatric oncology has opined as primary HLH but the option of bone marrow transplantation in the neonate was not feasible in our setting. Although started on steroids and other supportive measures as in HLH-2004 guidelines, on day 28, baby expired due to multiorgan dysfunction before we could start the chemotherapeutic agents. The genetic study was not done due to financial constraints.

CASE 2

A term AGA male baby born to a primi mother out of non-consanguinous marriage presented on day 12 with persistent fever, respiratory distress, and rashes over palms and soles, perioral, perineal, and penile areas. The baby had massive hepatosplenomegaly with anemia, low absolute neutrophil count,

thrombocytopenia, high CRP, and pneumonia requiring ventilation (Table 1 and 2). The baby had no response to antibiotics. Fever and pancytopenia persisted and work-up were suggestive of HLH (Table 3). However, bone marrow showed no hemophagocytosis. The baby was started on treatment as per the HLH-2004 guidelines. Genetic study was not done due to financial constraints. The baby expired due to multiorgan dysfunction.

CASE 3

After 1 year of death of Case 2, the female younger sibling of that baby got admitted on day 55 of life with fever, cough, rhinitis, and breathlessness suggestive of bronchiolitis. Respiratory symptoms subsided soon but the baby had hepatosplenomegaly and elevated liver enzymes. As it was during the first COVID-19 pandemic, multisystem inflammatory syndrome in children was also considered. COVID-19 RTPCR was negative. COVID IgG antibody test was not available at that time in the hospital as it was in the beginning of the pandemic period. Pancytopenia and elevated liver enzymes persisted along with high-grade fever. History of the elder sibling was noticed later and evaluation was positive for HLH including bone marrow showing hemophagocytosis. Medical treatment as per the HLH-2004 protocol could not stabilize the baby and she succumbed to death due to multiorgan dysfunction on day 75. Genetic study diagnosed the mutation- STX-BP2-, a homozygous missense variation (c.1730G>A;p.Gly577Asp). The parents were also heterozygous for the same mutation.

CASE 4

A term 2.6 kg female baby born to a primi mother with non-consanguineous marriage was referred at 2 h of life with severe meconium aspiration syndrome requiring mechanical ventilation. Anemia, thrombocytopenia, and massive hepatosplenomegaly were noticed from day 2 of life. CRP was positive and the first two blood cultures revealed pseudomonas sepsis. The baby had persistent fever spikes. Work up for HLH was positive (Table 3). Secondary HLH due to severe bacterial sepsis was the provisional diagnosis. Medical treatment with IVIG and steroids was initiated as per the protocol. The baby expired before starting chemotherapy. Whole exome sequencing detected STX-BP2 mutation (c.1697G>A) located on exon 19.

DISCUSSION

All the cases in our series were primary HLH. Out of the four cases discussed here, two were male and two were female. All of them were born out of non-consanguineous marriages with no significant antenatal or birth history. All had the typical clinical features of persisting fever, organomegaly, and bicytopenia. The siblings had erythematous maculopapular rashes over the body and perioral areas, which is a finding in 65% of all HLH patients in any age group. These skin lesions are pleomorphic and may be as complex as edema or purpura [1]. Hemophagocytosis in bone marrow is found in 76% of cases and has 83% sensitivity and only 60% specificity [1]. Other less common clinical manifestations include lymphadenopathy, CNS manifestation such as raised ICT, neck stiffness, hypotonia, hypertonia, seizures, cranial nerve palsies and ataxia, and acute liver failure. Whole exome sequencing in two babies showed STX-BP2 mutation. All the cases were expired. Although the initial symptoms will be looking like sepsis in HLH, fever not responding to the conventional treatment for sepsis, unusual and persistent hepatosplenomegaly, and persistent cytopenias should make one suspect some alternate diagnoses and HLH is one among them. If the clinical and biochemical criteria are satisfying then it is an indication for genetic evaluation in the neonates.

Secondary HLHS occurs in patients with a suppressed immune system resulting from the boosted activation of immune defense. Viral, bacterial, fungal, and parasitic infestations, malignant tumors and intravenous lipid solutions predispose newborns to secondary HLH [2]. The supportive treatment in babies with secondary HLH shows a better prognosis.

In a case report by Suzuki *et al*., a baby whose mother was positive for anti-Ro/SSA and anti-La/SSB antibodies presented with complete atrioventricular block and severe circulatory disturbance at 22 h after the birth along with features of HLH. The symptoms regressed with the administration of hydrocortisone [3]. Furthermore, there are case reports of neonatal dengue manifesting as secondary HLH and showing recovery with dexamethasone for 8 weeks [4,5].

Recently, there was a case report of a female newborn, born to a SARS-CoV-2-positive mother through cesarean section at 35 weeks of gestation who tested positive for SARS-CoV-2 on the 1st day after birth and presented with progressive respiratory distress, intermittent fever, splenomegaly, and cytopenia. HLH work-up was positive and the baby expired [6]. Furthermore, case report of HLH following mitochondrial respiratory chain disorder has been described in the literature [7]. There are two previous case reports of familial HLH in newborns presenting as non-immune hydrops, the first one in a twin pregnancy and the second one in siblings, respectively. In the first case report, the genetic study revealed homozygous missense mutations in the perforin gene in both twins and parents heterozygous for the same [8]. In the second case report, UNC13D mutation in consecutive siblings led to nonimmune hydrops and intrauterine death at 38 and 30 weeks, respectively, with heterozygous mutation in the parents [9]. Rare case reports of newborns presenting with cholestasis on day 1 and later diagnosed with HLH are also found in the literature [10].

NK cells, macrophages, and cytotoxic T lymphocytes are the primary mediators of tissue damage. Cytokine storm with Interferon-gamma, Tumor necrosis factor-alpha, (TNF A), IL-6, IL-,12, and IL-2R(CD-25) are seen. PRF 1 mutation is the most

common and accounts for 30–40% of cases with an early age of onset [11]. UNC 13D accounts for 30–40% of cases with more CNS involvement. STX-11 syntaxin gene mutation has a milder disease course with 5–25% cases. Our babies had a rare (5-25%) STXBP2 mutation with variable age of onset. This pathologic variant has no specific geographic restriction unlike other mutations [12]. The inheritance is mostly autosomal recessive biallelic type with parents heterozygous. Rarely heterozygous gain in function (autosomal dominant variants) of STX BP2 also has been reported.

Management aims to reduce hyper inflammation and immune dysregulation. The mainstay of treatment in primary HLH is hematopoietic stem cell transplantation (HSCT) [1]. Delayed diagnosis and treatment are associated with increased mortality. As the availability of neonatal BMT is limited and expensive, mortality can occur even before stabilizing the baby for the same. Histiocyte society treatment protocol HLH-2004 is being followed to make the patient fit for HSCT which includes etoposide, dexamethasone, and cyclosporine A. Prophylactic cotrimoxazole, an oral antimycotic, and IVIG (0.5 g/kg IV) once every 4 weeks (during the initial and continuation therapy) are the other supportive measures. The primary goal of chemotherapy in newborns is to maximize T cell function till HSCT. HSCT is curative with 64% survival at 3 years, but only 21–25% at 5 years. With no treatment, the median survival is 2 months from the time of diagnosis [1]. Diagnosis of any pathologic variant in the proband demands genetic testing for carrier state in parents, genetic counseling, preimplantation, or prenatal genetic testing.

CONCLUSION

HLH may be suspected in any neonate presenting with persistent fever and not responding to conventional treatment. Mutation analysis is very important in the neonatal period as familial HLH is AR in inheritance. Although secondary causes are rare in newborn, those secondary to infections and maternal autoantibody have responded with exchange transfusion. HLH is a condition with very high mortality even after HSCT. Confirmation of biallelic homozygous mutation warrants confirmation of carrier state in parents and genetic counseling followed by prenatal diagnosis.

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