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Case Report

Neonatology Section

Novel STXBP2 Mutation Causing Familial Haemophagocytic Lymphohistiocytosis Type 5 in a Preterm Neonate with Fatal Outcome: A Case Report

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ABSTRACT

Familial Haemophagocytic Lymphohistiocytosis (FHL) is an autosomal recessive disorder characterised by a hyperinflammatory state due to widespread infiltration of organs with macrophages and lymphocytes. Haemophagocytic Lymphohistiocytosis (HLH) presents with fever, hepatosplenomegaly, cytopenia, hyperferritinemia and haemophagocytosis in the reticuloendothelial tissues causing multi organ failure with fatal outcome. HLH is rare in neonates with an incidence of 1 in 50,000 to 1 in 150,000. FHL is diagnosed based on clinical criteria, biochemical abnormalities, and genetic mutation. Mutations involving the gene STXBP2 contributes to around 10% of cases of FHL and there are only a few cases of FHL5 reported from India. A six-week-old neonate presented with sepsis which was unresponsive to antibiotics. Persistent fever, bicytopenia, hepatosplenomegaly and laboratory tests made us suspect HLH, and evaluate further with whole exome sequencing. FHL5 was diagnosed based on the identification of homozygous missense mutation in exon 3 of STXBP2 gene (chr19: 7642803_7642803delA). The baby succumbed to sepsis and multi organ failure. HLH should be considered in the differential diagnosis of any sick infant who presents with prolonged fever, sepsis unresponsive to antibiotics and an unusual clinical course.

Keywords: Bicytopenia, Haemophagocytosis, Immunodeficiency, Neonatal sepsis, Stem cell transplantation

CASE REPORT

A six-week-old female infant was referred to the Department of Neonatology in view of fever, decreased activity, and refusal of feeds of one day duration. She was born at 36 weeks gestation to a 19-year-old G4P1L0A2D1 mother by emergency caesarean section done for foetal distress. Liquor was meconium stained. The baby was vigorous at birth and weighed 2747 g. The baby was a non consanguineous product and antenatal period was uneventful. The baby developed respiratory distress soon after birth with respiratory rate of 72/min (normal 40-60/min) with subcostal retractions and was admitted in a private hospital. The baby was treated for meconium aspiration syndrome and sepsis, with supplemental oxygen and antibiotics. As the baby's clinical condition was not improving, she was referred on day 15 of life. At admission, the baby was afebrile, weighed 2460 g and vital signs were normal. Sepsis screen was positive as C-Reactive Protein (CRP) was 32 mg/L and urine culture grew *E. coli*, which was sensitive to meropenem and amikacin. Blood and Cerebrospinal Fluid (CSF) cultures were negative. The baby received antibiotics for one week and was discharged home on breastfeeds.

On day 40 of life, the baby was admitted in a private hospital for anaemia (haemoglobin 7.4 g/dL) and received packed cell transfusion. The following day, the baby developed fever, exhibited decreased activity, refused feeds, and was referred to our unit.

On examination, the baby was febrile (temp 38.5°C), weighed 2500 g, was pale, sick with mottling, and had hepatosplenomegaly (liver and spleen were 3 cm below costal margin). Lab investigations showed: WBC 10×10^9/L, Haemoglobin (Hb) 12 g/dL, platelets 1.29×10^9/L, and CRP of 39 mg/L (normal <10 mg/L). Blood culture was sent and first line antibiotics were started (piperacillin, amikacin). CSF and urine examination were normal. The baby continued to have fever spikes and as CRP increased to 196 mg/L, antibiotics were upgraded to meropenem and vancomycin. Blood, CSF, and urine cultures were sterile. As the baby's clinical condition did not improve, she was investigated further for congenital infections and metabolic disorders.

Serology for Cytomegalovirus (CMV), herpes, rubella, toxoplasmosis, and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was negative. Fundus examination was normal. Bone marrow aspiration was inconclusive. Lab tests showed anaemia with thrombocytopenia and the baby received packed cell and platelet transfusions [Table/Fig-1]. As the baby had bicytopenia (thrombocytopenia and leucopenia), persistent fever unresponsive to higher antibiotics, with increasing hepatosplenomegaly, HLH was suspected. Ferritin (>3000 ng/mL) and triglycerides (350 mg/dL) were elevated and fibrinogen was low (0.93 g/L). The baby fulfilled five out of eight HLH-2004 criteria, which confirmed the diagnosis of HLH [1].

Parameters	Reference value	At admission	Three days after admission	10 days after admission
Haemoglobin (g/dL)	15-23	9.1	6.8	7.7
Haematocrit (%)	55.4-60.2	28.6	18.4	20.6
WBC ($\times10^9$/L)	10-24	10	3.8	7.2
Platelets ($\times10^9$/L)	100-400	129	30	40
CRP (mg/L)	<8	39	196	14
Triglycerides (mg/dL)	<150	-	350	-
LDH (units/L)	160-450	692	-	-
Ferritin (ng/mL)	25-200	-	>3000	-

D-dimer (mg/L)	0-0.5	3.98	-	-
Fibrinogen (g/L)	2-4	-	1.30	0.93
Fibrin Degradation Products (FDP) mg/L (SI units) or µg/mL (conventional units)	<10	6.97	-	-
Prothrombin time (sec)	11-14.5	16.5	20.1	-
Activated partial thromboplastin time (sec) (APTT)(s)	26-40	36.3	43.1	-
International Normalised Ratio (INR)	0.8-1.2	1.2	1.4	-

[Table/Fig-1]: Results of laboratory tests.

The baby's elder brother had late onset sepsis and succumbed at one month of life to haematochezia and coagulopathy, which could be due to HLH. Possible causes of secondary HLH (congenital infections and metabolic disorders) were excluded and whole exome sequencing was done. At six weeks of life, she succumbed to multiorgan dysfunction prior to starting chemotherapeutic agents. A homozygous missense variation in exon 11 of the STXBP2 gene c.940delA resulting in amino acid change p.K314R involving chromosome 19, classified as OMIM# 613101 was detected by targeted sequencing analysis, which confirmed the diagnosis of FHL5.

Whole exome sequencing of both parents showed the same mutation in STXBP2 gene. Both parents were heterozygous carriers and were counselled regarding prenatal testing using chorionic villus sampling in next pregnancy.

DISCUSSION

The HLH is a potentially fatal disease characterised by dysregulated immune response to antigens, resulting in uncontrolled activation of immune cells causing life-threatening cytokine storm [2]. HLH occurs in two major forms: Primary (or familial) HLH and secondary HLH. FHL is an inherited genetic disorder, which typically presents during infancy or early childhood. HLH is rare in neonates with an incidence of 1 in 50,000 to 1 in 150,000 [3]. Autosomal recessive familial HLH (FHL types 2-5), Griscelli Syndrome Type 2 (GS2), Chediak-Higashi Syndrome (CHS), X-linked Lymphoproliferative disease type 1 (XLP1), and X-linked Inhibitor of Apoptosis (XIAP) deficiency are the genetic conditions that predispose to primary HLH [4,5]. Mutations associated with 5 types of FHL are mutations in gene PRF-1 (FHL 2), UNC13D (FHL 3), STX11 (FHL 4) and STXBP2 (FHL 5), of which FHL 5 is the least common, which accounts for 10% of cases [6-11]. Around 27 cases of FHL 5 due to STXBP 2 mutation were reported worldwide, with majority of cases reported from Middle-East and Eastern Europe. FHL is diagnosed based on clinical criteria, biochemical abnormalities, and genetic mutations. According to HLH-2004 criteria, diagnosis of HLH is confirmed by either molecular diagnosis or if five out of eight criteria are fulfilled [1].

Secondary (or acquired) HLH is not inherited, and occurs due to a temporary disturbance of the immune system [12]. Secondary causes of HLH in neonates include infections (dengue virus, Epstein-Barr Virus (EBV), parvovirus B19, CMV, SARS-CoV-2, bacterial, fungal, parasitic), malignancies, maternal autoimmune diseases, and metabolic disorders [13]. Due to unusual clinical presentation, MIS-N was suspected which was ruled out by negative serology test. Diagnosis of HLH is based on the presence of at least five of the eight diagnostic criteria, namely, persistent fever, splenomegaly, cytopenias, hypofibrinogenaemia (<150 mg/dL) and/or hypertriglyceridaemia (>265 mg/dL), hyperferritinemia (>500 ng/mL), haemophagocytosis, low Natural Killer (NK) cell activity, and high concentration of soluble IL-2 receptor (sCD25/sIL-2R) [14].

The goal of management in primary HLH is to achieve remission by suppressing overactive immune system using a combination of steroids and chemotherapy. Familial HLH has a median survival of about two to six months. Median survival in untreated infants with active disease is less than two months after the onset of manifestations. About two thirds of children who receive HLH-2004 protocol achieve effective remission. Haemopoietic Stem Cell Transplantation (HSCT) is the only curative therapy for HLH and is successful in around 40% of cases. Around 25% of cases who undergo HSCT have a life expectancy of five years [15]. Previous sibling of this infant died at four weeks of age due to haematochezia and Disseminated Intravascular Coagulation (DIC) which are reported in FHL 5.

CONCLUSION(S)

The FHL should be suspected in infants who present with fever, bicytopenia, elevated sepsis markers, hepatosplenomegaly and are unresponsive to antibiotics. FHL should also be considered in those with persistent thrombocytopenia of unclear cause. Even while waiting for the results of genetic tests, treatment should be started in cases where there is a strong clinical suspicion of neonatal HLH. HSCT is the only definitive treatment for FHL and outcome is better in those who achieve remission prior to transplantation. After diagnosis, the median survival time without treatment is only two months. The most frequent causes of death are sepsis and multiorgan failure. Early diagnosis by genetic testing, screening of relatives and suspected cases, immunochemotherapy, achieving remission and HSCT improves outcome of this fatal disorder.

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