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Case Report

21q22.11q22.12 deletion syndrome with secondary hemophagocytic lymphohistiocytosis

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ABSTRACT

Haemophagocyticy lymyphohistiocytosis in the new-born is uncommon. Incidence is reported between 1 in 50,000 to 1,50,000 admissions. Usually it is primary or familial HLH in the first year of life. Secondary causes are due to viral, bacterial and fungal infections. A dysmorphic small for gestational age male neonate presented with sepsis and neonatal cholestasis. He also had associated HLH. Exom sequencing showed a 21q22.11q22.12 deletion. This has not known to have any association with familial HLH. He was managed with IVIG and steroids. The neonate made a recovery but succumbed later to an intercurrent illness.

Keywords: 21q22.11q22.12 deletion syndrome, Neonate, HLH

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) belongs to a group of disorders known as histiocytosis, which is characterized by an overabundance of tissue macrophages or histiocytes.[1] The term HLH originated from its distinct histomorphologic findings described as an accumulation of lymphocytes and histiocytes containing phagocytosed cells in various tissues.

This syndrome could be either familial or sporadic, which can be difficult to differentiate at the time of initial presentation.[2] Clinical presentation of HLH in the neonatal period is extremely rare.

The incidence of neonatal HLH is not confirmed and may range from 1 in 50,000 to 150,000.[3] A dysmorphic male neonate with sepsis, neonatal cholestasis and HLH also had 21q22.11q22.12 deletion syndrome.

CASE REPORT

A preterm (33 weeks),1420 gm, OFC 29 cm, length 44 cm SGA male neonate was referred to our hospital on 5th day of life with jaundice and clinical features of shock. There was facial dysmorphism, high arched palate, low set ears and microcephaly.

Routine investigations showed: Hb-7.9 g/dl, TLC-3.4×10^3/µl, platelet count-20×10^3/µl, S. bilirubin(T/D/I)-23.9/13.5/10.4 mg/dl, PT-36 seconds, INR 2.2 and APTT 54 seconds.

Shock was managed with intravenous fluid bolus, inotropes, packed cells and platelets transfusion along with broad spectrum antibiotics. Gradually the baby improved and inotropic support was withdrawn. Urine reducing substance was positive hence a provisional diagnosis of galactosemia was considered but further investigations for the same were negative. Blood culture was positive for

Staphylococcus aureus. After one week although baby showed clinical improvement the hematological parameters did not show significant change. In view of inadequate response to antibiotics a possibility of intra uterine infection was kept; thus, maternal and newborn TORCH titers were sent. Both the mother and baby had high titers CMV IgG 133 IU/ml and 114 IU/ml (cut off <12 IU/ml) respectively. Urine for CMV PCR was negative. Eye examination did not show any choroiditis.

Table 1: Investigations.

Day of admission (DOA); day of life(DOL)	Hb (g/dl)	TLC ($x10^3$/µl)	Platelets ($x10^3$/µl)	ANC	S. bilirubin (T/D/I) (mg/dl)	S. ferritin (µg/ml)	ALT AST (IU/l)	Fibrinogen and S. triglycerides (mg/dl)
DOL-3	13.3	4.3	18					
DOL-4	10.4	4.8	22	1248	20.8/11.1/9.7			
DOA-1	7.9	6.6	20	2904	23.9/13.4/10.5		ALT-18 AST-30	
DOA-2	7.0	7.2	45	2736				
DOA-4	10.7	4.8	23	3168	16.3/9.8/6.5			
DOA-5	7.8	3.3	24	1815				
DOA-6	9.6	4.1	40	1886				
DOA-9	9.1	5.4	25	1404	8.9/6.0/2.9		ALT-22 AST-17	
DOA-11	5.6	6.0	151	1800				
DOA-14	9.8	3.6	125	720	7.8/5.2/2.6			
DOA-17	7.4	3.2	42	1120	8.9/6.3/2.6			
DOA-20	5.4	2.2	22	704		1261		Fibrinogen-120 Triglycerides-120
DOA-23	9.8	3.6	169	2340				
2nd admission								
DOA-1	8.9	3.6	95	1800				
DOA-2	8.0	3.8	78	1881		>2000		
DOA-4	8.4	3.7	96	1902				
DOA-6	8.9	4.1	121	2110				

On the 10th day of admission, the baby had two episodes of seizures. MRI of brain showed agenesis of corpus callosum. Following more investigations done: serum Ferritin 1261 µg/ml, Fibrinogen 120 mg/dl, Serum Triglycerides 120 mg/dl. Bone marrow examination was done which showed haemophagocytosis. In view of these reports a diagnosis of HLH was made. IV immunoglobulin 2 gm/kg/day and dexamethasone 10 mg/M^2/day was started. After 1 week of therapy, platelet counts gradually improved and child was accepting feeds well hence was discharged on Injectable steroids and cholestasis regime. His clinical exome was also sent to evaluate his neurological status and to look for any evidence of primary HLH.

After 7 days baby was readmitted in view of dullness and poor feeding. Platelet count had again decreased to 22×10^3/µL, PCT was 18.2 ng/dl. Serum Ferritin increased to 2000 ng/ml. After taking blood culture antibiotics were started. A repeat course of IVIG was given two weeks after the first dose and the baby was discharged on Day 7 with steroid therapy being stopped. Subsequently the clinical exome report was available which showed a deletion in the 21 chromosomes.

21q22.11q22.12 deletion syndrome is a contiguous gene deletion syndrome with characteristics of facial dysmorphism, corpus callosum agenesis, thrombocytopenia, seizures and developmental delay. No gene mutation associated with primary HLH could be detected.

The child was doing well for two months after discharge. He was brought dead one morning with abdominal distension and obstructed inguinal hernia.

DISCUSSION

According to a review of neonates with HLH, the only genes found to be associated were PRF1 and UNC13D. Of the 2, PRF1 was found to be the predominant gene and more likely to be found in black and Hispanic patients, whereas mutations in UNC13D were more common in white patients.[5] Secondary HLH occurs in patients with a

suppressed immune system resulting from the boosted activation of immune defense. Viral and bacterial infections, fungal and parasitic infestations, malignant tumors, and intravenous lipid solutions predispose newborns to the secondary HLH.[5-7,10] Diagnostic criteria for newborns have not been established. In our patient, HLH was considered secondary as no associated gene could be identified. The criteria for diagnosis of HLH in older children is a molecular diagnosis or 5 out of 7 clinical criteria. Which are fever >5 days, splenomegaly, cytopenia involving at least two stems, hypertriglyceridemia and hypofibrinogenemia, ferritin ≥500 ng/ml, soluble CD25≥2400 U/ml, decrease/absence of natural killer cell (NK) activity, and hemophagocytosis without evidence of malignancy in the bone marrow, central nervous system, spleen, or lymph nodes.[6,10,11] Increased serum transaminases bilirubin, and LDH (>1000 U/l) levels, high protein values in cerebrospinal fluid, the existence of cerebral symptoms accompanied by pleocytosis, hypercytokinemia, generalized coagulation disorders, icterus, rashes and edema are supportive evidence.[5]

All these signs may not be noted at the onset of the disease, but may develop individually or in combination thereafter.[5,7] The present case had pancytopenia and hyperferritinemia as well as hemophagocytosis and cholestasis. HLH associated with neonatal cholestasis is known in the literature. The primary objective in HLH treatment is to suppress hypercytokinemia, which is responsible for the occurrence of devastating symptoms. The HLH-2004 protocol, a standardized treatment, includes the combined use of etoposide cyclosporine A, and corticosteroid.[9] The intravenous administration of IVIG may benefit patients with mild or acquired HLH. In our patient there was response to IVIG although steroids had to be discontinued because of sepsis.

When the HLH protocol is ineffective, antithymocyte globulin may be suggested. Daclizumab or alemtuzumab administration has also been reported in some cases. Allogeneic bone marrow transplantation is strongly recommended in familial cases, and it should be started as early as possible in bone marrow-suppressed patients.[5,6,8,9,11] HLH is rarely seen in the neonatal period, and abnormal clinical and laboratory findings consistent with the diagnosis of HLH may be seen in many other diseases.[7] HLH should be considered in the differential diagnosis of cholestasis in a newborn in the presence of additional factors like cytopenia and hyperferritinemia. The clinical exome report was suggestive of phenotype matching with 21q22.11q22.12 deletion contiguous gene syndrome with characteristics of facial dysmorphism, corpus callosum agenesis, thrombocytopenia, seizures and developmental delay.[12]

CONCLUSION

21q22.11q22.12 deletion syndrome is very rare. Only three case report have been reported in literature. Having an equally uncommon entity like HLH associated with it in a neonate presenting with sepsis and cholestasis was a challenge in diagnosis and management.

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