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Case Report

Identification of a homozygous nonsense variant of LYST gene: a case report of Chediak-Higashi syndrome

Sudesh Kumar*, Akansha Anushree, Tripathi Siddharth Niranjan

Department of Pediatrics, MGM Medical College and LSK Hospital, Kishanganj, Bihar, India

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***Correspondence:**
Dr. Sudesh Kumar,
E-mail: sudeshrekha65@gmail.com

ABSTRACT

Chediak-Higashi syndrome is a rare autosomal recessive disease manifested as hypopigmentation of skin hair, recurrent infection, abnormal organelles in circulating granulated cells, and neurological dysfunction. We describe a case of an 8-year-old female child diagnosed with Chediak-Higashi syndrome on the basis of the manifestation of recurrent chest infection with diarrhoea with multiple hypopigmentation patches and silvery hair, with a sibling of similar presentation without splenomegaly, which was further confirmed by genetic study as a homozygous nonsense mutation of the LYST gene. The child was treated with antimicrobials and a high dose of vitamin C and referred to a higher center for HSCT (hematopoietic stem cell transplantation). Chediak-Higashi scan be easily diagnosed before the accelerated phase by demonstrating large intra-cytoplasmic granules and cure by promoting bone marrow transplantation.

Keywords: Chediak-Higashi syndrome, Hypopigmentation, Melanosomes, Nonsense mutation, Recurrent infection

INTRODUCTION

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disease manifested as hypopigmentation of skin hair, recurrent infection, abnormal organelles in circulating granulated cells, and neurological dysfunction.[1,2] The prognosis is determined by primary immunological lymphoproliferative histiocytosis, known as the accelerated phase. An early-onset accelerated phase (less than 6 years) usually results in a severe manifestation and death in the first decade, while 10-15% of patients with late-onset and less-severe manifestations survive without bone marrow transplantation.[3]

CHS was first described in 1950, but the causative LYST gene mutation responsible for the disease was not revealed until 1996. The LYST gene (HGNC: 1968), containing 53 exons with an mRNA transcript of 13,503 bp, was identified for Chediak-Higashi syndrome disease.[4] We present this case, having obtained the informed consent of the patient and parent, of an 8-year-old female child who presented with recurrent chest infection and diarrhoea along with cutaneous hypopigmentation without an accelerated phase, along with an affected sibling, with genetically homozygous nonsense mutation LYST–NM¬000081.4:c6676C>T (p.Arg2226 in Exon 23 of the LYST gene).

CASE REPORT

An 8-year-old female, born of consanguineous marriage, admitted with complaints of fever and cough for 15 days and breathlessness for 12 days. After birth, up to 6 months of age, the child was completely alright. She then began to complain of recurrent cough and breathlessness.

The child was admitted to the intensive care unit 4–5 times before the 8 years of age. She also developed a history of recurrent diarrhoea. The child had no history of recurrent soft-tissue infection, joint pain, constipation, easy fatigue, and chest pain. The child was normally vaginally delivered at the hospital and exclusively

breastfed until 6 months of age. In family history, the mother had 4 children, the first of whom (a male) had expired within one hour of delivery. Another female child had expired at the age of 4 years, having had a similar history of recurrent cough and breathlessness. The third child is my index case, and the fourth is a year-old male with silvery hair and horizontal nystagmus without any other clinical features.

On examination, the child was conscious, dyspnoeic, and febrile and had a cachectic appearance. The vitals were RR-42/minute, HR-120/minute, and BP 80/50 mm/hg and SPO2 82% at room air.

Anthropometry measures were as follows: height 120 cm (25th centile); weight 10 kg (< 3rd centile); and head circumference 46 cm (<-3rd SD).

A head-to-toe examination revealed that the child appeared sick and had a cachectic appearance. She had silvery blackish hair, which was silver at birth. When she reached 2 years of age, it began turning black in colour (Figure 1).

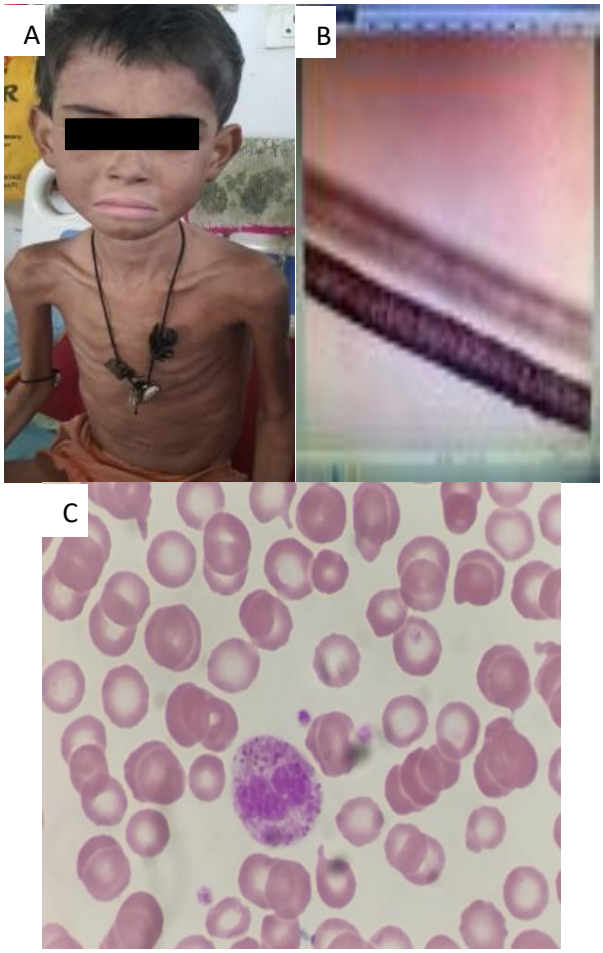

Figure 1: (A) patient with silvery hair and pigmentation patch. (B) light microscopic image of hair shaft, showing large aggregates of melanosomes and (C) intracytoplasmic granule.

There was an oral cavity mucosal ulcer over hard palate. There was hypopigmentation around the face and multiple hypo-pigmented patch over the trunk and limb.

Mild pallor and grade-two clubbing was present. The abdomen was slightly distended, and the liver was palpable 3 cm below the costal margin. In the respiratory system, bilateral crepitations were present. No abnormalities were found in the cardiovascular or central nervous systems.

On the basis of history and clinical examination, differential diagnoses including CHS, Griscelli syndrome, Hermansky-Pudlak syndrome, primary immunodeficiency, and cystic fibrosis with severe acute malnutrition were made.

Management and outcome

A complete blood count (Table 1) revealed leukopenia with relative lymphocytosis and mild neutropenia and severe microcytic hypochromic anaemia. A peripheral blood smear examination found large cytological granules in neutrophils and lymphocytes (Figure 1). Other investigations, including kidney-function and liver-function tests, were normal. Blood cultures showed no growth. The viral marker of HIV and HBsAg was non-reactive.

The bleeding profile–including bleeding time, PT, and APTT–was within normal limits. Serum ferritin and triglyceride levels were within normal limits. There was a 5-minute aqueous emersion test, and results were normal.

The chest X-ray showed bilateral patchy opacity. USG chest showed consolidation. No CECT chest was done. The immune profile was normal. Light microscopy of hair shaft showed macro aggregate of melanin (Figure 1). The gene study revealed homozygous nonsense mutation LYST–NM 000081.4:c6676C>T (p.Arg2226 in Exon 23 of LYST gene).

On the basis of the above findings, a diagnosis of CHS without accelerated phase with chronic lung disease with severe acute malnutrition was made.

The child was admitted to the paediatric intensive care unit for supportive treatment of oxygen with BIPAP, IV fluid, and broad-spectrum antimicrobials (Inj. ceftriaxone, Inj. Vancomycin, and Inj. fluconazole) and packed RBC transfusion.

Later, a high dose of vitamin C (20 mg/kg/dose) was given. Inj. adrenaline infusion was given to maintain the blood pressure.

After 5 days, the child was moved to the ward and remained there for around 14 days. The child was discharged and referred to a higher centre for HSCT.

Table 1: Investigational reports.

Laboratory parameters	Normal range	Result (5/8/2024)	Result (14/8/2024)
Total Leucocyte Count	4000-11000 /ul	3940/ul	4330/ul
Hemoglobin	11-16 gm/dl	4.7 gm/dl	8.3 gm/dl
Platelet count	1.5-4.5 lac/cmm	1.38 lac/cmm	1.28lac/cmm
Neutrophils	30-60%	33.4%	18.7%
Lymphocytes	31-51%	57.8%	69.1%
Reticulocyte count	0.2-2.5%	1.2%	1%
C-reactive protein	0-6 mg/l	22	15
Erythrocyte sedimentation rate	0-20 mm/h	14 mm/h	12mm/h
Peripheral blood smear	Microcytic hypochromic anemia with giant coarse granules seen in neutrophil, monocyte, and lymphocyte		
Liver function test			
Bilirubin (total)	0.2-1 mg/dl	0.49	-
Bilirubin (Direct)	0.1-0.2 mg/dl	0.26	-
SGPT	Less than 45 U/l	22	-
SGOT	Less than 35 U/l	31.86	-
Serum total protein	6-8 g/dl	6.90	-
Serum albumin	3-4.5 g/dl	2.90	-
Renal function test			
Serum urea	15-40 mg/dl	16.1	-
Serum creatinine	0.6-1.2 mg/dl	0.61	-
Immune profile			
Serum IgG	range 386–1470 mg/dl	864 mg/dl	-
Serum IgM	range 37–224 mg/dl	168.50 mg/dl	-
Serum IgA	range 29–256 mg/l	94.30 mg/dl	-
Serum ferritin	in female 13-150 ng/ml	63.6 ng/ml	-
Serum triglyceride	normal < 150 mg/dl	128 mg/dl	-
Gene study	Gene & transcript variant location zygosity in silico parameters** Disorder (OMIM) inheritance variant classification LYST NM_000081.4 c.6676C>T p.Arg2226* Exon 23 Homozygous CADD: 42 CHEDIAK-HIGASHI SYNDROME; CHS: 214500 autosomal recessive pathogenic		

Note: *-Genomic position based on assembly; **- GRCh37-Number of applied in silico programs predicting the effect of variant on the protein outcome.

DISCUSSION

Authors describe this case, with the informed consent of the patient and their parent, of an 8-year-old female child diagnosed with CHS on the basis of the manifestation of recurrent chest infection with diarrhoea with multiple hypopigmentation patches, silvery hair, and a sibling of similar presentation without splenomegaly, with severe anaemia, leukopenia with neutropenia, and giant intracytoplasmic granules in leucocytes with a normal bleeding panel.

Light microscopic examination revealed large aggregates of melanosomes. A gene study indicated homozygous nonsense mutation LYST; NM000081.4:c6676C>T (p.Arg2226 in Exon 23 of the LYST gene). The child was not in an accelerated phase because of the absence of generalised lymphadenopathy, splenomegaly, and bleeding, as well as normal triglyceride and serum ferritin levels. Phenotypic variant presentation CHS can indicate either a severe childhood-onset form or a milder adolescent form, depending on genetic nonsense or frame-shift mutation and missense variant.[5] The pathognomonic feature of CHS is the presence of massive lysosomal inclusion in all types of WBC, occurring through fusion, injury, and phagocytosis due to micro tubular defect. These granules are responsible for all clinical presentations of disease. These granules are found in melanocytes, type 2 pneumocytes, neurons, and the gastrointestinal tract.[6]

Increased susceptibility of microbes such as bacteria, viral, and fungi predominantly involving the skin, respiratory tract, and gastrointestinal are due to defective neutrophil and natural killer T cells.[7] My case was also suffering from a recurrent lower respiratory tract and diarrheal infection. It is essential to note that pseudo CHS, such as Griscelli syndrome and Hermansky-Pudlak syndrome–manifest as skin hypopigmentation, silvery grey hair, and neurological symptoms–can mimic conditions such as CHS, but the 2 are differentiated by the absence of intra cytoplasmic granules in WBC.[8] CHS

is a rare and fatal disease. Death usually occurs in the first decade of life due to severe infection, bleeding, or accelerated immunological lympho-proliferative histiocytosis.[9] Treatment of CHS is hematopoietic stem-cell transplantation, but in the accelerated phase. It may respond to systemic steroids plus etoposide and intrathecal methotrexate, but relapse of disease is inevitable.[9,10]

CONCLUSION

Chediak-Higashi is a rare and serious disease, with few documented cases in India. It can be easily diagnosed by a high index of suspicion of clinical features, along with family history and the presence of the intracytoplasmic granule in WBC, evidenced in a peripheral smear examination. If diagnosed before the accelerated phase, the disease can be cured by hematopoietic stem-cell transplantation, preventing morbidity and mortality in the first decade of life. Genetic screening and intrauterine diagnosis in pregnancy by foetal scalp hair or leucocyte foetal blood can prevent recurrence.

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