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A novel LYST mutation causing Chédiak Higashi syndrome in a South African child

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ABSTRACT

Chédiak Higashi syndrome (CHS) is a disorder of immune dysregulation characterised by oculocutaneous albinism. This report describes a 10-week old female with clinical and laboratory features of CHS. Genetic analysis confirmed a novel mutation in the LYST gene, predicted to skip exon 42 of the gene and result in a truncated protein product. To the best of our knowledge there is no previous complete description of CHS in a patient in South Africa.

1. Background

Genetic disorders of melanosome biosynthesis are rare. They cause oculocutaneous albinism characterised by variable degrees of hypopigmentation of the skin, hair and eyes. A sub-group of these conditions predispose to recurrent bacterial and/or viral infections and Haemophagocytic Lymphohistiocytosis (HLH) and includes Chédiak Higashi Syndrome (CHS), Griscelli Syndrome type 2, Hermansky-Pudlak Syndrome type 2 and Hermansky-Pudlak Syndrome type 10 [1]. All four syndromes show autosomal recessive inheritance and have similar clinical manifestations but CHS shows characteristic peripheral blood smear abnormalities. CHS is caused by pathologic mutations in the *LYST* gene located at chromosome 1q42.1-q42.2 (MIM #214500) that encodes the lysosomal trafficking regulator [2]. The pathognomonic feature of CHS is the presence of giant lysosomes and abnormal granules in all cell types [3,4].

2. Case report

A 10-week female presented to the emergency room with 1-week history of gastroenteritis, cough and fever. Her past medical history revealed intermittent fevers, recurrent petechial-like skin lesions and photophobia since 3 weeks of life, but no prior hospitalization. Her developmental milestones were normal, and vaccination status up-to-date. She is the only child of a non-consanguineous marriage. There is no family history of CHS, recurrent infections or infant deaths.

On examination she was acutely ill-looking, febrile, pale, jaundiced and dehydrated. She had mild respiratory distress and hepatosplenomegaly, but normal neurological function. Her scalp hair and eyelashes were silvery in colour, and her skin pale with generalized petechiae and ecchymoses; by contrast her mother had

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dark hair and skin.

Laboratory investigations revealed severe normocytic normochromic anaemia (Hb 5.1 g/dL), raised white cell count (23.78×10^9/L) and C-reactive protein (135 mg/L), metabolic acidosis, ferritin level of 1016 μg/L, elevated conjugated bilirubin and deranged liver enzymes, and her cytomegalovirus (CMV) viral load was 33,259 copies/mL.

The peripheral blood smear stained with May Grunewald Giemsa showed multiple giant granules within the neutrophils and large inclusions in the cytoplasm of occasional lymphocytes (Fig. 1A and B). The neutrophil granules were myeloperoxidase-positive. A punch biopsy of the skin of her upper arm showed melanin clumping, light microscopy of her hair showed decreased melanin pigment with clumping of melanin granules (Fig. 1C), and ophthalmology assessment revealed pale retinae, horizontal nystagmus and photophobia. These features are characteristic of CHS.

The genetic material of the patient was screened for sequence variants in the coding region of the *LYST* gene at the Ampath National Reference Laboratory (Centurion, South Africa) using a next generation sequencing approach (IonTorrent S5, Thermo Fisher Scientific). The sequence data was analysed electronically. Genbank accession number NM_000081.3 (*LYST*) was used as reference sequence with numbering starting at the A of the ATG initiation codon according to Human Genome Society guidelines (www.hgvs.org). A novel homozygous substitution was identified in intron 42 of the *LYST* gene, c.9784+2T > C. This sequence variant was confirmed by SANGER sequencing and is predicted to cause an abnormal donor splice site, resulting in the skipping of exon 42, and consequent shortened protein product. This sequence variant is classified as Likely Pathogenic (Class 4) according to the American College of Genetics and Genomics guidelines. Carrier testing for this variant in the mother revealed the same sequence change in intron 42 of the *LYST* gene, c.9784+2T > C in a heterozygous state, unfortunately the father refused testing.

Initial treatment included red cell transfusion and intravenous antibiotics for presumed sepsis. She fulfilled 3 of 8 criteria of HLH: fever, splenomegaly and elevated ferritin concentration, insufficient to diagnose this potentially life-threatening complication of CHS [5]. The CMV infection was treated with 1 week of ganciclovir followed by 2 weeks of valganciclovir. The acute manifestations resolved. She was discharged on trimethoprim/sulfamethoxazole prophylaxis.

At a recent follow-up visit 6 months after CHS diagnosis, the splenomegaly and abnormal liver enzymes had resolved, there was mild hepatomegaly and moderate neutropenia (1.2×10^9/L), serum ferritin concentration was normal, and CMV viral load was <62 copies/mL. She is currently well, with normal developmental milestones and growth trajectory.

3. Discussion

To the best of our knowledge there is no previous detailed description of CHS with complete genetic characterisation of a patient in South Africa.

Approximately 85% of patients with CHS progress to an accelerated phase during childhood, characterised by HLH [3,6], however in our patient the features initially suggestive of HLH were consistent with CMV disease, evidenced by their resolution and recent low CMV viral load.

The typical life expectancy in CHS is less than 10 years. However, patients who have been successfully treated for HLH and/or have experienced immunological reconstitution after haematopoietic stem cell transplantation (HSCT), the preferred long-term treatment option, may survive into adulthood, although the natural progression of CHS still results in neurological defects [7–9]. HLA typing has been done and the family is being prepared for HSCT.

The novel homozygous *LYST* mutation identified is likely pathogenic, it may confer a milder form of disease, as evidenced by this patient's response to minimal medical management and

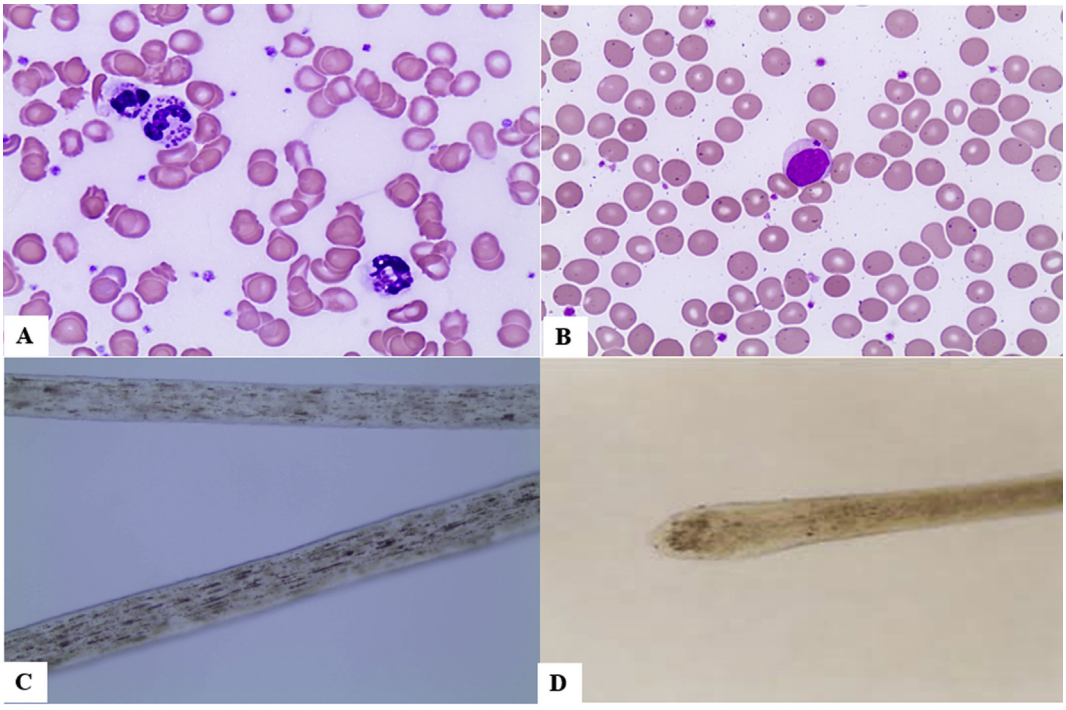

Fig. 1. Peripheral blood and hair shaft features of Chédiak Higashi syndrome: A, neutrophil with multiple granules, B, lymphocyte with inclusion, C, hair shaft with melanin clumping and D, normal hair shaft.

subsequent health at out-patient scheduled visits. Most of the mutations that result in an absent LYST protein are nonsense or null mutations, whereas missense mutations that encode a partially functioning protein result in milder forms of CHS [4]. The presence of the same mutation in the mother, in a heterozygous state, excludes a de novo mutation in our patient. Despite the absence of paternal testing we can infer autosomal recessive inheritance.

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