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Chediak-Higashi Syndrome Diagnosed from Mutation Carriers

Kouamé Cyprien Kouakou*, Augustine Djivohessoun, Isabelle Djoman, Andre Marius Gro-Bi, Charlène Soro, Komenan Amoro Mansou, Stella Nyango, Amorissani Folquet

Pediatrics Department of the Cocody University Hospital Center, Abidjan, Côte d'Ivoire
Email: *doccyprien@yahoo.fr, tinadjivo@yahoo.com, isadjoman@hotmail.fr, grobimarius2018@gmail.com, charlenesorho@gmail.com, amorokomenan@yahoo.fr, ebanguestella@yahoo.fr, amorissanifolquet@hotmail.fr

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Abstract

We report a case of a 9-month-old girl diagnosed as heterozygous to the Chediak-Higashi syndrome (CHS) after the death of her four brothers, who had similar symptoms of severe anemia, recurrent infections, and multiple blood transfusions. Genetic counseling motivated by family history led to targeted genomic DNA analysis, revealing a pathogenic variant of the LYST gene (c.8373_8376del (p.leu2791phefs*7)) in a heterozygous state. The clinical case reviews the pathophysiology and treatment options for CHS, emphasizing the importance of early diagnosis given the life-threatening potential of the disease. The authors advocate for a multidisciplinary approach to management and highlight the potential of genetic counseling to prevent further mortality in families with CHS.

Keywords

Chediak-Higashi Syndrome, Inbreeding, Genetic Counseling, Hemophagocytic, Lymphoproliferation

1. Introduction

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder generally characterized by partial oculocutaneous albinism (hypopigmentation of skin, eyes and hair), prolonged bleeding time, easy bruising, recurrent infection, abnormal function of natural killer cells, peripheral neuropathy [1] [2]. Cytology-wise, by fatal lymphohistiocytic activation in the absence of a bone marrow transplant [1] [2]. CHS is caused by mutations in the LYST gene (regulator of lysosomal trafficking) [3]. The role of the LYST gene in granule trafficking results in a defective release of melanin or cytolytic enzymes, causing skin and hair hypopigmentation

and cytotoxic defect [3]. It is a serious and potentially fatal disease in young children. Its management is multidisciplinary. Current treatment options are antibiotics, chemotherapy and bone marrow transplantation. We report one pediatric case of CHS with an update on epidemiology, clinical data, pathophysiology, and therapeutic aspects.

2. Case Report

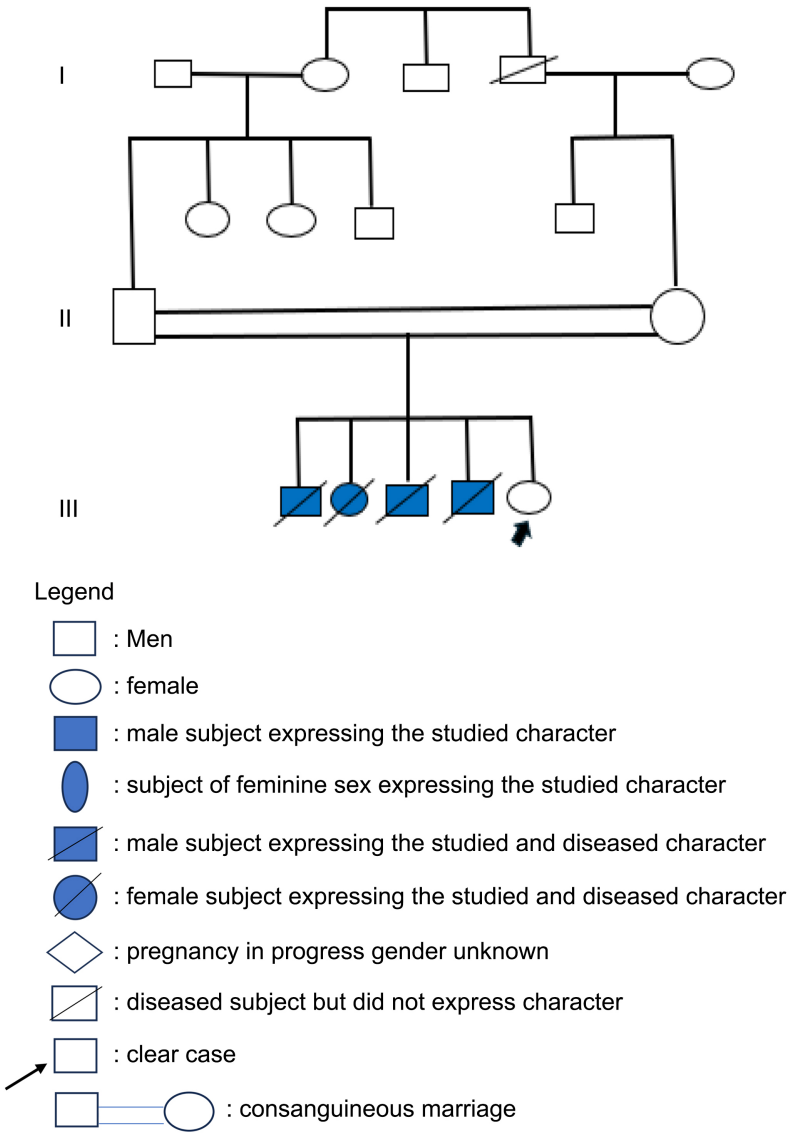

Figure 1. Family tree.

SB was born to consanguineous parents. His parents brought her to the clinical genetics' consultation at the age of eight months with a history of deaths of his four brothers at the age of 1 year (the first 2 children), 1 year 4 months, 4 years. The deaths occurred because of recurrent infections and undocumented multiple hospitalizations. **Figure 1** shows the family tree. The couple would like to be

informed of the risk of death for the SB child or if there is a genetic condition that could explain the children's deaths. The genetic counseling was delivered by a medical geneticist. After a phase of listening to the couple about their motivations and expectations, a collection of family history made it possible to establish the family tree (**Figure 1**). Parental inbreeding led to an autosomal recessive disease with mendelian-type transmission which would be the cause of the death of the children. Then a semi-structured interview lasting about 60 minutes was conducted to collect the personal and pathological history of the living child. Clinically, SB had blonde hair, normal-looking eyes, no hepatosplenomegaly and a normal neurological examination for his age. The ophthalmological examination was normal. The complete blood count was normal as well as the peripheral blood smear. Discussions with the parents had focused on the risk to the live infant. To address their concern and with the notion of inbreeding, they would probably be heterozygous carriers without a disease with a 25% risk of having an affected child. Genetic testing was offered to the couple and child via a complete exome panel customized for primary immunodeficiency genes. The extracted DNA was processed using the Exome CG-Cytogenomics capture assay (Nonacus) and the sequencer in a next-generation sequencer (Illumina) at an average coverage of 100×.

The mutation was confirmed by Sanger sequencing. The detected variants are classified according to the guidelines of the American College of Medical Genetics and Genomics (ACMG). This test revealed a heterozygous variant LYST c.8373_8376 del (p.leu2791phefs*7) in the couple and child. The patient's parents received genetic counselling during which the heterozygous outcome and the risk of future pregnancies were explained to them.

3. Discussion

Consanguinity decries the union between a couple who share at least one common ancestor [4]. Children born of consanguineous unions are at increased risk of autosomal recessive disorders, some of which may be inborn errors of metabolism. The disorders are due to the expression of autosomal recessive genetic mutations inherited from a common ancestor [4]. This was the case that we report in this observation. The parents, being first cousins, inherited the mutated gene from a common ancestor. They were heterozygous for the disease so could not express the disease. On the other hand, they could transmit it to their descendants. Since the diseased children had the same symptoms according to the parents, they were probably homozygous with respect to the disease. HCS is a rare genetic disorder with neutrophil dysfunction as a key feature [5]. Its exact prevalence is difficult to determine because some individuals are reported more than once in the literature [6]. In 85% of cases, people with the disease develop an accelerated phase of the disease [5] [7]. It can occur shortly after birth, as was probably the case with diseased children [5]. The diagnosis is usually suspected based on clinical features and confirmed when giant azurophilic granules are observed in all white blood cells on examination of the peripheral smear or bone marrow. Giant melanosomes

can be observed on cutaneous melanocytes. Genetic testing for mutations in the LYST gene confirms the diagnosis [7]. In the event of a new pregnancy for SB's mother, a prenatal test may be offered. Unfortunately, even if the genetic mutation is known in this family, there is no access to prenatal testing in Côte d'Ivoire. In postnatal care, clinical diagnosis is based on elective screening by performing a CBC associated with a blood smear (presence of giant inclusions) and an examination of the fundus (an aplastic fovea with a hypopigmented fundus [8].

4. Conclusion

Early identification of CHS is vital and CHS should be considered when the clinical picture includes hypopigmentation and recurrent infection. A simple and widely accessible examination of the peripheral blood smear can help in the diagnosis of CHS. Genetic tests to confirm the diagnosis are now available in Côte d'Ivoire.

Authors' Contributions

Kouakou Cyprien: Conception, data collection, data entry, data analysis, and drafting of the manuscript.

Djivohessoun Augustine: Participation in study design and manuscript writing.

Djoman Isabelle, Gro Bi Andre, Mansou Komenan: participation in drafting the manuscript.

Folquet A: Designing and carrying out the work of collecting the results, Reading and revising the manuscript.

All authors have read and approved the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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