Case Report

Two Novel Mutations Identified in an African-American Child with Chediak-Higashi Syndrome

Kerry Morrone, Yanhua Wang, Marjan Huizing, Elie Sutton, James G. White, William A. Gahl, and Karen Moody

1 Children’s Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY 10467, USA
2 Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY 10467, USA
3 Section on Human Biochemical Genetics, Medical Genetics Branch, National Human Genome Research Institute, NIH, Bethesda, MD 20814, USA
4 Department of Laboratory Medicine, University of Minnesota School of Medicine, Minneapolis, MN 55455, USA

Correspondence should be addressed to Karen Moody, kmoody@montefiore.org

Received 30 October 2009; Accepted 4 January 2010

1. Introduction

Chediak-Higashi Syndrome (CHS) (MIM: 214500) is a rare autosomal recessive immune disease characterized by oculocutaneous albinism, immunodeficiency, coagulopathy and late-onset, progressive neurological dysfunction. It also has an “accelerated phase” characterized by hemophagocytic lymphohistiocytosis (HLH). The disease is caused by mutations in the CHS1/LYST gene located on chromosome 1, which affects lysosome morphology and function. We report the case of an African-American child with CHS in Case. This 16-month old African-American girl presented with fever and lethargy. The proband had pale skin compared to her parents, with light brown eyes, silvery hair and massive hepatosplenomegaly. Her laboratory evaluation was remarkable for pancytopenia, high serum ferritin and an elevated LDH. Bone marrow aspirate revealed large inclusions in granulocytes and erythrophagocytosis consistent with HLH. Genetic evaluation revealed two novel nonsense mutations in the CHS1 gene: c.3622C > T (p.Q1208X) and c.11002G > T (p.E3668X).

Conclusions. Our patient is one of the few cases of CHS reported in the African American population. We identified 2 nonsense mutations in the CHS1 gene, the first mutation analysis published of an African-American child with Chediak-Higashi Syndrome. These two mutations predict a severe phenotype and thus identification of these mutations has an important clinical significance in CHS.
phenotype of this disease occurs in patients who carry at least one missense mutation causing a partially functioning CHD1. Individuals with the more severe CHS phenotype usually have null mutant CHS1 alleles, predicting the absence of the CHD1 protein. The greater the impairment of the lysosomal function, the more susceptible an individual is to infections [3, 5, 6].

The “accelerated phase” is the most life threatening clinical feature of CHS, due to the high risk of infection and hemorrhage [5, 8, 12]. Treatments with etoposide and corticosteroids have resulted in transient remissions, but relapses are frequent and bone marrow transplants have been the only effective cure [8, 12]. The determining factor for remission after bone marrow transplantation is disease status at transplantation, and transplantation is most successful when a patient with CHS is not in the “accelerated phase” [12].

The majority of patients with CHS are generally of Caucasian or Japanese descent [5]. So far, not more than 5 cases of Chediak-Higashi syndrome in African-American patients have been described, and to our knowledge, no mutation analysis in these patients was reported [13–18].

Here we present a detailed clinical presentation of an African-American child with CHS, born to nonconsanginous parents. In addition, we describe the CHS1 mutation analysis identifying two novel nonsense mutations in her CHS1 gene.

2. Case Presentation

A sixteen-month-old African-American girl, presented to the Children’s Hospital at Montefiore emergency room with a history of fever, decreased activity, poor feeding, increased sleepiness and irritability. She had no nausea, vomiting, diarrhea, urinary symptoms, cough or runny nose. The child was previously healthy, born full term without complications to a 24-year-old G2P1001 mother. On arrival to the emergency room she was febrile, tachypneic, tachycardic, and clinically in respiratory distress.

On examination she was noted to have silvery hair, blue eyes, and pale skin. Her eyelids were edematous, but she otherwise had a normal ear, nose, and throat exam. The heart and lung examination showed sinus tachycardia and tachypnea, but were otherwise within normal limits. The patient had a protuberant abdomen with massive hepatosplenomegaly. She had meningismus, but otherwise had a grossly normal neurologic exam and normal CSF studies and culture.

Initial laboratory results revealed pancytopenia, coagulopathy, metabolic acidosis, elevated LDH and normal uric acid. Our patient received a full sepsis, workup and was started on broad spectrum antibiotics for febrile neutropenia. The diagnosis of Chediak-Higashi syndrome was promptly determined after review of the peripheral blood smear and bone marrow biopsy (Figures 1 and 2). Bone marrow aspirate revealed large inclusions in myelocytes and erythrophagocytosis consistent with CHS and HLH. The bone marrow biopsy was diagnostic with sheets of histiocytes with pale foamy cytoplasm, and pink granules in neutrophils both consistent with HLH in the accelerated phase. Electron microscopy revealed large inclusions in
Figure 4: Hair shaft samples under high powered light microscopy. (a) African-American control hair sample, demonstrating evenly distributed pigment in the hair shaft. (b) Hair sample of a previously published severely affected Chediak-Higashi syndrome patient [19], demonstrating an atypical granular distribution of “pigmented clumps” in the hair shaft. (c) Hair sample of our African-American patient with Chediak-Higashi syndrome, demonstrating a similar atypical granular pigmentation pattern as the CHS patient in (b). All images were taken at the same settings using a 40X/1.3 oil objective on an Axiovert200M light microscope.

Figure 5: Two heterozygous nonsense mutations in the CHD1 gene in our patient; p.Q1208X in exon 8 and p.E3668X in exon 50.

3. Molecular Analysis

After written consent was obtained, our patient’s blood was sent for genetic testing to be done at the NIH. Genomic DNA was investigated for mutations in the CHD1 gene (GenBank NM_000081). Each of the 53 exons and their surrounding intronic regions were PCR amplified, sequenced and analyzed, using standard methods. Two heterozygous nonsense mutations in CHD1 were identified (Figure 5). Exon 5 displayed a c.3622C>T mutation, resulting in a change of a glutamine at codon 1208 to a termination codon (CAG>TAG; p.Q1208X). And exon 50 contained a heterozygous c.11002G>T mutation, resulting in a change of a glutamic acid at codon 3668 to a termination codon (GAA>TAA; p.E3668X). These mutations are predicted to result in nonsense mediated mRNA decay, and absence of a translated CHS1 protein.

4. Discussion

Chediak-Higashi syndrome is a rare autosomal recessive disorder characterized by varying degrees of oculocutaneous albinism, easy brusability and increased infections [3]. There is abnormal natural killer cell function with impaired...
chemotaxis and bactericidal activity. The underlying defects involve impaired lysosome-related organelle biogenesis [2, 6, 7, 21, 22].

We describe a case of CHS in the black population. Her clinical picture, laboratory studies, bone marrow, and genetic evaluation confirmed CHS. She presented with a severe phenotype in the accelerated phase of CHS and had certain unusual phenotypic features such as agranular platelets. We identified 2 novel nonsense mutations in the CHS1 gene (p.Q1208X and p.E3668X), which predict the absence of a translated CHD1 protein, along with a severe phenotype as seen in our patient. Hence identification of these mutations has an important clinical significance in predicting the phenotypic severity of patients with CHS. Furthermore, these mutations are the first CHD1 defects described in the black population, and may serve as a source for future mutation analysis in this population.

Acknowledgments

The authors thank Heidi Dorward for skillful analysis and imaging of hair samples. This work was partially supported by the Intramural Research programs of the National Human Genome Research Institute, National Institutes of Health, Bethesda, Md, USA.

References


Submit your manuscripts at
http://www.hindawi.com