

CHÉDIK-HIGASHI SYNDROME: AN ACCELERATED PHASE WITH HEREDITARY ELLIPTOCYTOSIS: CASE REPORT AND REVIEW OF THE LITERATURE

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Chédiak-Higashi syndrome (CHS) is a rare autosomal recessive disorder which possibly results from defective regulation of fusion of primary lysosomal granules, with delayed microbial killing.^{1,2} The condition is characterized by partial oculocutaneous albinism, frequent pyogenic infections, abnormally large granules in the leukocytes and other granule-containing cells (including platelets, melanocytes, renal tubular cells, pneumocytes, gastric cells, hepatocytes, neuronal cells and fibroblasts).³⁻⁵ About 50%-80% of patients with CHS enter into an "accelerated phase," manifested by fever, jaundice, hepatosplenomegaly, lymphadenopathy and widespread lymphohistiocytic organ infiltrates with hemophagocytosis, leading to pancytopenia, hypertriglyceridemia and hemodilution, and bleeding disorders secondary to low platelet and fibrinogen levels.^{3,6,7}

Attention to the disease was reportedly first drawn in 1940 by a physician who recognized peculiar leukocytes in a four-year-old Cuban girl and referred her to Dr. Chédiak. Subsequently in 1952, Chédiak described the full clinical and hematological features in four members of the same family.⁸ All the children were similarly affected, exhibiting pale hair and photophobia, with frequent infection and lymphadenopathy, and all died at an early age. It was then that the large inclusion-like granules were noted in the blood and bone marrow granulocytes.⁹ In 1954, Higashi described the same features in a Japanese infant, and added that these granules gave a positive peroxidase reaction.¹⁰ In 1948, Steinbrinck made a report of this blood picture, and as a result his name was included in the syndrome in the European literature.¹¹

The clinical onset of the "accelerated phase" of CHS may occur shortly after birth, or may be delayed for years, but it invariably leads to death.^{12,13} The descriptive term "accelerated phase" originated in 1964 and is still in use as

the pathophysiology of the process remains unknown.¹³ The molecular basis of CHS remains unknown as well.⁴ Functional studies suggest that genetic heterogeneity with defect in the microtubular function is suspected. The identification of the defective gene suggests that the disorder is in the organellar membrane docking and fusion.² Thirty years after the first description of CHS, 59 cases were reported, and to date, less than 100 human cases have been documented in the literature worldwide. We believe that congenital association of hereditary elliptocytosis (HE) is possibly a coincidence rather than a correlation, and the first case to be reported in the literature.

Case Report

A two-year-old male Saudi child, a product of normal pregnancy and delivery, was found to be very fair, and with blond hair which was different from the hair color of other family members. At one year of age, he was admitted to several hospitals in the Eastern Province for recurrent infections with anemia and thrombocytopenia. One month prior to admission to Madinah Maternity and Children's Hospital (MMCH), he had been admitted to a private hospital with high fever, neutropenia and thrombocytopenia, and had been diagnosed with hereditary elliptocytosis and infection. The patient received blood transfusion twice and was given antibiotics. His condition improved for three weeks, and he was admitted to MMCH on October 1999 with a high fever, diarrhea and vomiting. The parents were second-degree relatives and the boy was their first child. There was a family history of leukemia involving the patient's eight-year-old uncle.

Clinically, the patient appeared healthy, with pale skin and silver blond hair, partial albinism, otitis media, congested tonsils, enlarged liver and spleen about 3 and 8 cm, respectively, below the costal margin. Heart, lungs and genitalia, as well as chest x-ray, were normal. No evidence of meningeal signs or neuropathy was noted. Laboratory investigations revealed WBC of $3.0 \times 10^3/L$, Hb 7.2 g/dL, platelet $30 \times 10^3/L$, polycytes 15%, and lymphocytes 75%. Peripheral smear revealed hereditary elliptocytosis with giant granulation of neutrophils, monocytes and

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Accepted for publication 15 June 2001. Received 20 February 2001.

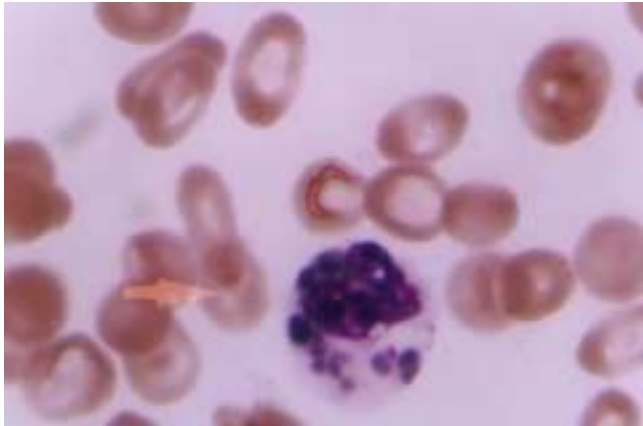


FIGURE 1. Peripheral smear of Chédiak-Higashi syndrome with abnormal granules in granulocytes (several abnormal granules) and lymphocytes (single abnormal granule) with elliptocytic change of RBC (Wrights' stain, 360x).

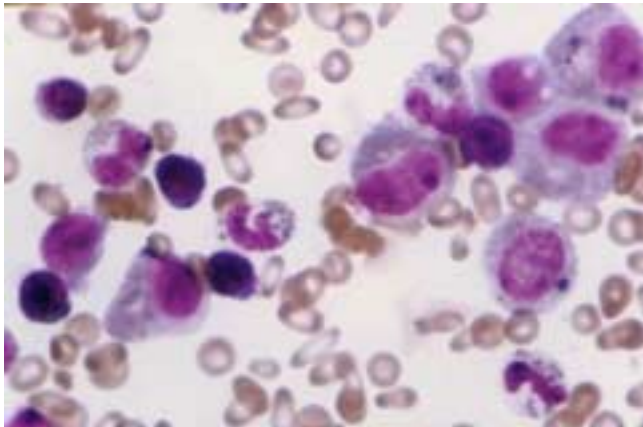


FIGURE 2. Bone marrow smear showing abnormal granules in the precursor cells of leukocytes (Wrights' stain, 320x).

lymphocytes (Figure 1). No evidence of congenital hemolytic anemia was noted because of the absence of reticulocytosis, poikilocytosis, polychromasia and nucleated red cells. Hb-electrophoretic pattern and osmotic fragility were normal. Routine urine, biochemical parameter and CSF examination were unremarkable. No growth of micro-organisms was observed in either urine or blood culture. Bone marrow smear showed striking giant granulation of neutrophils, lymphocytes and monocytes and their precursor cells (Figure 2), with accentuation of peroxidase-positive granules. It was confirmed as Chédiak-Higashi syndrome with hereditary elliptocytosis. Bone marrow transplantation (BMT) was performed from an unrelated donor from abroad. The boy was clinically well and seemed to be cured of the hereditary elliptocytosis 12 months after bone marrow transplantation.

Discussion

The Chédiak-Higashi syndrome (CHS) is a rare but global disease. It is inherited as an autosomal recessive disorder with equal sex distribution affecting predominantly

phagocytes and melanocytes. Apart from man, the disease has been recognized in Aleutian mink, beige mice, cats, cattle and killer whales.^{2,14}

A high proportion of CHS cases reported have been offspring of consanguineous marriage,^{7,15-17} as in our case, although other cases have also been reported in children of unrelated parents.¹⁸ CHS is a disease of infancy and early childhood, and few patients survive into their teenage years.¹³ The homozygous children are usually manifested by partial oculocutaneous albinism with occasional pale retinæ, translucent irides and photosensitive dermatitis, and later with recurrent pyogenic infection, including respiratory tract, mouth and cutaneous infection. Increased bleeding tendency is also a frequent feature of these children.^{6,7,15} However, in over 85% of cases, the disease remains mostly quiescent in early childhood with minor infections until it changes to the lymphoma-like "accelerated phase," characterized by nonresponding fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, coagulopathy, peripheral neuropathy and widespread lymphohistiocytic organ infiltrates, leading to infection and death.^{7,18}

Neurological manifestations such as peripheral neuropathy, long tract signs, seizures and mental impairment occur in approximately half of the patients.^{14,18,19} Our case did not have such a manifestation, probably due to the early detection. The patient was born with ashen-grey hair and very light complexion with normal eyes. Most of the reported cases had photosensitivity,^{3,14,16} but there was no evidence of that in our case. This child was healthy until 12 months of age, when he first presented with recurrent fever, diarrhea and vomiting. Common conditions in a child presenting with the above features usually include malaria, sickle cell anemia, kala-azar, or hepatitis. Other conditions such as infectious mononucleosis, malignancy, and hemolytic anemias are excluded.

The first approach to diagnosis was the laboratory reports of giant granulation in the leukocytes of peripheral blood smear and coexisting hereditary elliptocytosis (HE) without evidence of hemolysis, and confirmed by hair and bone marrow examination with accentuation of peroxidase stain.²⁰ None of the reported cases had evidence of HE. Characteristic giant granules in all leukocytes result from abnormal fusion of both lysosomal azurophil (primary) and specific (secondary) granules which contain CD₆₃ and myeloperoxidase,²¹ an enzyme characteristic of primary and secondary granules.¹⁴ This is consistent with a microtubular membrane defect leading to inappropriate fusion of

granules usually seen in all granule-forming cells.^{11,22,23} The effect of this abnormality in different tissues depends on the granule function in that particular cell line. Thus, in melanocytes, the defective granules produce a dilute pigment which is responsible for partial albinism.

Recent advances have shown that mutation, at least in seven genes, can cause a reduction in melanin pigment biosynthesis, producing the various clinical features associated with albinism.²⁴ A cytogenetic study of bone marrow cells showed monosomy of chromosomes 8 and 17 in 20% metaphases, while in studies of two other cases, karyotype was normal.²⁵ The gene responsible for CHS has not yet been mapped.^{17,26} Also noted in the study was a marked deficiency of antimicrobial protein, such as cathepsin G, and depressed expression of Mol 1CD 11b/CD 18), monocyte (with decreased chemotaxis), and NK cells (with abnormal function).²⁷

An alteration in erythrocyte membrane lipid matrix and membrane protein from four CHS patients and 15 relatives including obligatory heterozygotes were studied. The anomalous CHS membrane composition can be explained on the postulated effects on the CHS 1/Lyst gene.²⁸ Sometimes the patient presents only with albinism without any other clinical stigmata, even with an absence of infection.¹⁷ The macrophages usually demonstrate a normal rate of phagocytosis with delay in the early phase of intracellular bacterial killing which are compromised and depressed in CHS, while the late phase which depends on the primary lysosomal respiratory oxidative response and activation of myeloperoxidase-hydrogen peroxide-halide system is normal in CHS, resulting in susceptibility to infection.^{11,22}

The “accelerated phase” is believed to be a “malignant” transformation of the disease as a complication developing later, and may occur shortly after birth or may be delayed for years and invariably lead to death.¹³ Fukai et al.²⁹ reported a case in a Japanese female infant of consanguineous parents presenting with hyperpigmentation of sun-exposed areas of skin, who enjoyed good health until 12 years of age, when she developed pneumonia with hepatosplenomegaly.

Lymph node biopsy often shows a lymphoma-like picture. Autopsy examination shows marked lymphohistiocytic infiltration in the lung, liver, spleen, kidney and CNS, but without morphological features of malignancy. Our patient had no lymphadenopathy other than hepatosplenomegaly, probably due to the early detection. There were thrombocytopenia and severe leukopenia, possibly due to storage pool defects and intramedullary granulocyte destruction, respectively. Most of the reported cases demonstrate thrombocytopenia, coagulopathy and leukopenia.^{5,6} Clinical picture and laboratory data in our case indicated that the disease was in an “accelerated phase,” although tissue biopsy could not be done. There was no marker to predict this transformation, although spontaneous remission is known to occur.

Prenatal diagnoses of two cases of hereditary syndrome associated with albinism and immune defects were undertaken successfully using the morphological approach, as the responsible genes have not yet been mapped and immune abnormalities are too subtle to be diagnosed *in*

utero.^{26,30} This can help in early diagnosis, therapy and bone marrow transplantation (BMT) before the “accelerated phase” of the disease has developed. Haddad et al.³¹ reported the outcome of BMT in 10 such children—seven from an HLA-identical related donor and three from an HLA-nonidentical related donor. He found that the HLA-identical BMT was an acceptable curative treatment for CHS, whereas the HLA-nonidentical BMT remains an experimental approach. Interestingly, BMT prevented recurrence of the “accelerated phase” in patients with limited numbers of donor type leukocytes after transplantation and oculocutaneous albinism was not corrected. In another report of a one-month-old boy treated by BMT from an HLA-matched unrelated donor, an “accelerated phase” did not develop during 27 months of follow-up.¹⁶ BMT of our case was performed from an unrelated donor. At the moment, the child is clinically well, and has been cured of hereditary elliptocytosis after 12 months of follow-up.

The importance of careful examination of a well prepared and stained blood film by an experienced morphologist cannot be overemphasized. Once the crucial leukocyte finding of abnormal giant granulation is detected, the diagnosis then becomes easier. Since the disease is usually lethal in the first decade, its early detection may facilitate early BMT, which is the only curative approach. BMT from an unrelated donor may be an effective treatment option for those who lack sibling donors.

Acknowledgments

We are grateful to Mr. Saleh Mohammad Munadi, Laboratory Director, and Dr. Nabil Al Sayeed Shihata, Ex-Laboratory Director of the Madinah Maternity and Children Hospital, for their cooperation and support, and to Mohammad Farooq Ahmed, Laboratory Technologist, for his expert technical assistance.

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