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Case Report

Chediak-Higashi Syndrome: A Case Report

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ABSTRACT:
Chediak-Higashi syndrome (CHS) is an uncommon autosomal recessive disorder. It is presented as partial hypopigmentation of eyes, hair and skin along with recurrent infections, bleeding diathesis and neurological defects. It is a rare disease so much so only five hundred cases have been reported worldwide so far. This disease has two phases accelerated and adolescent or adult phase. Such patients show large peroxidase positive granules in the cytoplasm of leukocytes. It should be differentiated from other causes of albinism presenting with immunodeficiency.
Key words: Chediak-Higashi syndrome, silver hair, immunodeficiency

Introduction

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder and it is characterized by partial oculocutaneous albinism, recurrent pyogenic infections, mild bleeding tendency and late neurological deficits.[1] Diagnostic feature of this disease is presence of large intracytoplamic granules most readily visible in the cytoplasm of blood and bone marrow leukocytes.[2] It is a rare disease and less than 500 cases have been reported so far. 85% of patients undergo an accelerated phase within first decade of their life. This phase is usually manifested in childhood form of disease and it is fatal without treatment. 10-15% of cases have less severe form of disease.[3] We here present a case of CHS in a 4-month-old child.

Case Report

A 4-month-old baby boy was presented to us for workup of pneumonia. There was history of repeated chest infections since birth. On physical examination he had pallor and nystagmus. Partial cutaneous albinism and silver hair were present. He also had hepatoslenomegaly. Lymph nodes were not palpable. His milestones were normal and up to the age. His neurological examination was unremarkable. His eye examination was also normal and there were no cherry red spots.

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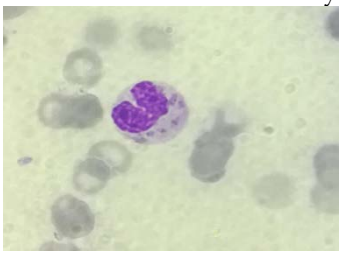
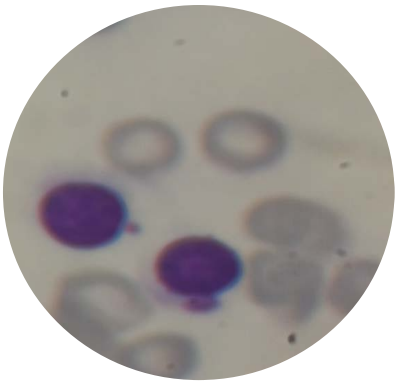
On complete blood count he had bicytopenia with hemoglobin level of 7.9 g/dl, platelet count of 51,000/mm^3 and total leukocyte count of 10,000/mm^3. Differential leukocyte count showed lymphocytosis with severe neutropenia. Lymphocytes were 77%, Neutrophils were 3% and Monocytes were 20%. On peripheral smear examination RBC's showed mild hypochromia and blue grey granules were seen in cytoplasm of leukocytes (lymphocytes and neutrophils). When his bone marrow aspiration was done, reduced cellularity with prominent lymphocyte population was observed. Leukocytes (Neutrophils, myeloctes, metamyelocytes and lymphocytes) showed giant blue grey granules in cytoplasm. Mild haemophagocytosis was also observed. Biochemical tests revealed Triglyceride level of 878 mg/dl (50-200mg/dl). Microscopic examination of his hair shaft revealed regularly arranged small clumps of melanin pigment. On basis of history, physical examination, microscopic findings of hair, peripheral smear and bone marrow aspiration findings diagnosis of Chediak Higashi Syndrome were made. Molecular studies were not carried out due to unavailability.



Photomicrograph of neutrophil showing giant ctyoplasmic granules (100 X, Wright Giemsa Stain)



Photomicrograph of giant cytoplasmic granules in lymphocyte (100X, Wright Giemsa Stain)

Discussion

Beguez Cesar first described CHS in 1943. Later Steinbrink's described the disease more precisely. Hematological characteristics of CHS were reported by Chediak in 1952. Higashi for the first time described giant peroxidase containing granules in cytoplasm of leukocytes, hence disease carries names of both Chediak and Higashi.[4]

Gene responsible for CHS was identified in 1996.[5] Beige mouse shows many features similar to humans with CHS. In beige mouse coat color is diluted. There are recurrent infections and giant granules are observed. Hence it is considered to be animal analogue of CHS in humans. This gene Lyst was mapped in 1996 and soon human LYST was identified. LYST gene is located on chromosome 1q42. Both Lyst and LYST shows 86.5% homology in sequence.[4] LYST gene is involved in synthesis of proteins, vesicle formation, fusion or trafficking of intracytoplasmic granules. This gene is believed to be responsible for maintenance of lysosomal granules in the leukocytes and fibroblasts. Maintenance of dense bodies in platelets, neutrophilic granules and melanosomes in melanocytes is also a function of this gene. Abnormal fusion of primary granules with secondary granules results in formation of large granules.[6] Abnormalities of neutrophils in CHS include neutropenia, impaired chemotaxis, and delayed fusion of phagolysosomes thus impairing bactericidal activity of neutrophils. Antibody dependent cytolysis of tumor cells by lymphocytes is impaired. Function of natural killer cell is also reduced.[7]

CHS presents at an early age. Patients have repeated infections, partial oculocutaneous albinism, mild bleeding tendency and progressive neuropathy.[1,8,9] Pulmonary infections, otitis media, skin and mucosal infections are most commonly observed in these patients.[7]Most common pathogens responsible for infection in CHS are Staphylococcus aureus, Beta-hemolytic Streptococci and Pneumococcal species. Partial oculocutaneous albinism is observed in skin, hair and eyes. Patients may have photophobia and nystagmus can also be seen.[6]These patients may have easy bruisability, epistaxis, petechiae and mucosal bleeding. Neurological involvement is variable in CHS. Patients may have peripheral and cranial neuropathy, sensory deficits, autonomic dysfunction, stroke, coma and convulsions.[4]

Two phases of CHS have been identified. 50% to 85% of patients present in "Accelerated phase". This phase is usually observed in children. Children presents with excessive hemophagocytic lymphohistiocytosis (HLH) characterize by fever, jaundice, anemia, lymphadenopathy, neutropenia, thrombocytopenia and extensive lymphohistiocytic infiltration of various organs. Before entering into accelerated phase there is history of repeated infections, but some patients have accelerated phase as primary presentation.10%-15% of cases have "adolescent" and "adult" form of CHS and have less severe clinical course. Such children mostly have mild hypopigmentation, less infections, mild bleeding and they reach adulthood without progressing to 'accelerated phase'. As these patients reach adolescence or adulthood, they may have progressive neurologic symptoms.[10,3]

CHS is diagnosed when a child presents with hypopigmentation of hair, skin or eyes accompanied by recurrent pyogenic infections. For confirmation of diagnosis laboratory evaluation, imaging techniques and histological findings are helpful. There can be anemia and neutropenia on complete blood counts. Platelet count can be normal or reduced but basically platelets are functionally abnormal. Storage pool deficiency in platelets can be observed by platelet function studies. Immunoglobulin and complement levels are normal. Peripheral blood smear shows giant azurophilic granules in leukocytes. Bone marrow aspirates shows numerous large peroxidase positive intracytoplasmic granules in cells of myeloid lineage. Ultra-structural analysis of granules shows giant lysosomes and fibrillary structures in myeloid cells. There is reduced number and irregular morphology of platelet-dense bodies.[3]Clumped melanin granules are observed in microscopic examination of the hair. Giant melanosomes are observed in microscopic examination of skin keratinocytes and melanocytes. Diffuse atrophy of the brain and spinal cord is observed on computed tomography scans and magnetic resonance imaging of brain. Electromyography may show delayed nerve

conduction and electroencephalography may show seizure activity. Molecular genetic testing of *CHS1/LYST* gene mutations gives definitive diagnosis. Prenatal diagnosis of CHS can be done by genetic testing on chorionic villus cells, amniotic fluid cells, or fetal blood leukocytes.[11]

Differential diagnosis of CHS includes other causes of oculocutaneous albinism with immunodeficiency. CHS should be differentiated from oculocutaneous albinism (OCA), Hermansky-Pudlak syndrome (HPS), Griscelli Syndrome and Waardenburg syndrome. Oculocutaneous albinism (OCA) is a group of four autosomal recessive disorders. It is caused by complete absence or a reduction of synthesis of melanosomes in the melanocytes thus resulting in hypopigmentation of the hair, skin and eyes. There is reduced visual acuity due to foveal hypoplasia and misrouting of the optic nerve fibers.[12]Griscelli syndrome has symptoms similar to CHS like partial oculocutaneous albinism, immune deficiency, accelerated phase with pancytopenia and hemophagocytosis but there is large clump of melanin pigment in hairs. Hermansky–Pudlak syndrome presents as hypopigmentation, bleeding tendency and deposition of ceroid lipofuscin in various organs. In Waardenburg syndrome there is sensory deafness and partial albinism. Main differentiating feature between CHS and other similar diseases is presence of large intracytoplasmic granules in CHS.[1,7,12,13] Haemopoietic stem cell transplant is main treatment. Complications of disease are managed supportively. Timely diagnosis is most important, and examination of a peripheral blood smear can be used for screening of both forms of disease. Childhood form of disease has poor prognosis. Repeated infections or the development of HLH results in death in first decade of life.[3]

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- Hina Bilal: Came up with conception, planned, interpreted and analyzed the data
- Farva Raza participated in conduction of study
- Naseer Ahmad participated in interpretation, analysis and discussion