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Chediak-Higashi Syndrome: A Review of 3 Cases

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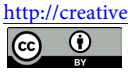

Abstract

Chediak-Higashi syndrome is a rare and life-threatening autosomal recessive disease characterized by frequent bacterial infections, bleeding tendency, oculocutaneous albinism and progressive neurological dysfunction. Here we present a series of three cases of Chediak-Higashi syndrome that were diagnosed between January 2014 and May 2022 (two cases were female and one male; aged 3.5 months to 4 years; born to first and second degree consanguineous parents). All of them presented the typical somatic and biological characteristics of this syndrome with gray hair in one case. Two cases of Chediak-Higashi were retained on bone marrow biopsy and one case on skin biopsy at the level of the scalp. Two cases were in the accelerated phase with a good response to treatment according to HLH 2004 protocol. All patients died of septic shock.

Subject Areas

Pediatrics

Keywords

Chediak-Higashi Syndrome, Albinism, Hemophagocytic Lymphoproliferation

1. Introduction

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive multisystemic disorder characterized by hypopigmentation of the skin, eyes and hair, prolonged bleeding time, easy bruising, recurrent infection, abnormal natural killer cell function, peripheral neuropathy [1], and lethal lymphohistiocytic activation

phases in the absence of bone marrow transplantation, also known as accelerated phases [2].

CHS is caused by mutations in the LYST (lysosomal trafficking regulator) gene. The role of the LYST gene in granule trafficking results in defective release of melanin or cytolytic enzymes, causing hypopigmentation of the skin and hair and a cytotoxic defect [3].

Chediak-Higashi syndrome is a serious and life-threatening condition in children at an early age. Its management is multidisciplinary.

The current therapeutic options are: antibiotics, chemotherapy and bone marrow transplantation.

We report three paediatric cases of CHS with an update on the epidemiological, clinical, pathophysiological, and therapeutic data.

2. Cases Report

2.1. Case 1

This was a 3.5-month-old girl from a second-degree consanguineous marriage, the younger of two siblings, who was admitted with mucocutaneous pallor and a hemorrhagic syndrome in the context of a fever that had been present for five days prior to her admission.

The clinical examination showed a conscious infant, hypotonic, pale, febrile at 39˚C, dehydrated with a recoloration time higher than 3 seconds, tachycardia and polypnea with a generalized cutaneous-mucosal pallor, greyish hair (**Figure 1**), petechial purpuric spots on the neck and the lower limbs, hepatomegaly at three fingerbreadths, splenomegaly overflowing the costal margin by 2 cm, the lymph nodes were free.

The biological assessment showed renal failure (creatinine level 8.8 mg/l, uremia 0.92 g/l, hyperkalemia 5.8 mmol/l, natremia 143 mmol/l, C-reactive protein (CRP) 16.7 mg/l, hypertriglyceridemia 3.96 g/l, hepatic cytolysis with ASAT at 359 IU/L (10 times normal), low fibrinogen level at 0.8 g/L, prothrombin rate (PT) at 73%, activated partial thromboplastin rate (APTT) of the patient at 25 s (control APTT 25 s), elevation of LDH (lactate dehydrogenase) at 1438 IU/L. The ferritin level was above 40,000 µg/L.

The haemogram revealed bicytopenia with normocytic normochromic anaemia with a haemoglobin level of 4.4 g/dl and thrombocytopenia of 11,000/mm^3, leukocytes of 8220/mm^3, neutrophils of 1050/mm^3, lymphocytes of 5870/mm^3 and monocytes of 1270/mm^3.

The blood smear was normal. The myelogram showed a rich marrow, megakaryocytes were present, with giant granulations, images of hemophagocytosis of neutrophil precursors, large azurophilic inclusions in the cytoplasm of blasts and images of hemophagocytosis (**Figure 2**).

The lumbar puncture showed 1090 elements, the glycorachia was 0.86 g/l, the serologies for hepatitis B and C, HIV, EBV and CMV were negative, and the immunoglobulin assay was normal.

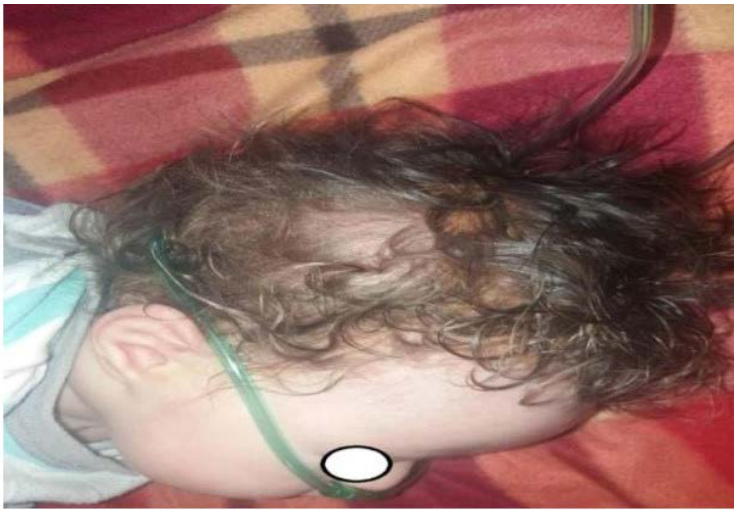

Figure 1. Infant with silver hair.

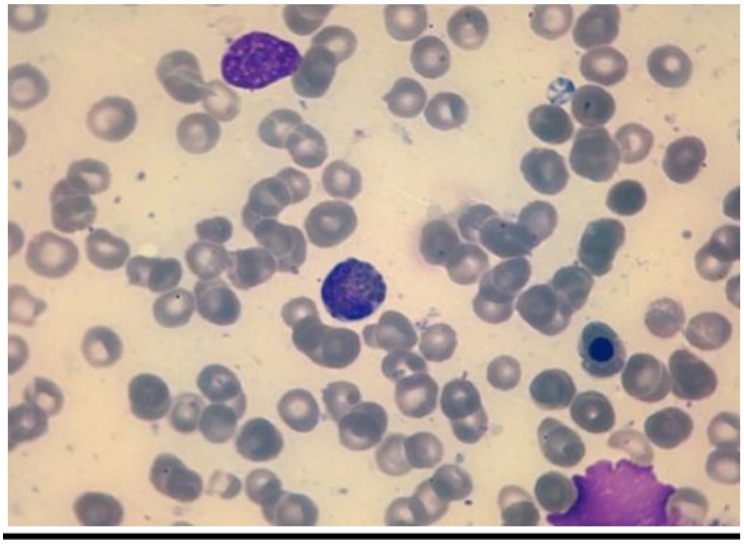

Figure 2. Medullary smears showing CHS inclusions mainly in neutrophils and eosinophils neutrophils and eosinophils.

In view of this picture, the diagnosis of hemophagocytic lymphohistiocytosis (HLH) due to Chediak-Higashi disease was retained.

The patient was put on the HLH2004 treatment protocol: intravenous (IV) corticosteroid boluses with weekly tapering, oral cyclosporine, intrathecal injections of methotrexate and HSHC twice a week for 3 weeks and then once a week with monitoring of the hemophagocytic lymphohistiocytosis status, and antibiotic therapy based on third-generation cephalosporins (C3G) in meningeal doses.

The evolution was marked by the normalization of the biological balance and the stabilization of the infant's condition during the first 3 weeks.

Around the 4th week, the patient presented with multi-visceral failure, prompting her transfer to the pediatric intensive care unit. The clinical course

was fatal due to septic shock.

2.2. Case 2

A 12-year-old child from a first-degree consanguineous marriage, second of four siblings, diagnosed with Chediak-Higashi at the age of 4 years.

Clinical signs

- Notion of BCGitis, death of 3 brothers, notion of repeated infection
- Skin albinism, prolonged fever, splenomegaly

Biological signs

- Pancytopenia, hyperferritinemia, hypofibrinogenemia
- Bone marrow: intra-cytological inclusion typical of Chediak-Higashi syndrome

Admitted to our facility for a prolonged fever evolving seven days prior to admission with an altered general condition.

The clinical examination revealed a conscious child, pale, with discolored conjunctivae, febrile at 38.7˚C, tachycardia, stable on the respiratory plan, presence of ecchymotic spots on the back and the internal face of the left thigh, skin albinism with grayish hair, splenomegaly extending beyond the umbilicus, mucositis at the ENT examination, and divergent strabismus with horizontal bilateral nystagmus.

The biological workup showed a C-reactive protein (CRP) at 87 mg/l, hypertriglyceridemia at 2.23 g/l, low fibrinogen level at 1 g/l, correct renal and hepatic workup, normal kalemia at 3.7 mmol/l, hyponatremia at 125 mmol/l, LDH (lactate dehydrogenase) at 354 IU/L. Serum ferritin was elevated to 2951.9 µg/L. Serological markers were negative for cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, parvovirus, toxoplasma, rubella and hepatitis B virus.

The CSF study was normal, the haemogram showed pancytopenia with anaemia at 5.34 g/dl microcytic hypochromia, neutropenia at 50/mm^3 and thrombocytopenia at 10,000/mm^3, the blood smear was normal. The myelogram showed a rich marrow, megakaryocytes were present with giant granulations, images of hemophagocytosis, neutrophil precursors, the presence of large azurophilic inclusions in the cytoplasm of blasts and images of hemophagocytosis.

Given the clinicobiological signs, the diagnosis of hemophagocytic lymphohistiocytosis (HLH) in Chediak-Higashi disease was retained.

The patient was put on the HLH 2004 therapeutic protocol with oral ciclosporin, transfused with red blood cells and platelets concentrates. Antibiotic therapy based on 3rd generation cephalosporins and amikacin was started and then changed to Imipenem, Vancomycin and Fluconazole due to persistent fever. The evolution was favorable with the normalization of hemophagocytic lymphohistiocytosis (HLH).

After six months, the child presented a severe sepsis picture motivating his transfer to pediatric intensive care unit.

The clinical evolution was fatal with death of the patient by septic shock.

2.3. Case 3

This was a 4-month-13-day-old female infant from non-consanguineous parents.

He was hospitalized in our department for chronic greenish diarrhea evolving 1 month before his admission.

He had a family history of two deaths in the siblings, a boy with a respiratory illness at the age of 4 months and a girl with a heart disease (not documented) at the age of 8 months.

The clinical examination noted a pale, apyretic infant, hemodynamically and respiratorily stable, with a weight delay (less than three standard deviations). Unlike his parents, he had a fair complexion and brown hair, no hepatosplenomegaly or palpable adenopathy.

The biological workup showed triglyceridemia at 0.99 mmol/L, C-reactive protein (CRP) at 10 mg/L and lactate dehydrogenase (LDH) at 402 IU/L. Ferritinemia was 1307 mg/L. AST was 94 IU/L (twice normal), HIV serology came back negative and the weighted immunoglobulin and lymphocyte subpopulation assays were normal.

The haemogram revealed normocytic normochromic anaemia with a haemoglobin of 9.2 g/dL and reticulocytes of 60200/mm^3, platelets of 320,000/mm^3 and leucocytes of 16000/mm^3. On the blood smear there were no large abnormal intracytoplasmic inclusions in the leukocytes. The myelogram showed the absence of overload cells and images of hemophagocytosis.

Skin biopsy of the scalp showed melanopenic hypopigmentation (leukoderma), rather in favor of Chediak-Higashi syndrome.

The diagnosis of Chediak-Higashi syndrome was retained without hemophagocytic lymphohistiocytosis (HLH).

The patient was put on Cotrimoxazole at a dose of 30 mg/kg/day, 3rd generation cephalosporins at a dose of 70 mg/kg/day, Metronidazole 30 mg/kg/day with oral rehydration salts. The evolution was favorable after 10 days of treatment.

Two months later, the infant was readmitted to our department with severe febrile respiratory distress and an oxygen saturation of 76% on room air.

The patient was put on 3rd generation cephalosporins at a dose of 70 mg/kg/day and Amikacin at 15 mg/kg/day with upper airway release but the clinical evolution was fatal with death of the patient by septic shock.

3. Discussion

CHS was first described by Beguez-Cesar in 1943, and in 1957 Donohue and Bain focused on a leukocyte granulation abnormality described by Chediak (Cuban hematologist) in 1952 and by Higashi (Japanese pediatrician) in 1954.

About 200 cases of Chediak-Higashi disease are described in the literature, with obvious similarities and differences [4] [5].

CHS can be suspected when presenting with partial oculocutaneous albinism

with a history of recurrent infections, nystagmus, photophobia, peripheral neuropathy, and mental retardation [6].

Most cases also present with leukopenia, thrombocytopenia and coagulopathy. Photosensitivity has been reported in many cases [6].

Recurrent infections seen in Chediak-Higashi disease may be related to functional abnormalities of granulocytes and defects in cytotoxicity of T lymphocytes and NK (natural killer) cells by retention of cytolytic enzymes in lysosomes that take the form of abnormal giant structures in the cytoplasm of blood leukocytes and bone marrow precursors, facilitating the cytological diagnosis of the disease [7] [8].

A genetic study of the patients showed that this disease is due to homozygous or heterozygous composite mutations of the LYST (lysosomal trafficking regulator) gene, located on the long arm of chromosome 1, which encodes the CHS protein. Karim *et al*. found LYST (lysosomal trafficking regulator) mutants with no function in severe forms diagnosed in childhood. However, in adult forms, the mutant alleles probably encode LYST polypeptides with partial function [9]. However, the genotype/phenotype correlation remains controversial, and other studies suggest the intervention of environmental factors [10]. Jessen *et al*. show a more significant "immunotype"/phenotype correlation, *i.e*. the degree of impairment of lytic functions. Cytotoxic T lymphocytes will probably predict the risk of transition to the accelerated phase [11].

There are two phases in the evolution of the disease: a stable or chronic phase and a progressive or accelerated phase.

The stable phase is characterized by recurrent infections. This phase can be managed by the appropriate use of antibiotics or antifungals and proper hygiene. Approximately 10% of patients survive infancy despite severe infections, but develop severe and debilitating manifestations, such as mental retardation, neuropathy, and seizures in adolescence and young adulthood.

A majority (85%) of patients with Chediak-Higashi syndrome develop an accelerated phase of the disease characterized by fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, coagulopathy, neurological abnormalities [12], and diffuse mononuclear cell infiltrates in the organs. Originally considered a malignant lymphoma-like tumor, the accelerated phase is now known to be a hemophagocytic lymphohistiocytosis characterized by multivisceral inflammation [13].

The accelerated phase can occur shortly after birth, or years later as in our second case [6].

During the accelerated phases, treatments with etoposide, corticosteroids and intrathecal injections of methotrexate have been suggested, but this aplasiant chemotherapy only results in a very transient remission [13].

4. Conclusion

Allogeneic bone marrow transplantation has been proposed as the only possible curative treatment, when performed early, before the onset of the accelerated

phase. Once the accelerated phase has occurred, the syndrome is fatal within 30 months [1]. This highlights the need for early identification of the disease.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Rudramurthy, P. and Lokanatha, H. (2015) Syndrome de Chediak-Higashi: Une série de cas du Karnataka, en Inde. *Indian Journal of Dermatology*, **60**, 524. https://doi.org/10.4103/0019-5154.159662

[2] Chouchene, S., Abderrazak, F., Hammami, S., Guediche, M.N., Jmili, N.B. and Hassine, M. (2014) La maladie de Chediak-Higashi: A propos d'un cas et revue de la literature. *Hématologie*, **20**, 161-165. https://doi.org/10.1684/hma.2014.0948

[3] Elevli, M., Hatipoğlu, H.U., Civilibal, M., Duru, N.S. and Celkan, T. (2014) Chediak-Higashi Syndrome: A Case Report of a Girl without Silvery Hair and Oculocutaneous Albinism Presenting with Hemophagocytic Lymphohistiocytosis. *Turkish Journal of Hematology*, **31**, 426-427. https://doi.org/10.4274/tjh.2014.0049

[4] Introne, W., Boissy, R.E. and Gahl, W.A. (1999) Clinical, Molecular, and Cell Biological Aspects of Chediak-Higashi Syndrome. *Molecular Genetics and Metabolism*, **68**, 283-303. https://doi.org/10.1006/mgme.1999.2927

[5] Pujani, M., Agarwal, K., Bansal, S., *et al*. (2011) Chediak-Higashi Syndrome—A Report of Two Cases with Unusual Hyperpigmentation of the Face. *Türk Patoloji Dergisi*, **27**, 246-248. https://doi.org/10.5146/tjpath.2011.01082

[6] Palaniyandi, S., Pasupathy, U., Ravichandran, L., Rajendran, A., Suman, F.R. and Rajendra Prasad, S. (2017) Chediak-Higashi Syndrome Presenting in the Accelerated Phase. *South African Journal of Child Health*, **11**, 104-106. https://doi.org/10.7196/SAJCH.2017.v11i2.1277

[7] Ganz, T., Metcalf, J.A., Gallin, J.I., Boxer, L.A. and Lehrer, R.I. (1988) Microbicidal/Cytotoxic Proteins of Neutrophils Are Deficient in Two Disorders: Chediak Higashi Syndrome and "Specific" Granule Deficiency. *Journal of Clinical Investigation*, **82**, 552-556. https://doi.org/10.1172/JCI113631

[8] Faigle, W., Raposo, G., Tenza, D., *et al*. (1998) Deficient Peptide Loading and MHC Class II Endosomal Sorting in a Human Genetic Immunodeficiency Disease: The Chediak-Higashi Syndrome. *Journal of Cell Biology*, **141**, 1121-1134. https://doi.org/10.1083/jcb.141.5.1121

[9] Karim, M.A., Suzuki, K., Fukai, K., *et al*. (2002) Apparent Genotype-Phenotype Correlation in Childhood, Adolescent, and Adult Chediak-Higashi Syndrome. *American Journal of Medical Genetics*, **108**, 16-22. https://doi.org/10.1002/ajmg.10184

[10] Kaya, Z., Ehl, S., Albayrak, M., *et al*. (2011) A Novel Single Point Mutation of the LYST Gene in Two Siblings with Different Phenotypic Features of Chediak Higashi Syndrome. *Pediatric Blood & Cancer*, **56**, 1136-1139. https://doi.org/10.1002/pbc.22878

[11] Jessen, B., Maul-Pavicic, A., Ufheil, H., *et al*. (2011) Subtle Differences in CTL Cytotoxicity Determine Susceptibility to Hemophagocytic Lymphohistiocytosis in Mice and Humans with Chediak-Higashi Syndrome. *Blood*, **118**, 4620-4629. https://doi.org/10.1182/blood-2011-05-356113

[12] Ghaffari, J., Rezaee, S.A. and Gharagozlou, M. (2013) Chédiak-Higashi Syndrome. *Journal of Pediatrics Review*, **1**, 80-87.

[13] Eapen, M., DeLaat, C.A., Baker, K.S., Cairo, M.S., Cowan, M.J., Kurtzberg, J. and Filipovich, A.H. (2007) Hematopoietic Cell Transplantation for Chediak-Higashi Syndrome. *Bone Marrow Transplantation*, **39**, 411-415. https://doi.org/10.1038/sj.bmt.1705600