Disease statistics

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The Life Saving Cord Blood Bank

CHEDIAK HIGASHI SYNDROME

INTRODUCTION

- Chediak-Higashi syndrome (CHS) is a rare childhood autosomal recessive disorder that affects multiple systems of the body.[1]
- CHS was described by Beguez Cesar in 1943, Steinbrinck in 1948, Chédiak in 1952, and Higashi in 1954.[2, 3]
- Chediak-Higashi syndrome is a condition that affects many parts of the body, particularly the immune system.
- This disease damages immune system cells, leaving them less able to fight off invaders such as viruses and bacteria. As a result, most people with Chediak-Higashi syndrome have repeated and persistent infections starting in infancy or early childhood. These infections tend to be very serious or life-threatening.
- Chediak-Higashi syndrome is also characterized by a condition called oculocutaneous albinism, which causes abnormally light coloring (pigmentation) of the skin, hair, and eyes. [4]

1.http://emedicine.medscape.com/article/1114607-overview
2. Demirkiran O, Utku T, Urkmez S, Dikmen Y. Chediak-Higashi syndrome in the intensive care unit. *Paediatr Anaesth*. Aug 2004;14(8):685-8.
3. Kanjanapongkul S. Chediak-Higashi syndrome: report of a case with uncommon presentation and review literature. *J Med Assoc Thai*. Apr 2006;89(4):541-4.
4. http://ghr.nlm.nih.gov/condition/chediak-higashi-syndrome

- This disease was initially attributed to a dysfunction of leukocytes, but now it is known to cause a general dysfunction in numerous cell types including melanocytes (causing albinism), neutrophil leukocytes and monocytes (causing immune deficiency with susceptibility for pyogenic infections), platelets (causing prolonged bleeding), and Schwann cells (causing peripheral neuropathy).[1]

1. http://www.medlink.com/medlinkcontent.asp

HOW COMMON IS CHEDIAK-HIGASHI SYNDROME?

- Chediak-Higashi syndrome is a rare disorder.
- About 200 cases of the condition have been reported worldwide.[1]
- Symptoms of Chediak-Higashi syndrome usually appear soon after birth or in children younger than 5 years.
- Death often occurs in the first decade as a result of infection, bleeding, or development of the accelerated lymphoma like phase, but survival into the second and third decades has been reported.[2]
- Chediak-Higashi syndrome affects all races. *Al-Khenaizan* (2003) suggests that Chediak-Higashi syndrome may be underreported in persons of darker-skinned races.[3]

1. http://ghr.nlm.nih.gov/condition/chediak-higashi-syndrome
2. http://emedicine.medscape.com/article/1114607-overview#a0199
3. Al-Khenaizan S. Hyperpigmentation in Chediak-Higashi syndrome. *J Am Acad Dermatol*. Nov 2003;49(5 Suppl):S244-6.

INHERITANCE PATTERN OF CHS

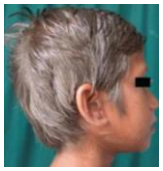
- Chediak-Higashi syndrome is inherited as an autosomal recessive genetic trait.
- The responsible gene has been mapped to chromosomal locus 1q42.1-q42.2 and is known as CHS1.
- Recessive genetic disorders occur when an individual inherits the same abnormal gene for the same trait from each parent.
- If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease, but usually will not show symptoms.
- The risk for two carrier parents to both pass the defective gene and, therefore, have an affected child is 25% with each pregnancy.
- The risk to have a child who is a carrier like the parents is 50% with each pregnancy.
- The chance for a child to receive normal genes from both parents and be genetically normal for that particular trait is 25%.
- The risk is the same for males and females.[1]

1. https://rarediseases.org/rare-diseases/chediak-higashi-syndrome/

CLINICAL PRESENTATION [1, 2]

- Albinism , giving a lighter complexion than unaffected family members [3]

- Silvery sheen to hair which may be fair in colour

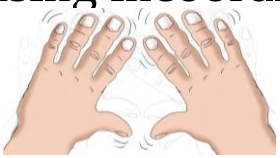


- Impaired vision
- Photophobia
- Frequent infections (skin, mucous membranes, respiratory)

- Epilepsy
- Mental retardation

- Enlarged liver and spleen

- Jaundice
- Ataxia causing incoordination and a typical ataxic gait
- Tremor



- Epilepsy
- Peripheral neuropathy causing motor and sensory changes and weakness (if patient survives into adulthood) [4]

1.Sondheimer N; Chediak-Higashi syndrome; Medline Plus
2. Nowicki R,Sczarmach S; Chediak-Higashi Syndrome; eMedicine, 2009
3. Oculocutaneous Albinism, Type II; OCA2, Online Mendelian Inheritance in Man (OMIM)
4. Misra VP, King RH, Harding AE, et al; Peripheral neuropathy in the Chediak-Higashi syndrome. Acta Neuropathol (Berl). 1991;81(3):354-8.

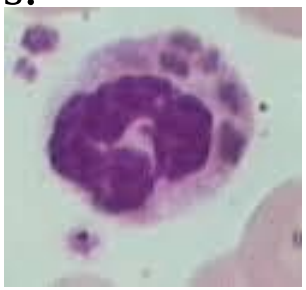
DIAGNOSIS

- **Partial oculocutaneous albinism (OCA)**-Pigment dilution of the skin and hair may be appreciated at birth on physical examination. However, complete ophthalmologic examination may be necessary to identify the diagnostic finding of reduced iris pigment manifest as iris transillumination. [1]
- **Immunodeficiency.** A significant history of infections, particularly bacterial infections of the skin and respiratory tract, is characteristic.

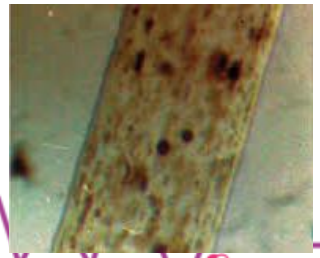
  Natural killer (NK) cells are generally present in normal numbers but with abnormal (reduced) function. [1]
- **Neurologic features.** Neurologic manifestations are variable but include cognitive impairment, peripheral neuropathy, ataxia, and parkinsonism. Symptoms can appear anytime from childhood to early adulthood. [1]

1. Wendy J Introne, MD, Wendy Westbroek, PhD et al., Chediak-Higashi Syndrome. GeneReviews® [Internet], 2015.

- **WBC giant inclusions-** The finding of giant inclusions in polymorphonuclear neutrophils (PMNs) and (to a lesser extent) in lymphocytes is the most reliable diagnostic clinical criterion for CHS, but they may be overlooked in a routinely evaluated CBC unless a peripheral smear is reviewed. Peroxidase-positive giant inclusions can be seen in leukocytes, megakaryocytes, and other bone marrow precursors.[1]



- **Pigment clumping on hair-** Light microscopy hair analysis is noninvasive and quick. If a blood smear shows enlarged granules, the hair sample should be evaluated for CHS. This assessment can be routinely done with polarized light microscopy.[2]



1. Wendy J Introne, MD, Wendy Westbroek, PhD et al., Chediak-Higashi Syndrome. GeneReviews® [Internet], 2015
2. Valente NY, Machado MC, Boggio P, Alves AC, Bergonse FN, Casella E, Vasconcelos DM, Grumach AS, de Oliveira ZN. Polarized light microscopy of hair shafts aids in the differential diagnosis of Chédiak-Higashi and Griscelli-Prunieras syndromes. Clinics (Sao Paulo) 2006 Aug;61(4):327–32. .

TREATMENT OF CHS

- There are a few therapeutic methods for CHS.
- Antibiotics can be used in cases with infections and blood precipitates used in hemorrhagic cases.
- Chemotherapy with different drugs such as vine Christine, etoposide, steroid and Intrathecal methotrexate in exacerbated phase were effective, but they were low effective on the exacerbation of the disease. [1]
- Combination therapy with rituximab and cyclosporine cause complete remission. [2]

1. Skubitz KM: Qualitative disorders of leucocytes. In Lee GR, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM. (Eds): Wintrobe's Clinical Hematology. 12th ed., Philadelphia, Williams & Wilkins, 2009, 1548-1564.
2. Ogimi C, Tanaka R, Arai T, Kikuchi A, Hanada R, Oh-Ishi T. Rituximab and cyclosporine therapy for accelerated phase Chediak-Higashi syndrome. Pediatr. Blood Cancer 2011; 57(4): 677-80.

- In some cases, high dosage of methylprednisolone with or without splenectomy had a positive effect on CHS. [1]
- Allogenic Bone Marrow Transplant (BMT) was reported as another treatment option for CHS.
- The results of other studies were also acceptable if early BMT was performed [2, 3] before exacerbation phase. [4, 5, 6]
- BMT causes improvement of hematologic and immunologic symptoms but it has no effect on neural and cutaneous-ophthalmic effects because of irreversible degenerative changes. [7]

1. Aslan Y, Erduran E, Gedik Y, Mocan H, Yildiran A. The role of high dose methylprednisolone and splenectomy in the accelerated phase of the ChediakHigashiM syndrome. Acta Haematol 1996; 96(2): 105- 7.
2. Filipovich AH, Shapiro RS, Ramsay NK, Kim T, Blazar B, Kersey J, et al. Unrelated donor bone marrow transplantation for correction of lethal congenital immunodeficiencies. Blood 1992;80(1): 270-6.
3. Kersey J, Filipovich A, McGlave P, et al. Donor and host influences in bone marrow transplantation for immunodeficiency disease and leukemia. Semin Hematol 1993; 30: 105-9.
4. Haddad E, Le Deist F, Blanche S, Benkerrou M, Rohrlich P, Vilmer E, et al. Treatment of ChédiakHigashi Syndrome by allogenic bone marrow transplantation: report of 10 cases. Blood 1995; 85(1): 3328-33.
5. Mottonen M, Lanning M, Saarinen UM. Allogeneic bone marrow transplantation in Chediak- Higashi syndrome. Pediatr Hematol Oncol 1995; 12(1): 55-9.
6. Trigg ME, Schugar R. Chediak-Higashi syndrome: hematopoietic chimerism corrects genetic defect. Bone Marrow Transplant 2001; 27(11): 1211-3.
7. Sung JH, Meyers JP, Stadlan EM, Cowen D, Wolf A. Neuropathological changes in Chediak-Higashi disease. J Neuropathol Exp Neurol 1969; 28(1): 86- 118.

CORD BLOOD TRANSPLANTATION

- Accelerated Phase (APs) occur in 85% patients and usually the main cause of mortality and hematopoietic stem cell transplantation from HLA-matched related and unrelated donors is the only effective treatment for CHS and prevents recurrences of APs.

1. In the study conducted by *Rawad (2010). B*, 3 patients were evaluated who underwent unrelated Cord Blood transplantation at King Hussein Cancer Centre. All patients tolerated conditioning well. Hematological and Immunological defects of CHS had been corrected in both the patients. They showed no evidence of recurrence. [1]

1. Rawad Rihani, MD et al., Unrelated Cord Blood Transplantation Can Restore Hematologic and Immunologic Functions in Patients with Chediak–Higashi Syndrome. Pediatric Transplantation; 2010; 1-31.

2. The team from the University of California at Los Angeles has reported in abstract form successful UCB transplantation of 3 patients with Chediak-Higashi. Limited information is available on long-term outcome. [1]

3. In 2009, Zhang, 14-month-old girl from Anhui Province was diagnosed with Chediak Higashi, in Shanghai Children's Medical Centre. The little girl fortunately found a HLA – matched unit of cord blood stem cells and has got a successful transplantation. [2]

1. Wang, K., Lin, E., Moore, T. & Roberts, R. (2009) Cord Blood Transplantation for Treatment of Chediak-Higashi Syndrome. Clinical Immunology, 131, S77-S78.
2. http://www.shanghaicordblood.org/new-eng/scripts/TraCases.asp

Thank you