Chediak-Higashi syndrome

Chediak-Higashi syndrome is inherited as an autosomal recessive disease. It was described over 50 years ago. Clinical reports have identified mutations throughout the CHS1/LYST lysosomal trafficking gene.[1] The nature of the mutation can be a predictor of the severity of the disease.[2] There are a number of animal models including mouse, cat, cattle, mink and killer whale.[1]

Chediak-Higashi syndrome epidemiology

The disease is exceptionally rare with fewer than 500 cases reported in the literature.[3]

Chediak-Higashi syndrome symptoms (presentation)[3] [4]

Chediak-Higashi syndrome is characterised by partial oculocutaneous albinism, immunodeficiency, and a mild bleeding tendency.

In 85% of cases, Chediak-Higashi Syndrome develops into an accelerated phase characterised by pancytopenia, high fever, and lymphohistiocytic infiltration of the liver, spleen, and lymph nodes.[5]

Clinical features of Chediak-Higashi syndrome include:

- Impaired vision, photophobia.
- Albinism of the OCA2 type, giving a lighter complexion than unaffected family members.[6]
- Silvery sheen to hair which may be fair in colour.
- Frequent infections (skin, mucous membranes, respiratory).
- Epilepsy.
- Mental retardation.

- Enlarged liver and spleen, jaundice.
- Ataxia causing incoordination and a typical ataxic gait; tremor.

Differential diagnosis

Initially the condition may present as one of the varieties of albinism but the recurrent infections should make one suspect the diagnosis. The Hermansky-Pudlak syndrome and Griscelli's syndrome are similar but distinct conditions.[3]

Investigations[4]

The diagnosis is established in a proband with giant inclusions within leukocytes on peripheral blood smear and/or by the identification of biallelic pathogenic variants in LYST on molecular genetic testing.

- Blood smear shows giant granules in the neutrophils that stain for peroxidases.
- Bone marrow smears show giant inclusion bodies in leukocyte precursor cells.
- Giant granules are also found in cells from biopsy of skin, muscle and nervous system.
- Platelet or leukocyte levels are abnormally low.
- Genetic testing may show mutations in the CHS1 gene.
- Light or polarised light examination of hair shafts can help to diagnose Chediak-Higashi syndrome but cannot differentiate it from the appearance seen in Griscelli's syndrome.[7]
- Fluorescence cytometric analysis of cellular granularity and surface molecules offer useful diagnostic information.
- EEG may be abnormal.
- Brain MRI or CT scan may show small brain due to atrophy.
- Oral radiographs may reveal extensive loss of alveolar bone, often resulting in tooth exfoliation. .

- EMG or nerve conduction velocity testing may show delayed nerve conduction.
- A red light reflex is present in the eye (this is frequently seen in albinism).
- There are abnormalities of immune function including reduced level of CD4 lymphocytes.

Associated diseases

- Infection is a constant problem.
- For a better understanding of the visual defects and the problems related to the OCA2, see the separate record on Albinism.

Chediak-Higashi syndrome treatment and management[4]

- Initial chemoimmunotherapy followed by transition to continuation therapy for the accelerated phase.
- Allogenic stem cell transplant as soon as possible to cure haematological and immunological defects.
- L-dopa may be considered for those with parkinsonism.
- Home modifications and intensive rehabilitation for those with ataxia and other neurological complications.
- Corrective lenses to improve visual acuity, sunglasses to protect sensitive eyes from UV light.
- Sunscreen to prevent sun damage and skin cancer.
- Management of other presenting features, eg, epilepsy.

Genetic counselling

Chediak-Higashi Syndrome is inherited in an autosomal recessive manner. When both parents are heterozygous, each sibling of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Prenatal testing of CHS is possible if the pathogenic variants have been identified in the family.

Complications[4]

Frequent infections lead to hypersplenism which in turn causes thrombocytopenia and haemorrhage.

About 85% of patients develop an unusual lymphoma. This is called the accelerated phase and is characterised by generalised lymphohistiocytic infiltrates, fever, jaundice, hepato-splenomegaly, lymphadenopathy, pancytopenia and bleeding.[1]

Prognosis

Without stem cell transplant, death before the age of 10 is common.[1]

The prognosis for the accelerated phase is poor and the only treatment is allogenic haematopoietic stem cell transplantation (HSCT).[8]

All affected individuals including adolescents and adults with atypical Chediak-Higashi syndrome and children with classic Chediak-Higashi syndrome who have successfully undergone allogenic haematopoietic stem cell transplantation develop neurological findings during early adulthood (peripheral neuropathy causing motor and sensory changes and weakness).[4]

Further reading

- Ajitkumar A, Yarrarapu SNS, Ramphul K; Chediak-Higashi Syndrome. StatPearls, Jan 2023.

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Originally Published: 20/11/2023	Next review date: 20/09/2023	Document ID: doc_1933

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