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Chédiak–Higashi syndrome

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ABSTRACT

Chédiak-Higashi syndrome is a rare autosomal recessive congenital immunodeficiency mainly characterized by a condition called oculo-cutaneous albinism. The affected subjects have light-colored hair, vision problems, blood clotting (coagulation) abnormalities and in adulthood varying neurologic disorders. Recurrent infections, particularly viral infection with other disorders in childhood are usually life threatening.
It has demonstrated mutations throughout the CHS1/LYST gene. The nature of the mutation can be a predictor of the severity of the disease.
The current therapeutic options are: Antibiotics, chemotherapy and bone marrow transplantation.
This review will discuss the clinical and molecular aspects of this syndrome for better understanding of the factors that may cause abnormalities.

Introduction

Chédiak–Higashi syndrome (CHS; MIM, 214500) was first described by Bequez- Cesar and then by Steinbrinck in 1948 and ultimately by Chédiak (1952) and Higashi (1954). CHS is a rare autosomal recessive disorder which causes skin involvement, immune deficiency, hematologic disorder, neurologic manifestations and recurrent infection. [1,2] Up to now, about 500 cases of the disease were reported.[3] CHS also, occurs among other mammalian species such as cattle, cats, mink, mice, killer's whales.[4, 5] All age groups and races are involved equally but the onset of the disease begins after birth or less than 5 years of age. Oculocutaneous albinism associated with sensory and motor neurologic defects have been observed among patients with

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CHS.[2] At least half of the cases are accompanied with neural defect. In most cases, recurrent respiratory and skin infections have been reported. Acceleration phase of the disease is the most important and dangerous complication of the disease which occurs in 85% of the cases. The diagnosis of disease is confirmed by laboratory findings including cytoplasmic giant granules in blood cells such as leukocytes.[6] The treatment choice is bone marrow transplantation and in most children, death occurs due to the infections and/or bleeding at 10 years old.[2] The aim of this review article was to present the epidemiology, etiology, clinical manifestation, diagnosis and treatment of CHS.

Clinical manifestations

Infection: There is recurrent infection especially pulmonary infection such as pneumonia in CHS patients. Other common infections are otitis media, dermal and mucosal infections. Furthermore, gastrointestinal involvement as a form of enterocolitis has been observed. Staphylococcus aurous, Beta-Hemolytic Streptococci and Pneumococcal spices are more common pathogens.[1, 2]

Oral cavity: Severe gingivitis and gingival hemorrhage and early dental loss are symptoms of CHS[7] due to bone loss of alveoli in which inflammation rises associated with various microorganisms including Prophyromonas gingivalis, Prevoteua intermedia and Tannerella forsyttia.[7] Other symptoms extended into the oral cavity are aphthous, pyoderma and oral ulcer.

Skin: hypopigmentation has been reported due to disturbance in melanin migration because of giant mellanosums.[8-10] Moreover, Hyperhidrosis and miliaria has been observed. Occulocutaneous albinism has been seen in skin, hair and eyes. Albinism can involve all three organs or some of them. Furthermore, it can be presented completely, partially or even not present.[2] Silvery hair on scalp, body, eyebrows and eyelashes are the other symptoms. Pigmentations may occur on expose areas of the bodies.[11, 12] Most of the patients have photosensitivity.[5, 13 - 14] The other lesions such as erythema multiform might be seen.

Eyes: Ophthalmic symptoms include photophobia, horizontal or rotating nystagmous and increasing red reflex.[2] Iris color may be grayish, bluish and/ or brownish. Also, the loss of vision may be present in these patients.[2, 13, 15, 16]

Neurological manifestations: About half of the cases with CHS have neural manifestations. These manifestations include: neuropathy, stroke, coma and convulsion. Neurological manifestations in exacerbation phase include behavioral disturbances, walking disturbances, cerebellar ataxia, dysesthesias, Parkinsonism and paresthesia. The other manifestations are; cranial nerve palsy, no-stretching of muscles, sensory defect and muscular weakness, dementia and convulsion.[2] Polyneuropathy is the most common manifestation of the neural system.[17] Spinocerebellar degeneration and cerebellar cortical atrophy, spinal cord atrophy and essentially cerebral disseminated atrophy at temporal lobe have been observed in CHS. Mental retardation and neural deafness have also been reported.[18, 19 and 20]

Exacerbation phase: This phase is the most important and hazardous complication of CHS and 50% to 85% of the patients are involved in the exacerbation phase. Most of the patients who have entered in this phase after birth or after several years and die several months later.[21] Manifestations in this phase include fever, jaundice, hepato-spleenomegally, and lymphadenopathy, disseminated lympho-histocytic infiltration of organs with hemophagocytosis that causes pancytopenia, hemorrhagic diathesis due to platelet and fibrinogen deficiencies.[13,22] Hypogammaglobulinemia and neutropenia have

also been seen in this phase .[23, 24] The relationship between EBV and onset of exacerbation phase has been explained.[22, 25 and 26]

Hemophagocytosis by histiocyte in these patients does not differ from hemophgocytic syndromes associated with viruses (HSAV).[27]

Other symptoms: Growth retardation was observed in a number of CHD patients.[28] Anemia, thrombocytopenia and lymphoma might be seen.[29, 30] IgG depletion was reported in one of the patients.[31] In another study, hereditary elliptocytosis was reported.[32]

Ujama et al. reported two main types of CHS. More common type of CHS present in childhood and manifest through recurrent infections and lead to early death or exacerbation phase due to loss of function mutations.[2] The rare type of CHS in adults manifests by neurological features such as Parkinsonism, dementia, Spinocerebellar degeneration and peripheral neuropathy without increasing rate of infection due to missense mutations.[19, 28 and 33]

Hereditary: Although CHS develops in children whose parents have familial relationship, there are many cases that parents are not related to one another.[14, 34, 35] However, 50% of the patients suffer from familial related CHS.[3] For example, in a report by Carnide, only two of the seven patients have parents with familial relationship.[31] Lyst/CHS1 gene is located on 1q42-q43.[36] Different genotypes associated with different phenotypes and type of null homozygous protein allele is associated with more severe diseases.[33] A single mutation associates with a mild disease.[37] CHS1 gene is composed of 51 codis exons with 11406 bp coded protein with 429-KD weight.[36-38] This protein is cytosolic and composed of 3801 aminiacides and contains one homology Pleccizine domain, one BEACH domain, repeated WD-40 in C-terminal region.[38] About 31 types of mutations have been reported in CHS gene, which include frame shift, nonsense, missense.[39-43]

Pathogenesis

The presence of giant granules in neutrophils and other cells causes non-metabolism, digestion and killing of microbes. Granules are composed of abnormal fusion of primary granule (azurophilic) with secondary granule (specific).[44, 45] Abnormal function of protein kinase C is responsible for abnormal functions of PMN cells, fibroblast and NK cells.[36, 46, 50] Abnormal function of T-cell cytotoxic associated with neutrophil and monocyte chemotaxis dysfunction has been observed. Mild to moderate bleeding may occur and become severe in exacerbated phase, associated with platelet dysfunction and thrombocytopenia.[51] Meanwhile, the fusion of giant granules with phagosomes causes immune dysfunction.[52, 53]

Sung et al. described three types of pathological finding for CHS.[1] Lymphohistocytic cell infiltration in different organs develops at the end stage of disease in older children.[2] Degenerative changes are developed in the axons and myelin sheaths as the severity is accommodated by the severity of the infiltration.[3] Abnormal intra cytoplasmic inclusions arise in neurons including astrocyte, neural cells, satellite cells, and posterior spinal ganglion and Schwan cells in all age range of the patients.[54] Cellular and humeral immune deficiencies are realized in CHS.[3]

Diagnosis

Early diagnosis of CHS is very important. The mean age for diagnosis of CHS is about 6 years of age and also about 25% of the patients can be diagnosed after 10 years of age.[1, 2] The diagnosis of the disease during prenatal period is confirmed by the presence of positive phosphatase acid in lysosomes via amniotic fluid cells, CVS and fetal blood leukocyte.[57, 58]

The presence of giant granules in the hair shaft is useful in diagnosing the disease in prenatal period and after birth.[59, 60]

Therefore, the diagnosis of CHS is based on:

1) The presence of positive peroxidase giant granules in PMN cells including leukocytes, platelets, melanocytes, hepatocytes, renal tubal cells, thyroid cells, neural cells, lymphocytes, monocytes, pneumocytes, fibroblasts, pancreatic cells and gastric mucosal cells. However, neutrophil giant granules are pathognomonic.

2) Genetic assessment. Lyst/CHS1 gene mutation is located on chromosome one (31). Another diagnostic test is cytometric fluorescence analysis, which determines cellular granularity and cell surface molecules. Also, the presence of giant granules in leukocytes by light microscopic assessment from peripheral blood smear or bone marrow aspiration, for example; the wright staining technique can be used for the diagnosis of CHS. NBT test is normal in CHS.[28, 31]

Laboratory findings including; anemia, thrombocytopenia, leukocytosis, leukopenia have been seen in CHS.[28] Microangiopathic hemolytic anemia following septicemia or disseminated intravascular coagulopathy (DIC) was developed.

In bone marrow aspiration, erythrocyte hyperplasia associated with immature myeloid precursor cells is detectible and lymphocytosis in the bone marrow is observable.[28]

Differential diagnosis

1) Griscelli syndrome has similar symptoms of CHS including partial cutaneous-ophthalmic albinism, humeral and cellular immune deficiency, exacerbated phase with pancytopenia, hemophagocytosis, increased serum triglyceride levels, decreased fibrinogens, decreased plasma protein and hemorrhagic disorders. There is no giant granule. Melanosomes are normal.[61] Mutation in myo5a and RAB27A genes is developed.[62]

2) Hermansky-pudlak syndrome: there are also no giant granules. Depletion of platelet storage is associated with bleeding. Pulmonary fibrosis occurs. There are no lymphocytic and neutrophil defects.[10]

3) AML and CML may be associated with giant granules like CHS that is called pseudo CHS anomaly.[16]

4) The other diseases in differential diagnosis from CHS: Prader Willi and Angelman are two other diseases with hypopigmentation but no ophthalmic albinism. Waardenburg syndrome, Lazy leukocyte syndrome and pyoderma gangernosome are in differential diagnosis.[29]

5) In lazy leukocyte syndrome, there is no skin lesion pus but neutrophilia is present.[29]

6) Neonatal Hyperphagia, hypogonadism and mental retardation are present in prader willi.[30]

7) In Angelman syndrome there is severe mental retardation, microcephaly, neonatal hypotonia, ataxia and inappropriate laughter.[30]

8) Warden burg: Neural crest defect, piebaldism, white forelock hypopigmentation, congenital deafness and broad nasal root.[8]

9) Albinism

Treatment

There are a few therapeutic methods for CHS. Antibiotics can be used in cases with infections and blood precipitates used in hemorrhagic cases. Although previous studies showed that ascorbic acid may improve chemotaxis and bactericidal activities of neutrophils in CHS patients in in-vitro, but which is not established in in-vivo. The positive effect of it (ascorbic acid) was not reported in literatures[63] however, in recent studies, a positive effect has been reported in remission phase (without accelerated phase).[64]

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.[16] Combination therapy with rituximab and cyclosporine cause complete remission.[65].

In some cases, high dosage of methylprednisolone with or without splenectomy had a positive effect on CHS.[66] GCSF was the cause of decreasing of infection during a six-month period.[67]

IL-2 had a positive effect on treatment of CHS that improved T- cells containing Surface gdTCR which could be a therapeutic option in future.[68, 69]

Allogenic BMT was reported as another treatment option for CHS. In Haddad's study performed with various haploids and no haploids, improving in cytotoxic effects of the cells was observed in 7 cases.[70] The results of other studies were also acceptable if early BMT was performed.[71, 72] before exacerbation phase.[70, 73, 74]

BMT causes improvement of hematologic and immunologic symptoms but it has no effect on neural and cutaneous-ophthalmic effects because of irreversible degenerative changes.[54]

Prognosis

Delay on diagnosis is associated with poor prognosis due to decreasing success of BMT. The mean survival of the involved children is 6 years.[75] Most of the patients have died in the second decade of their life.[53, 76] As a final note, CHS is a rare disease with poor prognosis.[8, 30, 77] There is the possibility of relapse from the disease after chemotherapy in exacerbation phase. There are several studies related to survival of the patients with CHS up to the second or the third decade of their life. [8, 78]

Conclusion

Chediak-Higashi syndrome is a rare genetic disorder which affects many organs, particularly the immune system. The defects mainly seen in immune system cells result in the progression of infections such as viral and bacterial. Therefore, most of the patients with Chediak-Higashi syndrome have repeated and persistent infections starting in infancy or early childhood which are in some cases life-threatening and few people with this condition can live to adulthood. This syndrome is caused by mutations in the LYST gene. LYST gene assists for making a protein known as the lysosomal trafficking regulator. Mutations in the LYST gene result in abnormal function of the lysosomal trafficking regulator protein which affect on the size and function of lysosomes. The effective treatment is bone marrow transplant, that improves the hematologic and immune abnormalities, but the neurologic problems persist.

Conflict of Interest

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