Report of Six Cases of Chediak–Higashi Syndrome with Regard to Clinical and Laboratory Findings

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ABSTRACT

Chediak – Higashi Syndrome (CHS) is a rare, primary Immunodeficiency disorder with an autosomal recessive (AR) inheritance and characterized by recurrent infection, partial occulocutaneous albinism and an accelerated phase.

In this report we describe clinical and laboratory findings from 6 CHS patients.

Clinical and laboratory information of six patients who were referred to our center during the last 20 years (from 1983 – 2003) were reviewed.

Onset age of disease was between 3 months to 10 years. All patients had history of consanguineous parents and two patients were siblings. All patients had oculocutaneous albinism, nystagmus, recurrent infections which included upper and lower respiratory tract (U&LRT) infections, stomatitis, thrush, and skin abscesses and hepatitis. In laboratory findings, all patients had neutropenia and normal immunoglobulins and normal CD3, CD4, CD8and CD19 lymphocyte by flowcytometry and three of the four patients had chemotatic defect. Five patients certainly had giant granule in bone marrow neutrophil and in one patient it was equiovocal. Three patients had an accelerated phase, and for one patient bone marrow transplantation was done that was tolerated well and had been well after 7 years.

We emphasize the need for early diagnosis on basis of characteristic facies and diagnostic laboratory examinations and early bone marrow transplantation (BMT) in patients.

Key words: Chediak – Higashi Syndrome, Primary Immunodeficiency.

INTRODUCTION

Chediak–Higashi syndrome is a rare autosomal recessive disorder of all lysosomal granules–containing cells with clinical features involving the hematologic and neurologic systems. This immunodeficiency was first reported by Beguez-Cesar in 1943 and then further described by Chediak and Higashi a decade later.[1]

This syndrome consists of partial oculocutaneous albinism with photophobia and rotary nystagmus, neurologic feature, prolonged bleeding times, easy bruisability, frequent pyogenic infections and intermittent febrile episodes.[2]

Oculocutaneous albinism is prominent and together with photophobia and silvery hair is helpful in

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early diagnosis.[3]

The hallmark of CHS is giant abnormal granules in all granule-containing cells including melanocytes, neutrophil (peripheral leukocyte and their bone marrow precursors), central and peripheral nerve tissue, fibroblast and hair.[1]

Patients with CHS exhibit alterations in neutrophils. .These alterations include neutropenia which may be profound, decreased deformability resulting in impaired chemotaxis, and delayed phagolysosomal fusion resulting in impaired bactericidal activity.[3]

The underlying defect in CHS remains elusive, but the disorder can be considered a model for defects in vesicle formation, fusion, or trafficking. This immunodeficiency disorder is characterized by abnormal intracellular protein transport. The CHS gene was characterized in 1995 as the LYST (lysosomal trafficking regulator) gene or CHS1 gene and is localized to bands 1^{q42-43}.[3]

Eighty-five percent of patients with CHS enter an accelerated phase, characterized by a lymphocyte and macrophage activation syndrome episode with diffuse lymphohistiocytic infiltration of liver, spleen, lymphnodes and bone marrow leading to fever , hepatosplenomegaly , lymphodenopathy , abnormal liver function tests , pancytopenia and infiltration of CNS with a high mortality.[3]

Death often occurs in the first decade as a result of infections, bleeding or development of accelerated lymphoma like phase, but survival upto the second and third decades has been reported.[3]

Bone marrow transplant is the treatment of choice for CHS.[3]

With regard to the fact that early diagnosis of CHS and early BMT are life saving for patients, this study reviewed clinical and laboratory findings of 6 cases with the diagnosis of CHS.

MATERIALS AND METHODS

We retrospectively reviewed clinical and laboratory findings of medical file of 6 cases with the diagnosis CHS who we referred to Department of Clinical Immunology and Allergy of Children's Hospital Medical Center, Tehran University of Medical Sciences during the last 20 years (1983-2003).

The diagnosis of CHS was based on an association of characteristic findings which included "partial oculocutaneous albinisim, photophobia, rotary nys-

Table 1. Clinical data of 6 cases with CHS.

Patients No.	Sex	Parents consanguinity	Age at Diagnosis	Age at clinical presentation	Partial Albinism & Silvery hair	Photophobia & Nystagmus	Symptom and Sign at diagnosis
1	Female	Yes	4 years	2.5 years	+	+	Frequent U&LRT infection
2	Male	Yes	2.5 years	7 months	+	+	Skin infection, otitis, fever unresponsive to antibiotic, hepato splenomegaly
3(sibling) of case 2)	Female	Yes	4 years	3 months	+	+	Mouth ulcers, thrush, prolonged fever, hepatosplenomegaly lymphadenopathy
3	Male	Yes	2 months	1 month	+	+	Frequent U&LRT infections, otitis thrush, diarrhea, perirectal abscess, splenomegaly
4	Male	Yes	3 years	2 months	+	+	Frequent otitis, septicemia, mouth abscess, bleeding tendency
5	Female	Yes	11 years	10 years	+	+	Hepatitis, weakness, weight loss

Table 2. Laboratory data of 6 cases with CHS.

Patients No:	ANC (absolute neutrophil count)	Chemotaxis	Ig's	Flowcytometry (CD_3, CD_4, CD_8, CD_{19})	Giant granute in neutrophil	Consideration
1	1200/mm^3	ND	Normal	N	Positive in PBS & BMA	____
2	608	↓	Normal	N	Positive in PBS & BMA	____
3	750	↓	Normal	N	Positive in PBS Positive in -BMA	Sibling of case 2
4	420	Normal	Normal	N	Equivocal	____
5	195	↓	↑	N	Positive in BMA	BMT is done, History of
6	400	ND	↑	N	Positive in BMA	5 deaths of siblings History of 3 deaths of siblings

ND__ not determind N__ normal PBS__ peripheral blood smear

↓-Decreased ↑-Increased BMA__Bone marrow aspiration

tagmus and silvery hair" together with recurrent infections and detection of giant granules in blood and bone marrow leukocyte.

RESULTS

Clinical data

Age of presentation time was between 1 month to 10 years (median: 2/2 years)

Age of diagnosis was 2 years to 11 years (median 4/3 years) and female / male ratio was 1/1.

Other features included: consanguinity (n-6/6), presence of an affected sibling (n-1/6), repeated infections (n-6/6), and accelerated phase (n-3/6).

Hypopigmentation of skin and thin hair with silvery tint, photophobia and nystagmus were noticed in all patients. (Table 1).

Laboratory data:

Neutropenia (ANC <1500) was present in all patients. Chemotaxis was reduced in three patients out of four cases when chemotaxis was done, giant granule in neutrophils was present in 5 patients, and in case 4 was equivocal.

All patients had normal immunoglobulins, T and B cells with flowcytometry.(CD3, CD4, CD8, CD19) (Table 2).

For case 5, BMT was done which was tolerated well and has been doing well after 7 years.

DISCUSSION

This study reported clinical and laboratory findings of 6 cases of CHS (3 females and 3 males). Frequency of this AR diseases is unknown because it is rare.[3]

Female / male ratio was 1/1 which was compatible with AR inheritance.

Median age at presentation time was 2/2 years and at diagnosis was 4/3 years. Median time for delay of diagnosis was 2 years that could be due to delay in referral of these patients to medical centers .

Other studies conducted with regard to clinical presentation of CHS report similar findings as described in this study (Tables 1 and 2) , Seven patients with CHS in Brazil[4] and eight cases from three families in Jordan , have been reported.[5]

In addition to characteristic clinical presentation, recently new interesting findings were reported:

Cardiac failure and arrhythmias in an infant with CHS suggest that cardiac arrhythmias should be considered in CHS patients with high fever. An impaired negative chronotropic effect of diadenosine polyphosphate on the cardiovascular system could to be the underlying cause for this phenomen.[6]

Detection of progressive visual loss and constriction of visual field with increasing age in a 12 year old Japanese girl with ocular albinism due to CHS was reported by Saynagik et al.[7]

Hyper pigmentation of extremities and in sun ex-

posed areas from early stage of the disease in a four-year-old boy[8] and two adult siblings with CHS,[9] pointed out that hyperpigmentation of the skin may be a good diagnostic sign of CHS in Japanese cases.

In this study, 3 patients progressed to accelerated phase that is a non malignant lymphohistiocytic lymphoma like infiltration of multiple organs that is precipitated by viruses particularly by infection with EBV and charaterized with anemia, bleeding episodes and overwhelming infections leading to death. Prognosis in this phase is poor and in different studies, aggressive treatment was done with multiple drugs which Included high dose intravenous Immunoglobulin.[10] Acyclovir,[11] high dose Methyl prednisolone and splenectomy.[12] Ascorbate and GCSF[13] and antineoplastic agents such as Vincristine and Vinblestine have also been used.[3]

Bone marrow transplant is the treatment of choice. BMT corrects the immunologic status but does not affect pigment dilution. BMT is indicated before the accelerated phase of disease develops. Without BMT, children with CHS usually die before the age of 10yr. Elie Haddad et al in Necker Hospital (Paris) on 10 case of CHS showed that HLA – identical BMT was an acceptable curative treatment for CHS whereas HLA non-identical BMT remained an experimental approach.[14]

In this study BMT was performed for one patient (case no. 5) who is well after 7 years of follow-up.

We emphasize on early diagnosis of CHS patients on characteristic clinical findings and the presence of giant granules in neutrophils, and state that early diagnosis and early BMT are life saving.

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