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Chédiak-Higashi syndrome: presentation of seven cases

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Context: Chédiak-Higashi Syndrome (CHS) is a rare autosomal recessive disease characterized by recurrent infections, giant cytoplasmic granules, and oculocutaneous albinism. **Objective:** To describe clinical and laboratory findings from CHS patients. **Design:** Case report. **Setting:** The patients were admitted into the Allergy and Immunology Unit of the Instituto da Criança, a tertiary public care institution. **Cases Report:** Seven patients had oculocutaneous albinism, recurrent infections and giant cytoplasmic granules in the leukocytes. One patient had low IgG levels and three showed impaired bactericidal activity of neutrophils. Six patients died of infectious complications during the accelerated phase. Therapy included ascorbic acid and antibiotics. Chemotherapy was used for the accelerated phase in two patients. Bone marrow transplantation (BMT) was proposed for one patient. **Discussion:** The authors emphasize the need for early diagnosis and therapy of CHS. BMT should be indicated before the accelerated phase of the disease has developed.

Uniterms: Chédiak-Higashi. Primary immunodeficiency. Phagocyte. Child.

INTRODUCTION

Chédiak-Higashi Syndrome (CHS) is a rare disease of recessive autosomal inheritance, clinically characterized by partial oculocutaneous albinism and recurrent infections.¹⁻⁴

Albinism has been described in the skin, eyes and hair. The color of the hair is grey or silver. CHS patients also present sensory and/or motor neurological disorders.² The infections mainly occur in the skin and respiratory tract, most frequently associated with *Staphylococcus aureus* and *Streptococcus beta-haemolyticus*.^{1,2}

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About 85% of the patients develop an accelerated phase, characterized by visceral lymphohistiocytic infiltration associated with fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, tendency towards bleeding, and neurological complications. The histopathological findings are similar to those of familial erythrophagocytic lymphohistiocytosis and virus-associated hemophagocytic syndrome.⁵

CHS patients not submitted to bone marrow transplantation die at a mean age of 10 years as a consequence of infections or severe bleeding.²

Typical laboratory findings are the presence of giant cytoplasmic inclusions observed in several types of cells such as leukocytes, platelets, melanocytes, hepatocytes, as well as tubular kidney cells, gastric mucosa cells, pancreas, neural tissue and thyroid. These inclusions are formed after multiple cytoplasmic granule fusions. These granules acquire a purpuric red color when Wright or similar stains are applied.⁶ Ultrastructural studies have

shown that abnormal pleomorphic granules originate from vacuoles of the Golgi complex. The internal cellular structure is not organized and the coalescence of high density lysosomal vacuoles determines the presence of abnormal granules inside the cells of CHS patients.⁷⁻⁹

The immunological abnormalities described in CHS are not restricted to phagocyte dysfunction such as reduction of bactericidal capacity and impaired chemotactic activity of phagocytic cells.¹⁰ Other immunologic functions are also affected such as the activity of natural killer cells and antibody-dependent cell-mediated cytotoxicity (ADCC).^{2,4} According to the recent classification of immunodeficiencies published by the World Health Organization (WHO,1995), CHS is considered to be an inherited metabolic defect.¹¹

The treatment of choice for CHS is bone marrow transplantation. Antibiotics for infections and chemotherapy for the accelerated phase are indicated for the disease.

Considering the rarity of CHS and the few case reports of this syndrome in the literature, the purpose of this study was to evaluate the clinical and laboratory findings from CHS patients seen at the Allergy and Immunology Unit of the "Instituto da Criança", Dept. of Pediatrics, Faculty of Medicine of the University of São Paulo.

CASES REPORT

CHS patients registered at the Allergy and Immunology Unit from 1983 to 1996 were retrospectively evaluated and submitted to a basic protocol for immunodeficiencies previously established for patients suspected of having immunologic diseases.¹²

The diagnosis was established according to the following criteria: family history or consanguinity, occurrence of recurrent infections, partial albinism and detection of giant intracytoplasmic granules in leukocytes and/or bone marrow aspirate.

Immunological evaluation included the following tests: blood count, serum immunoglobulin determination, iso-hemagglutinins, antibody function (anti-poliovirus and anti-measles antibodies, Schick test for diphtheria antibodies), delayed cutaneous hypersensitivity test (PPD, SK-SD, trycophitin, candidin), proliferative response of lymphocytes to mitogens (phytohemagglutinin - PHA), and T cell subpopulations.¹³ Phagocytes were evaluated by the nitrobluetetrazolium test (NBT) and bactericidal capacity by acridine orange staining.¹⁴

Other laboratory tests were done according to clinical conditions, such as serology for viruses (Epstein-Barr and cytomegalovirus), evaluation of hepatic function, amongst others.

Specific therapy included ascorbic acid (500mg/day), antibiotics and cytostatic agents during the accelerated phase. Bone marrow transplantation was proposed, depending on clinical conditions and donor availability.

CHS was established for seven children, four girls and three boys, with age at diagnosis between eight months and four years (mean = 2.6 months). The patients presented weight and height percentiles above 2.5, according to Marques et al,¹⁵ thus not showing any signs of malnutrition and low height at admission.

All patients presented phenotypic features of oculocutaneous albinism, included grey hair color, which was the cause of admittance for one patient. Recurrent infections were observed in 6/7 patients, with predominance of respiratory tract infections, and the clinical symptoms were easily controlled with antibiotics (Fig. 1).

The diagnosis was confirmed after the detection of intracytoplasmic granules in the leukocytes and/or bone marrow aspirate (Fig. 2).

A family history of consanguinity was verified in 2/7 patients and clinical symptoms suggestive of CHS were reported in relatives of two children.

T cell function was evaluated in three children without the detection of any disturbance. Hypogammaglobulin was detected in a 4 year old patient during the accelerated phase: IgG = 410 mg/dl, IgM = 40 mg/dl, IgA=58mg/dl (reduced in relation to normal values for Brazilian children, according to Fujimura et al, 1990¹⁶). The humoral response was normal in four other patients. The values obtained for the NBT test stimulated with phorbol myristate acetate were normal (n=3), but the bactericidal capacity of these patients was impaired. Pancytopenia was detected during the accelerated phase (n=6). Serology for Epstein-Barr virus performed on four

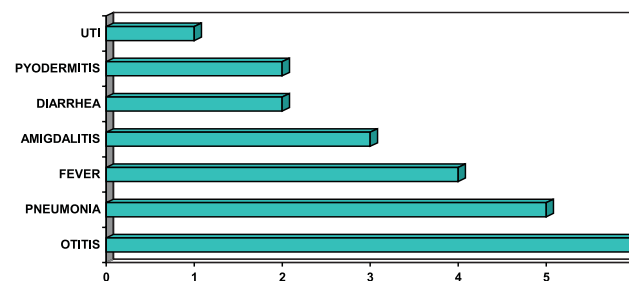


Figure 1 - Infections presented by CHS patients (n=7).

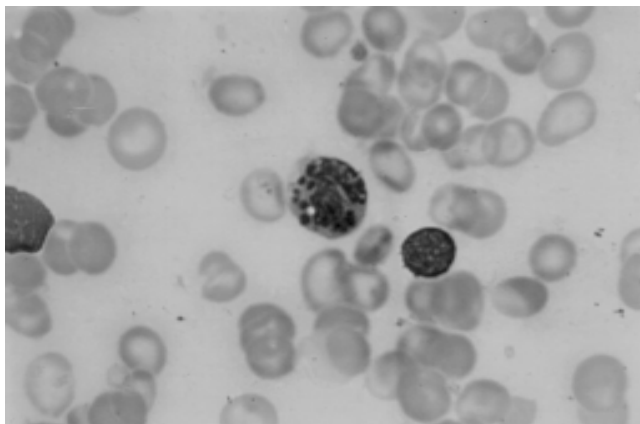


Figure 2 - Intracytoplasmic granules in patients with Chédiak-Higashi Syndrome.

patients was negative. IgG for cytomegalovirus was detected in 75% of the patients evaluated.

All patients received ascorbic acid, and antibiotics were introduced early during infections. Chemotherapy with cyclosporine, methylprednisone and etoposide was applied to one patient during the accelerated phase. These drugs did not improve his clinical condition and he died.

Six patients developed the accelerated phase and died at a mean age of five years. These children presented infections and/or bleeding that worsened their clinical conditions. One girl is still being followed up and has been submitted to laboratory tests for bone marrow transplantation.

DISCUSSION

There are isolated reports of CHS in the literature,^{5,17} except for the review published by Blume & Wolff and the clinical experience of Haddad et al.^{3,18} The present study reports the clinical and laboratory data and the evolution of seven CHS patients after 16 years of follow-up.

Familial consanguinity has been observed in 50% of the cases described in the literature.³ This finding was only detected in two families in the present study, although two other families reported relatives who died with symptoms suggestive of CHS.

The diagnosis of our patients was confirmed at a mean age of two years and six months as was also observed by Haddad et al.¹⁸ These authors reported the identification of a two month old child with CHS. The mean age reported in the literature is about six years for patients not submitted

to bone marrow transplantation, with only 25% of the patients being older than 10 years.³ Late diagnosis results in a worse prognosis with a lower chance of indication for bone marrow transplantation.

Recurrent infections were the predominant clinical manifestations affecting the respiratory tract. These infections became more frequent closer to the accelerated phase and, according to Bejaoui et al.,⁵ they are associated with fever in this phase.

Before the accelerated phase, specific antibiotics control the infection without prolonged administration, as observed in non-immunodeficient patients, but in contrast to what occurs in patients with phagocyte disorders such as chronic granulomatous disease and severe neutropenia.¹⁹

Oculocutaneous albinism was detected in all of our patients, affecting three organs (skin, hair and eyes). Blume & Wolff,³ in a study of 54 patients, reported 38 with complete albinism, seven with albinism in two organs, seven with albinism in one organ, and absence of albinism in two patients. Barak & Nir² reported that skin and hair changes could not be detected, but photophobia, rotating nystagmus and increased red reflex are expressions of eye involvement. One of the ten patients described by Haddad et al.¹⁸ did not present hypopigmentation or ocular symptoms, but had silver-colored hair.

Neuropathy was observed in 3/7 children, with stroke in one patient, coma in another and seizures in the third. Neurological manifestations have been associated with the accelerated phase and the most common symptoms are behavioral disorders, gait disorders, dysesthesias and paresthesias.² Other findings include paralysis of cranial nerves, absence of muscle stretching, sensory deficit and muscle weakness.² Spinocerebellar degeneration is also associated with CHS, and Kondo et al.²⁰ described one patient with cerebellar cortical atrophy.

Other immunodeficiencies can present clinical manifestations similar to those of SCH. Griscelli's syndrome, described in 1978, was characterized as: partial oculocutaneous albinism, humoral and cellular immunodeficiencies and an accelerated phase with hemophagocytosis, pancytopenia, increased serum triglycerides, hypofibrinogenemia with bleeding and hypoproteinemia. Nevertheless, Griscelli's syndrome has no giant granulocyte lysosomes or organelles similar to lysosomes abnormally bound to the membrane, and the melanosomes are normal. This disease is rarer than CHS.²¹

Impaired bactericidal activity, observed in two of the present patients, demonstrates the relevance of this mechanism, not linked to oxidative metabolism in bacterial lysis, as described previously.¹⁴

Hypogammaglobulinemia and neutropenia are laboratory data observed in the accelerated phase.^{3,22}

Several reports describe the association between the Epstein-Barr virus (EBV) and evolution to the accelerated phase.^{18,23-26} Hemophagocytosis by histiocytes was frequently observed in CHS cases with or without lymphoma and could not be differentiated from other hemophagocytic syndromes associated with viruses (HSAV).²⁸ McClain et al studied 20 cases of HSAV, 11 of whom had previous sporadic or idiopathic cases of immunodeficiency, and identified Epstein Barr virus in 17/20 patients.²⁶ The involvement of cytomegalovirus or herpes simplex virus was not detected by others.^{3,22} A search for viral infections was performed in 4 of our children, with negative EBV serology and positive IgG for cytomegalovirus in three patients.

Ascorbic acid improves the chemotaxis and bactericidal activity of neutrophils in CHS patients in vitro, but this finding was not confirmed in vivo. These neutrophil disorders are associated with decreased intracellular levels of cyclic monophosphate acid (increased in CHS patients) which is a potent inhibitor of cellular microtubular function.^{29,30} Our patients did not show improvement with this therapy, but we should emphasize that most of them had advanced disease. Gallin et al did not observe immunological or clinical efficacy after an 8 month treatment of two patients with ascorbic acid, even under controlled clinical conditions.³⁰

The therapy of choice for CHS is bone marrow transplantation (BMT). Haddad et al¹⁸ described 10 CHS cases submitted to BMT, seven with haploidentical donors and three with non haploidentical donors. After

a variable period of follow-up of 1.5 to 13 years, six patients who received bone marrow from haploidentical donors and one in the non-haploidentical group were found to have stabilized with improvement in natural killer cell activity.^{18,31} Other reports have shown a good prognosis after BMT, but the procedure should be indicated as soon as possible.^{32,33} Six of our seven patients died before BMT was proposed and one has been prepared for this procedure, for whom the parents are the only possible donors.

Recently, it was observed that CHS patients present increased numbers of T lymphocytes expressing surface gdTCR too. This T cell subpopulation shows increased cytotoxic capacity in vitro after interleukin 2 stimulation.^{34,35} The evidence from this stimulation suggests future prospects for the therapeutic use of this interleukin in CHS.³⁵

Consanguinity or relatives with a history suggestive of immunodeficiencies contribute to the diagnosis of CHS. A prenatal diagnosis can be made by evaluating positive phosphatase acid in lysosomes from cultures of amniotic fluid cells, chorial villus cells, or leukocytes of fetal blood.^{36,37}

This report highlights the delay in referral of CHS patients to a specialized center, which may result in undercontrol of infections and late indication of BMT. Early diagnosis is extremely important and family data and the phenotype previously described could suggest the diagnosis. BMT, even with non haploidentical donors, represents an alternative therapy that may contribute to a better quality of life, resulting in changes in CHS prognosis.

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RESUMO

Contexto: A Síndrome de Chédiak-Higashi (SCH) é uma doença autossômica recessiva rara, caracterizada por infecções de repetição, grânulos citoplasmáticos gigantes e albinismo óculo-cutâneo. **Objetivo:** Descrever os achados clínico-laboratoriais de pacientes portadores de SCH. **Tipo de estudo:** Relato de caso. **Local:** Unidade de Alergia e Imunologia do Instituto da Criança, uma Instituição pública de cuidados terciários. **Pacientes:** Os sete pacientes apresentavam albinismo óculo-cutâneo, infecções de repetição e grânulos gigantes citoplasmáticos em leucócitos. Um paciente apresentou níveis séricos diminuídos de IgG e três apresentavam capacidade bactericida de neutrófilos reduzida. Seis pacientes faleceram durante infecção, na fase acelerada. A terapêutica incluiu ácido ascórbico e antibioticoterapia. A quimioterapia foi aplicada em dois pacientes na fase acelerada. O transplante de medula óssea (TMO) foi proposto para um paciente. **Discussão:** Os autores ressaltam o diagnóstico precoce e o tratamento da SCH. O transplante de medula óssea deve ser indicado antes da fase acelerada da doença.