

Chediak-Higashi Syndrome

H.N. Usha
Preetha D. Prabhu
M. Sridevi
Kishore Baindur
C.M. Balakrishnan

The Chediak Higashi Syndrome (CHS) is a rare autosomal recessive disease characterized by partial oculo-cutaneous albinism, frequent pyogenic infections, presence of giant granules in leucocytes and other granule containing cells(1). To date less than 150 cases have been reported in the world literature. This includes a pregnant lady who delivered a normal child(2). The first case in India was reported in 1982(3). In 85% of the patients who survive their teens, a fatal accelerated phase ensues(1,7).

Case Report

A 1^{1/2}-year-old boy born of first degree consanguinous parentage was admitted with progressive distension of the abdomen, pallor and abnormal discoloration of the body since the age of 4 months. The child also

From the Departments of Pediatrics and Clinical Pathology, St. Martha's Hospital, Bangalore 560 009.

Reprint requests: Dr. H.N. Usha, D-1, Staff Quarters, St. John's Medical College and Hospital, Bangalore 560 034.

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had history of recurrent gastrointestinal and respiratory infections. The present admission was for acute diarrhea. Developmental milestones were normal and he was immunized till date. There was no family history of similar complaints.

Examination revealed a IV2 year old boy, anthropometrically normal for age, pale and febrile. There was shiny silvery grey discoloration of the hair and slate grey discoloration of the skin over the face, back, trunk and abdomen with mottled areas of hypopigmentation over the abdomen. Extremities were hyperpigmented. Eyes were light brown in color and there was no photophobia/nystagmus. The fundus was normal. There were occasional small palpable discrete nontender cervical lymphnodes. Examination of the abdomen revealed hepatomegaly with a nontender liver, smooth surface, sharp border and span of 7.0 cm. Spleen was palpable 6 cm below, the left costal margin. There was evidence of free fluid in the peritoneal cavity. Cardiovascular, respiratory and central nervous system were normal.

The findings of the laboratory investigations were as follows: Hb-7.0 g/dl, a total leukocyte count of 8000 cells/ μ L, P28, L70 and E2; and ESR 8 mm at end of hour. Platelet count was 82,000/ μ L and reticulocyte count 1.6%. The peripheral smear showed abnormal large irregular slate grey granules in neutrophils (*Fig.1*). These were myeloperoxidase positive. Large azurophilic granules were seen in lymphocytes and monocytes. The bone marrow smear showed abnormal granules in cells of the myeloid series. In addition pale eosinophilic cytoplasmic inclusions were seen in myeloblast. LFT, renal function tests, and chest X-ray were within normal limits. Ultrasound abdomen showed hepatosplenomegaly with

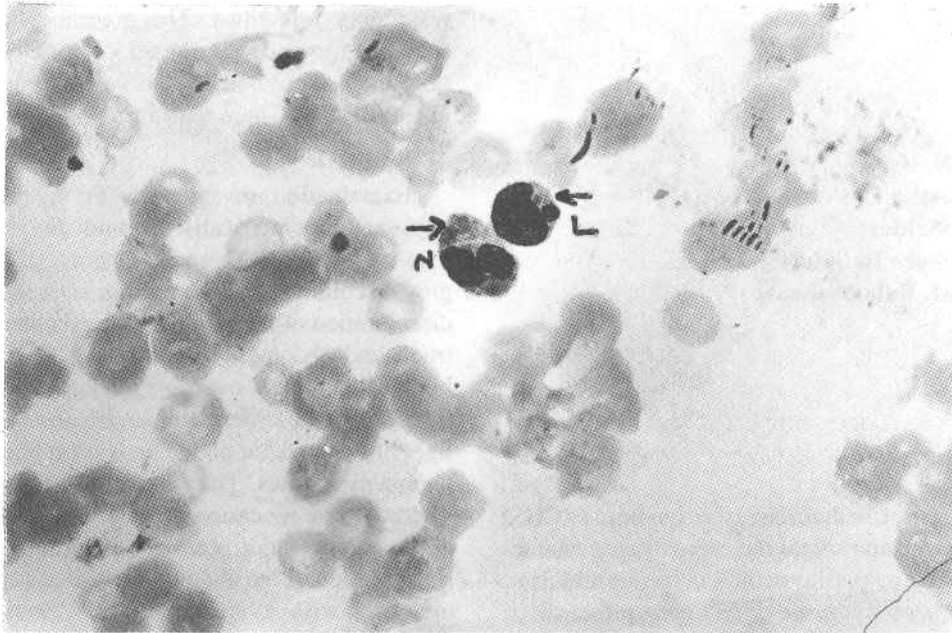


Fig. 1. Peripheral smear showing abnormal granules in neutrophils.

free fluid in the peritoneal cavity. Liver biopsy showed features suggestive of chronic active hepatitis with lymphohistiocytic infiltration. Skin biopsy revealed abnormal giant melanin granules in the epidermis (*Fig. 2*).

Based on these findings, a diagnosis of Chediak Higashi Syndrome was made. The lymphohistiocytic infiltration into the organ suggested that the patient was in the "accelerated phase" of the disease.

The child was treated with ascorbic acid, antibiotics, and blood transfusion. On follow up, he had 4 more attacks of respiratory infections over a period of 2 months. The liver size remained the same and clinically there was no jaundice. He was

readmitted 2 months later with fever, jaundice increasing pallor and bleeding from mouth, gastrointestinal tract and at sites of injections. Investigations now showed pancytopenia with grossly deranged liver function tests. He died within 24 hours after admission of hemorrhage. Post mortem liver biopsy showed massive hepatic necrosis with diffuse lymphohistiocytic infiltration.

Family members were screened and were found to be normal. The mother who was expecting during the child's illness subsequently gave birth to a normal female child.

Discussion

The Chediak Higashi Syndrome (CHS)

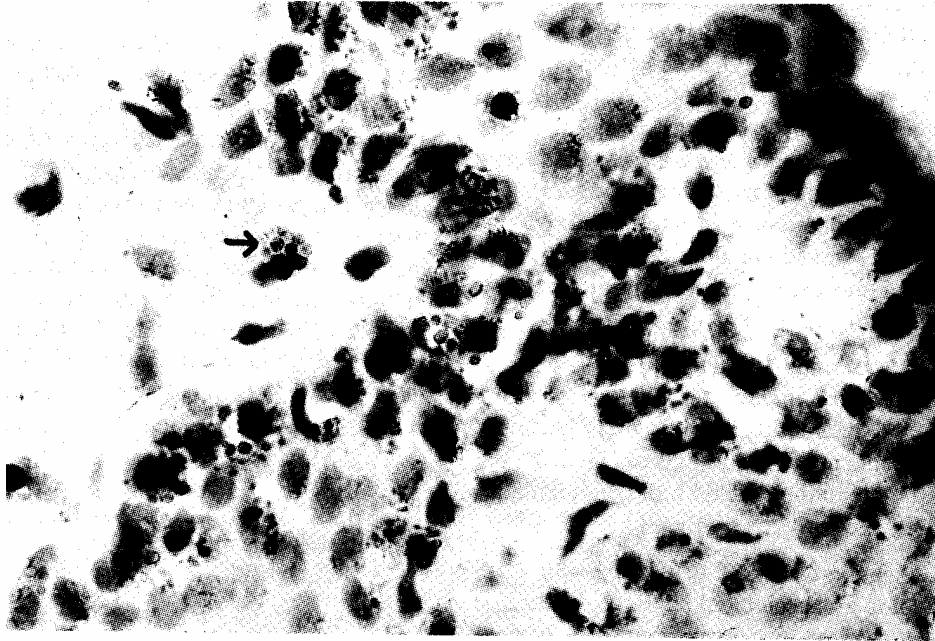


Fig. 2. Skin biopsy showing abnormal giant melanin granules in the epidermis.

was first described by Bequez-cesar in 1943 in 3 siblings bearing the main clinical features, Steinbrinck reported another case in 1948. Chediak, a Cuban hematologist in 1952 and in 1954 Higashi, a Japanese pediatrician described a series of cases and found maldistribution of myeloperoxidase in neutrophilic granules of affected patients. In 1955 Sato coined the eponym Chediak-Higashi syndrome(4).

Our child had clinical features and laboratory findings consistent with CHS. Hyperpigmentation of the extremities which generally manifests after prolonged exposure to sunlight was seen much earlier in this child.

The pathological hall mark of CHS is

the presence of massive lysosomal inclusions in all white cells, formed through a combined process of fusion, cytoplasmic injury, and phagocytosis due to a microtubular defect. These granules exhibit both azurophilic and specific granular markers which are responsible for all the clinical features of the disease (*e.g.*, malfunction of melanocytes leads to pigmentary changes eyes/skin/hair-anyone or all the three). These granules are also found in the melanocytes, renal tubular cells type II pneumocytes, chief cells and parietal cells of the gastric glands, hepatocytes, neurons and fibroblasts.

Increased susceptibility to infection especially skin and respiratory tract, less

commonly gastrointestinal tract is due to the defective function of neutrophils (poor mobilization from bone marrow, defective chemotaxis and decreased bactericidal activity). The average age of manifestation is 5.85 yrs, most patients die before the age of 10 years. However, there are reported cases of patients as old as 27 years of age(5). The mode of inheritance is autosomal recessive and 48% are found among children of consanguinous parentage as in this child.

Neurological abnormalities like clumsiness, abnormal gait, dysesthesias and parasthesias and mental retardation are rare. Mental retardation, if present is generally independent of neurological involvement and more among children of consanguinous parentage(6).

A majority (85%) of patients with CHS develop an accelerated phase of the disease characterized by fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia, coagulopathy, neurological abnormalities and diffuse mononuclear cell infiltrates into the organs which was noticed in our child. It may occur shortly after birth or may be delayed for years and is usually fatal either due to infection or hemorrhage.

A recent report of 4 cases concluded that in almost all cases the accelerated phase has been designated as reactive and resembled the virus associated hemophagocytic syndrome(7).

Ascorbic acid (20 mg/kg/dose) has been shown to have a corrective effect on microtubular defect(8). Treatment of the accelerated phase is unsatisfactory. Splenectomy, cytotoxic drugs are not of much use. Bone marrow transplants in early stages of the disease had shown good results(9). The Epstein-Barr virus is believed to play an important role in the accelerated phase

and treatment with acyclovir has been attempted.

Since the disease is autosomal recessive in transmission, screening of the patients relatives by examination of the blood smears is recommended. The presence of unusually large number of large often granulated lymphocytes, and variations in neutrophils (hypersegmentation, nuclear chromatin clumping and prominent cytoplasmic granulation) have been reported in many number of patients families. Prenatal diagnosis is possible by demonstrating characteristic CHS cells in cultured chorionic villi cells as seen in experimental animals(10).

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Jarcho-Levin Syndrome

Mohnish Suri
Madhulika
H. Pemde
A.K. Gupta
I.C. Verma

The Jarcho-Levin syndrome (JLS) is a clinico-radiological entity characterized by short-neck, short-trunk, normal sized limbs and multiple vertebral and rib defects on skeletal survey. This syndrome was first described by Jarcho and Levin in 1938(1). About 65 cases have been reported in the

From the Departments of Pediatrics and Radiology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029.

Reprint requests: Professor I.C. Verma, Genetics Unit, Department of Pediatrics, Old Operation Theatre Building, All India Institute of Medical Sciences, Ansari Nagar, New Delhi 110 029.

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literature(2,3). Recently, this syndrome has been divided into two major subtypes: spondylothoracic dysostosis and spondylocostal dysostosis(3,4).

We describe two cases of the Jarcho-Levin syndrome, one of each subtype (spondylothoracic dysostosis and spondylocostal dysostosis). The cases illustrate the typical findings of the syndrome and highlight the differences between the two subtypes of this syndrome.

Case Reports

Case 1: A 2-month-old boy was brought to the Pediatric Out-Patient with a 1.5 months history of fever and respiratory distress. He was born by Cesarean section at term, to a 28-year-old father and 25-year-old mother. His birth weight was 2,500 g and he cried 30 minutes after birth. However, he was noted to have severe respiratory distress at birth, with a respiratory rate of 150 per minute. He was the second child of non-consanguineous parents. His sister had died at four days of age due to cyanotic congenital heart disease.

On examination his weight was 3.75 kg (10-25th centile), length 49 cm (<5th centile) and head circumference 36 cm (10-25th centile). The upper segment to lower segment ratio was 1.33. There was severe respiratory distress with a respiratory rate of