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Original Article

Chediak Higashi Syndrome – Too little, too late?

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Abstract:

Introduction: Chediak-Higashi syndrome (CHS) is a rare multi-system disorder resulting from mutations in the Lysosomal Trafficking Regulator Protein (LYST) gene. The resultant dysfunctional vesicular transport causes severely disturbed cellular functions such as phagocytosis and lysosomal trafficking. Clinically, affected patients present with recurrent pyogenic infections, partial albinism and peripheral neuropathies. Disease onset is usually in the first year of life however, late presentations have been reported. Presence of giant neutrophilic granules in blood smears provide the first clues to diagnosis. Bone marrow transplant improves the immune deficiency. In resource deprived countries, antibiotic prophylaxis and genetic counselling remains the only option.

Materials and Methods: We report 8 cases diagnosed with CHS between 2008 and 2016 in two tertiary care hospitals of Peshawar. Complete history and physical examination was performed. In addition, microscopic examination of Giemsa stained peripheral blood and bone marrow smears was performed. Myeloperoxidase staining was performed on blood and bone marrow smears.

Results: The mean age of patients at diagnosis was 36 months (range 3 months – 10 years). Main presenting features were a history of recurrent chest and skin abscesses. All patients had variable degrees of oculocutaneous albinism and silvery grey hair. Six patients had one or more siblings with similar symptoms or death during infancy or early childhood. All patients fulfilled the criteria for 'accelerated phase' of CHS at diagnosis. Cytopenias in peripheral blood and hemophagocytosis was invariably present in all patients. Myeloperoxidase staining of the blood and bone marrow smears showed large peroxidase positive granules in mainly myeloid cells. Supportive therapy such as prophylactic antibiotics and high dose vitamin C were prescribed and patients were discharged after the acute episodes. No follow-up was performed.

Conclusion: CHS patients were diagnosed based on clinical presentation and peripheral blood and bone marrow findings of large myeloperoxidase positive granules in myeloid cells. Most of these patients had been admitted in hospitals before but were not diagnosed on first admission. The majority of cases presented in accelerated phase, were discharged without family testing, genetic counselling or bone marrow transplant. In conclusion, a high-degree of suspicion is necessary for the diagnosis of rare diseases such as CHS. Furthermore, a pro-active concerted approach by the hematologists and pediatricians is of paramount importance to offer the available treatment options and genetic counselling.

Keywords: Chediak-Higashi syndrome, immunodeficiency, hepatosplenomegaly.

Introduction

Chediak Higashi Syndrome (CHS) is a rare autosomal recessive disorder.[1]First described by Béguez-César in 1943[2]then by Moises Chediak[3]and OtotakaHigashi[4]this was recognized as hereditary qualitative abnormality of peroxidase positive neutrophilic granule. Not only the neutrophil structure and function is abnormal in this disease, recurrent infections, hepatosplenomegaly, neuropathy, ocular and cutaneous albinism and bone marrow failure are characteristic features of the disease.[5]The peroxidase positive granules of the neutrophils in CHS originate from azurophilic granules. [6]The vesicular abnormality is not only to the neutrophils and various white cells such as T-lymphocytes and natural killer cells are also affected. In addition, abnormally functioning granules are also visible in the melanocytes of the dermis. The

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dysfunctional melanosomes fail to be transported to the more superficial layers, resulting in pigmentary dilutional effect. This leads to partial albinism in the skin and in a similar manner the pathology affects the hair and ocular fundi. Neurological manifestations are also linked to a dysfunctional lysosomal trafficking system.If the patients don't die of the immune deficiency, they develop neuropathies later in life. Till date, fewer than 500 cases have been reported in literature. [7] However, the exact prevalence of disease is not known.

The genetic defect in CHS is in the Lysosomal Trafficking regulator protein (LYST or CHS-1) gene, identified on the chromosome 1q42-43. Various mutations such as deletions, insertions, missense, non-sense and splice variants have been reported.Due to the nature of the mutations and its impact on the protein synthesis, the disease can present from mild to severe phenotypes.The majority of children affected have parents with consanguineous marriages. LYST gene encodes for a protein responsible for synthesis of storage/transport of lysosomal/storage vesicles. Consequently, loss-of-function mutations lead to abnormal vesicular transport in various cell types – including granulocytes, neurons melanocytes and natural killer cells.

Patients usually present during infancy with recurrent infections and signs of oculocutaneous albinism. Provisional diagnosis can be made on peripheral blood or bone marrow morphology whereas mutational analysis of LYST gene is confirmatory. The clinical course of the disease is progressive and if not treated with bone marrow transplant, the median survival is 6 years. Atypical phenotypes may present later in childhood and may have a milder disease course. Hematopoietic Stem Cell Transplant (HSCT) has been the cornerstone of treatment in advanced setups. However, only hematological deficiencies are improved. Such patients develop neuropathies later in their lives. Symptomatic treatment with antibiotics to cure and prevent infections is provided. Disease usually culminates in an 'accelerated phase' characterized by increasing cytopenia, organomegaly and a lymphohistiocytic infiltrate in the bone marrow.

Approximately 500 cases of CHS have been reported. To our knowledge only 4 have been have been reported in Pakistan(8, 9).Despite its rarity, this disease has been of significant academic interest. It is essential that the frequency and demographic features and the course and prognosis of this disease in Pakistan be reported.

This study aims to present the clinical features and treatment records of 8 cases of CHS diagnosed between 2008 and 2016 at two tertiary care hospitals in Peshawar.

Patients & Methods

The study was conducted between 2008 and 2016 at Hayatabad Medical Complex and Rehman Medical Institute, Peshawar, Pakistan. All patients diagnosed at these hospitals were included in the study. Patient's clinical records and investigations were studied. Due to the study design, formal ethics board approval was not sought. Bone marrow and blood smear slides were stained with Giemsa stain. Bone marrow slides were fixed in ethanol and stained with Giemsa. Slides were mounted with DPX and covered with cover slip. Sudan-Black B and Myeloperoxidase staining was performed. Patient data were recorded in a spreadsheet (Microsoft Excel) after their identities were replaced with unique participant numbers. Analysis was performed on Microsoft Excel 2016.

Results

Total of 8 patients were diagnosed at the two centers during the period of 8 years. Out of these, 4 were males and 4 were females (Male: Female 1:1). The age of patients ranged from 3 months to 10 years (mean age at diagnosis was 36 months). The demographic features are presented in table 1. All patients had history of recurrent infections and skin lesions. The skin lesions were healed abscesses and hypopigmented patches. Two patients (no.1 and 7) had petechial hemorrhages. Failure to thrive and stunting was noted in patients 1-3 and 4, 5 respectively. Variable degrees of albinism and silvery hair were noted in most but not all patients. Patient 1 had partial cutaneous albinism and photophobia, patient 2 had nystagmus and albinism, patient 3 and 4 had thin grayish hair. Clinical and haematological parameters are presented in table 2.

All patients had a history of repeated hospital admissions due to infections. However, diagnosis of CHS had not been made in previous admission. All patients had been admitted in at least two of the three tertiary care public sector hospitals in Peshawar. At least 6 patients had one or more siblings who had similar symptoms or had died of undiagnosed conditions. Notably, parents of one patient contacted their obstetrician for genetic counselling. According to the parents, the obstetrician asked the parents to avoid conception for 9 months after the death of their first

son, and upon conception, performed fetal ultrasound for congenital anomalies. When ultrasound report showed no congenital anomaly, the obstetrician reassured them to continue the pregnancy.

Hemograms and peripheral blood smears were evaluated. All patients had some degree of cytopenias on hemograms. All patients had anemia, 3 patients had leukopenia, and 6 had thrombocytopenia (Table 2). Bone marrow aspiration was performed. In majority of cases, bone marrow hypercellularity was noted. Most neutrophils contained giant granules and cytoplasmic inclusions. Some degree of hemophagocytes was also noted in all cases. Clinical and laboratory findings suggested diagnosis of accelerated phase of CHS in all 8 cases.

Myeloperoxidase or Sudan-Black B stain was performed on peripheral blood and bone marrow slides. Peripheral blood films and bone marrow aspirate films showed myeloperoxidase positive giant granules in neutrophils (Figure 2). Patients were started on antibiotics and oral Vitamin C and were lost to follow up. Genetic counselling was not provided to any family.

Discussion

We report 8 cases of CHS presenting at two tertiary care hospitals in Peshawar over a period of 9- years. This, in our knowledge, is the largest case series reported in Pakistan.

The mean age of diagnosis has been reported to be 5.85 years.[10,11] In our patients, age at diagnosis varied from 3 months to 10 years (mean 36 months). Despite the younger age of diagnosis in our patients, it is remarkable that all patients presented in accelerated phase. Whether this represents patients with genetic mutations resulting in total loss-of-function of the LYST gene, or it is due to other factors such as recurrent infections, cannot be concluded.

Cutaneous manifestations are common and include partial albinism, photophobia etc. Nearly 85% of the patients develop an accelerated phase characterized by lymphoma like signs including persistent fever hepatosplenomegaly, lymphadenopathy and lymph histiocytic infiltration of tissues.[12-15]In our cases, all had variable degrees of lymphadenopathy, visceromegaly, and peripheral blood cytopenias. Deranged liver enzymes, low fibrinogen levels, and hypertriglyceridemia are common in presenting cases.[16]In our cases, liver functions were not tested.

Prophylactic antibiotics are recommended by a few to prevent recurrent infections. Although there has been no convincing evidence to prove clinical improvement, keeping in view its safety, high dose ascorbic acid is advised to all the patients. Moreover, meticulous child and caregiver education on infection prevention is recommended.[16]Our patients were discharged on antibiotics and Ascorbic acid, however, none received infection prevention counselling.

Splenectomy may be beneficial in cases of accelerated phase.[17]Allogenic bone marrow transplantation is the treatment of choice and should be performed early from an HLA matched family or unrelated donor. Bone marrow transplant does not alleviate neurological or skin problems.[18]Other treatment modalities in accelerated phase include acyclovir, interferon, vincristine, vinblastine and cholchicine.[18] In is noteworthy that none of patients underwent bone marrow transplant.

In summary, we have reported 8-cases of Chediak-Higashi syndrome presenting at two tertiary care hospitals in Peshawar, Pakistan. Our patients tended to present at an earlier age with aggressive disease. Despite family history, genetic counselling is not offered to most patients. Genetic diagnosis of mutations is not available. Despite availability of Next Generation Sequencing technology, offering diagnosis of this rare disease is considered financially unsustainable. Patients mainly received symptomatic treatment and were lost to follow up. It is recommended that patient and parent education and genetic counselling be provided to all CHS patients. Despite its weaknesses the study highlights the need for a rare genetic disease registry, the lack of diagnostics and counselling available and the loss-to-follow up of such patients.

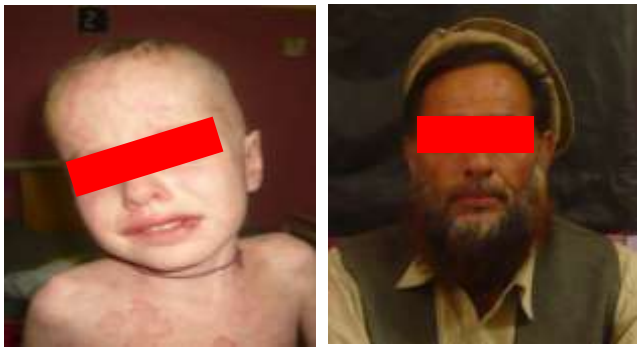

Figure 1: Father (Right) and son (Left): Note oculocutaneous albinism on the boy.

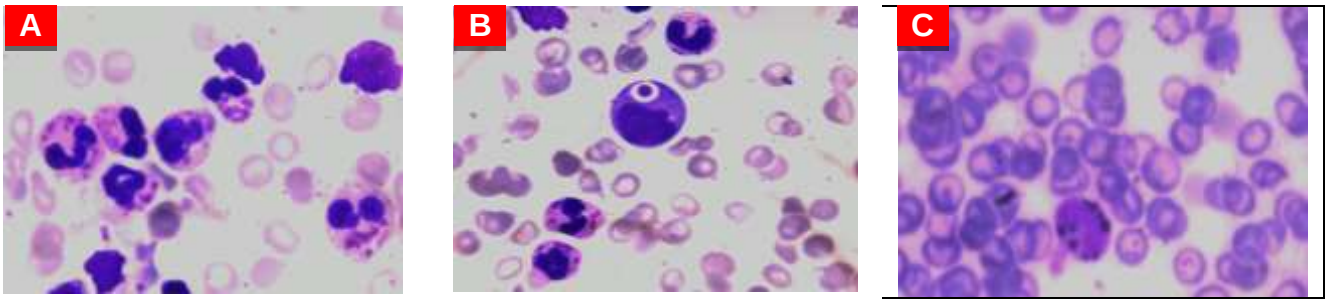

Figure 2 (a): Bone marrow aspirate of patient 2 showing giant granules in myeloid cells, (b): Bone marrow aspirate showing cytoplasmic inclusions, (c) Cytochemical stain Sudan Black B staining the granules of myeloid cells.

Table 1: Demographic and clinical features of the patients diagnosed with CHS.

Pt No	Age	Sex	Hepato-splenomegaly	Oculo-cutaneous albinism	Clinical severity
1.	3 months	M	No	Yes	Accelerated phase
2.	8 months	F	No	Yes	Accelerated phase
3.	14 months	M	Yes	Yes	Accelerated phase
4.	2 years	M	Yes	Yes	Accelerated phase
5.	2 years and 6 months	F	Yes	Yes	Accelerated phase
6.	3 years	M	Yes	Yes	Accelerated phase
7.	5 years	F	Yes	Patchy hypopigmented areas	Accelerated phase
8.	10 years	F	Yes	Patchy hypopigmented areas	Accelerated phase

Table 2: Haematological Paramters of CHS patients

Pt. #	Hb (g/dl)	Total Leukocyte count (/µL)	Plt count (/µL)
1.	7.9	14,700	23,000
2.	5.9	1800	82000
3.	10	7800	55000
4.	7.7	7800	54000
5.	6.6	12900	55000
6.	9.3	41,800	153,000
7.	5.8	900	1500
8.	5.6	1100	22000

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