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Chédiak Higashi Syndrome -A hematological Diagnosis and Review of Literature

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ABSTRACT

Chediak Higashi Syndrome is a rare autosomal recessive disease come in picture early in age, mainly paediatric group and is fatal. In India, till the year 2000, only five cases have been reported. In this study ,we present all the cases reported in India, their clinical presentation, CBC ,PBS ,Bone marrow findings, skin biopsy or hair study (if performed) and their correlation to see the accelerated phase of the disease and approach to the management. Determined peripheral blood smear examination is the key to arrest the diagnosis of Chediak Higashi Syndrome in developing country like India, defining it is the most easiest, quickest, cheap, easily available investigation in our country.

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Abbreviations: CHS-Chediak Higashi Syndrome, HLH-Hemophagocytic Lymphohistiocytosis, EBV-Epstein Barr Virus, CBC-Complete Blood Count, PBS-Peripheral Blood Smear, GBP-General Blood Picture, BMA-Bone Marrow Aspiration, BMB-Bone Marrow Biopsy, FNAC-Fine Needle Aspiration Cytology, LYST-Lysosomal Trafficking Regulator Gene, URTI-Upper Respiratory tract infection, PUO-Pyrexia of Unknown Origin, MPO-Myeloperoxidase, SBB-Sudan Black B, LN- Lymph Node, ESR-Erythrocyte Sedimentation Rate, MAHA-Microangiopathic Hemolytic Anemia, DIC-Disseminated Intravascular Coagulation, ADC-Apparent Diffusion Coefficient, MRI- Magnetic Resonance Imaging, MRS-Magnetic resonance spectroscopy, USG-Ultrasonography, PLT-Platelet Counts, TLC-Total Leucocyte Counts ,DLC-Differential Leucocyte Counts.

Background

Chédiak Higashi syndrome (CHS) is a genetic disorder, a rare autosomal recessive condition initially described by Beguez-Cesar in 1943 and later explained by Chédiak in 1952 and Higashi in 1954, who discovered the disturbed granular distribution, i.e., myeloperoxidases(MPO) enzymatic granules in affected patients' neutrophils [1-3]. However, it has also been observed in lymphocytes and misdiagnosed as "reactive granular lymphocytes" and "toxic granulation" in neutrophils.

The underlying defect is a mutation in the "lysosomal trafficking regulator(*LYST*)" or the "*Chédiak Higashi syndrome* (*CHS1*)" gene. This specific gene is responsible for the regulation of lysosomal trafficking and the synthesis, fusion, and transport of cytoplasmic granules in leukocytes. This gene is located on the long arm of chromosome 1 [1q42-43]. Around 40 different mutations have been discovered, including nonsense and missense mutations, deletions, and insertions [4-5].

The *LYST gene mutation* disturbs protein synthesis and leads to defects in the storage and secretory functions of granules (lysosomal) of leukocytes, fibroblasts, dense bodies of platelets, azurophilic granules of neutrophils, and melanosomes of melanocytes. The defects result in enlarged vesicles and non-functional lysosomes, which are microscopically seen as large or giant-sized single or multiple granules in leucocytes [6-8].

The exact prevalence and incidence of CHS are unknown, due to undiagnosed cases and early mortality .There has been fewer than 500 cases reported in the literature worldwide. In India till the year 2000, only five cases have been reported. Unfortunately, the disorder has no treatment till date and more than 80% of diseased are dead very early in life, i.e. first decade. Only few patients survived up till second decade of life and they tend to show many clinical manifestations lead to low immunity and have poor quality of life [9-11].

Molecular genetic testing can also be used to identify the root cause gene, the LYST gene. Because of a lack of availability, awareness, and poverty, molecular testing for gene detection remains a challenge in developing countries such as India.

Materials and Methods

This is effectively a systematic review of all the reported cases of *Chédiak Higashi syndrome* in India. Also, this is to present a case report of a 7 years male child, presented with pain abdomen, fever and delayed milestone. As per best of the research, it's a second case reported in North India, reported as an incidental finding in a microscopic review of a peripheral blood smear (PBS) of complete blood counts (CBC) findings suggestive of pancytopenia. [Table-1] **Literature testify the extreme rarity of this entity, and remains unrecognised** in India may be due to **the fact that** this specific diagnosis **has not been considered in differential diagnosis. Therefore, limiting** the research **investigation** to **India to ascertain the diagnostic challenges encountered. Molecular** testing **remains** a problem in developing **countries**, rarely available in higher medical **institutions also**.

Eligibility Criteria

All studies performed in patients with CHS were considered eligible.

The inclusion criteria considered were:

1. All types of studies, done in English language describing cases of CHS.
2. Cases reported in Indian population, in order to identify the diagnostic challenges in India.

The exclusion criteria were: Studies representing uncertain diagnosis of CHS.

Information Sources and Search Strategy

The literature search for the present review study was conducted at Pubmed, Pubmed Central, MEDLINE, Embase, DOAJ, Index Copernicus, Google Scholar online library up to 30 July 2022. The search strategy used a combination of the following keywords; "Chédiak Higashi Syndrome" or "Chédiak Higashi Syndrome in India" or "Chédiak Higashi Syndrome-peripheral smear findings". The additional filter "Language: English" was used.

Study Selection

Studies were selected in two stages of screening by two independent reviewers. At first level, title and abstract screening was performed to exclude irrelevant articles or articles that did not meet the inclusion criteria. In the second screening, full articles were read and the study eligibility was verified.

Data Collection Process/Data Items

Data were extracted based on the general study characteristics (author and year of publication, study design) and case characteristics (number of cases, age, ethnicity, sex, similar manifestations in siblings, hereditary history ,association with other infections and its frequency, association with Hemophagocytic lymphohistiocytosis(HLH), skin & hair clinical manifestation, diagnostic PBS findings, CBC findings, radiological findings, treatment, follow-up, etc.

Study Design

Of all the selected studies, one is original article, one is case series and 27 are case reports. Collectively, these studies accounted for 29 cases of CHS, including the present case.

Discussion

The clinical details and **investigations** performed **on** all **cases (n=29) diagnosed with** CHS in India are summarised in detail in [Table 1]. The survey revealed that **each** case **was an incidental diagnosis made** while screening PBS **to amend the** CBC or general blood picture (GBP) **examination**. **Also note that there was no clinical suspicion of CHS in any** of the above **cases**. Most of the patients visited the paediatric and dermatology outpatient departments **for acute** illnesses.

Table 1

Study	Age/Sex	Clinical presentation	CBC findings	PBS & Bone marrow findings	Skin biopsy/ Hair study	Additional findings H/o consanguineous marriage
Mukta Pujani et al. (2011) [12]	2yr/ M (2 cases-siblings)	Fever and recurrent infections-URTI,, Pyrexia of unknown origin (PUO) Hair-silvery grey hair Skin- diffuse hyperpigmentation Hepatosplenomegaly Cervical & Axillary LN Delayed milestone	Bicytopenia Hb- 4.5 g/dl TLC- 9500/cumm N18L80M02 PLT-70,000/cumm ESR-45 mm/1st hr	Giant granules in neutrophils(MPO +) Single large size granule in lymphocytes RBC- Microcytic hypochromic BM-normocellular giant granules as in PBS(MPO& SBB+)		H/o- Present
A Roy et al. (2011) [13]	5m/F 3yr/M 7m/F 3yr/M 8m/F (5 cases)	Fever and recurrent infections-URTI,PUO Hair-silvery grey hair Skin- diffuse hyperpigmentation Hepatosplenomegaly (4/5 cases) Lymphadenopathy(3/5 cases) Delayed milestone(3/5 cases)	.Anemia- (5/5) Leucopenia-(2/5) Leucocytosis-(3/5) Thrombocytopenia –(4/5)	All cases- giant inclusion bodies in leucocytes BM- erythroid hyperplasia, increased immature myeloid cells & lymphocytes, giant granules in leucocytes	Skin biopsy-sparse but coarse granular melanin pigment in basal layer Liver biopsy-kupffer cell hyperplasia,few show hemophagocytosis	2 /5 cases- show Microangiopathic hemolytic anemia (MAHA),possibly due to DIC H/o- Present in 3/5 cases

Karande S et al. (2014) [14]	Toddler	Fever and recurrent infections-URTI,PUO Hair&Skin- hypopigmentation B/L pedal edema Hepatosplenomegaly	Pancytopenia	PBS-Classical finding	Hair study-evenly distributed but large granular melanin pigment	Coexisting HLH – Accelerated phase of CHS
Raghuveer C et al. (2015) [15]	6yr/F (3 cases-siblings)	Recurrent URTI Hair-silvery grey hair Skin- diffuse hyperpigmentation		PBS-Classical finding	Skin biopsy-scattered large coarse melanocytes in basal layer Hair study-evenly distributed but large granular melanin pigment	H/o-Present
Jaiswal P et al. (2015) [16]	4m/M	Fever Hair- Blonde Eyes&Skin- hypopigmentation Cleft lip Hepatosplenomegaly	Bicytopenia Hb- 4.7 g/dl TLC- 7500/cumm N05L94M01 PLT-10,000/cumm	PBS- macrocytic RBCs with fair no of smudge cells. Classical finding BM-hypercellular, erythroid hyperplasia, megaloblastic maturation, giant granules in myeloid cells& increased histiocytes and hemophagocytic activity		Accelerated phase of CHS H/o-Present
Rudramurthy P et al. (2015) [17]	5yr/F 3yr/F 2yr/F 5m/M 3yr/M	Fever and recurrent infections-URTI,PUO Hair-silvery grey hair Skin- dermatitis(2/5) Hepatosplenomegaly Lymphadenopathy- (3/5)	Anemia (4/5)	PBS- single large granule predominantly seen in lymphocytes	Skin biopsy(1/5 cases)-lack of melanin pigment	H/o-Present(all cases)
Chennagiri et al. (2016) [18]	3yr/F	Fever and recurrent infections-URTI, ear oral thrush, angular stomatitis Hair-silvery grey hair Skin-generealised hypopigmentation Hepatosplenomegaly Cervical LN	Bicytopenia Hb- 8 g/dl TLC- 5000/cumm N10L90 PLT-1 lac/cumm	PBS-classical finding, absolute neutropenia BM-hypercellular, erythroid hyperplasia, megaloblastic maturation,		H/o-Present
Kishore et al. (2016) [19]	1yr/M	Fever and recurrent infections and ear bleeding Hair-silvery grey hair Iris - hypopigmentation Skin-generealised hypopigmentation Massive Hepatosplenomegaly	Pancytopenia Hb- 8.9 g/dl TLC- 2200/cumm PLT-30,000/cumm	PBS- microcytic hypochromic RBCs with classical finding BM-classical finding & increased hemophagocytic activity	Hair study-evenly distributed melanin pigment	H/o-Absent
S.Palaniyandi et al. (2017) [20]	3m/F	Fever and recurrent infections-URTI Hair-silvery grey hair Skin- hypopigmentation Hepatosplenomegaly Axillary LN	Bicytopenia Hb- 6.6 g/dl PLT-60,000/cumm	PBS-Classical finding	Skin biopsy-irregularly placed giant melanosomes	HLH criterion met – CHS associated with HLH H/o-Present
Shravani et al. (2017) [21]	11m/F	Fever and recurrent infections-URTI,repeated hospitalisation Hair&Skin- hypopigmentation Massive Hepatosplenomegaly Generalised LN	Bicytopenia	PBS- normocytic normochromic RBCs, lymphocytosis, thrombocytopeniaaand typical granules	Hair study-decreased pigment granules	H/o-Present
Rishivardhan Reddy et al. (2019) [22]	1.5yr/M	Fever and recurrent infections-URTI,PUO Hair-silvery grey hair Skin- hypopigmentation Hepatosplenomegaly B/l Cervical,submandibular& Axillary LN	Pancytopenia Hb- 7.6 g/dl TLC- 3500/cumm N12L80E02M06 PLT-35,000/cumm	PBS & BMA- Classical finding	Skin biopsy-sparse melanin pigment & giant melanocytes	H/o-Present
Goel P et al. (2019) [23]	4yr/M	Fever and recurrent infections-URTI,PUO Hair-silvery grey hair Skin- generalised hypopigmentation Splenomegaly	Pancytopenia Hb- 4.1g/dl TLC- 1280/cumm PLT-28,000/cumm	PBS,BMA& BMB-Classic finding(predominantly lymphocytes and monocytes)		H/o-Absent

Sriram R et al. (2020) [24]	4yr/F	Fever and recurrent infections-URTI,ear Hair-silvery grey hair Skin- multiple macules on face and neck Hepatomegaly Cervical & Axillary LN	CBC-within normal limits	PBS-Classical finding		H/o-Present
Aggarwal et al. (2020) [25]	2.5yr/F	Fever and recurrent infections-URTI,PUO Hair-blonde.hypopigmented eyebrows and eyelashes Skin- diffuse hyperpigmentation Hepatosplenomegaly B/l Cervical & Axillary LN	Bicytopenia Hb- 6.7 g/dl TLC- 13,500/cumm PLT-reduced	PBS- microcytic hypochromic cells with few atypical cells show giant granules in leucocytes		HLH criterion met-CHS associated with HLH H/o-Present
Gopaal et al. (2020) [26]	30m/M	Seizures and fever Hair-silvery grey hair Skin- hypopigmentation Hepatosplenomegaly Cervical & Axillary LN Xray- bilateral lung infiltrate	Pancytopenia Hb- 5.9 g/dl TLC- 9700/cumm PLT-20,000/cumm PT-30.4 sec INR- 2.40	PBS-Classical finding		HLH criterion met and EBV IgMAb positive - CHS associated with HLH and EBV H/o-Present
Sumit Sen et al. (2020) [27]	10yr/M	Fever and recurrent infections-URTI,PUO Skin- abnormal pigmentation Hepatosplenomegaly Younger brother died at age of 6 yr	Mild Bicytopenia Hb- 10.2 g/dl TLC- 6200/cumm N15L75E02M08 PLT-1.2 lac/cumm	PBS-Classical finding		H/o-Present
Kekatpure M V et al. (2020) [28]	6yr/M	Fever ,abnormal gait, oculocutaneous albinism,nystagmus,peripheral neuropathy Hepatosplenomegaly Generalised LN	Pancytopenia	PBS-Classical finding BMA- classical finding and features of hemophagocytosis		Associated Accelerated phase CHS with EBV (ELISA +) MRI – "Striking picture "- B/L globus pallidal involvement H/o-Present
Raj et al. (Present study) (2022)	7yr/M	Fever and recurrent infections-URTI, pain abdomen, h/o PICA Hair- sparse light grey hair Skin- macules on face and scabies Mild Hepatosplenomegaly Delayed milestone	Pancytopenia Hb- 7.2 g/dl TLC- 3200/cumm N19L80M01 PLT-40,000/cumm ESR- 48 mm/1st hr	PBS- Microcytic hypochromic to normocytic normochromic RBCs along with few target ,tear drop and polychromatophilic cells .Classical single large inclusion seen predominantly in lymphocytes and few neutrophils (Figure 1)	Hair study- evenly distributed melanin pigment	H/o-Absent

In the present survey, all patients belong to the paediatric age group of 3 months to 10 years. The earliest cases, detected within 3 months of symptomatic infants, have an average age of 2.5 years. Male preponderance is well established (M:F= 2.2:1). Siblings are equally affected in most cases, with a strong positive history of parental consanguinity in India. In other countries, however, no definite correlation of consanguineous marriages of parents of affected children with CHS has been documented. One case was reported with a history of a sibling's death due to an unknown cause. Similarly, other countries show siblings with similar presentation who are diagnosed with CHS.

The most obvious presenting complaints are fever, recurrent upper respiratory tract infections (URTI), anorexia, and abdominal pain. The most characteristic signs are hair and skin changes in the form of silver-gray hair and changes in skin pigmentation (mainly hypo-pigmentation). Lymphadenopathy is a common finding in 55% of cases, primarily in the neck and more commonly in the axilla. However, there is generalised lymphadenopathy associated with CHS patients who are *Epstein Barr Virus (EBV) IgM-antibody* positive. Most have features indicative of reactive lymphoid hyperplasia. Milestone delays have been observed in some of these cases. Because leukocyte granules become inactive in CHS, all patients are highly susceptible to infection due to decreased immunity, resulting in higher hospitalisation rates in this paediatric group. It has been noted that no difference is found in clinical presentation, peripheral smear findings, or hair and skin studies in diseased children with CHS who belong to other countries.

The Ultrasonography(USG) finding; hepatosplenomegaly observed in 86% of CHS cases, has been found to be useful in screening PBS and bone marrow smears for underlying etiology. One of the patients with gait abnormalities and peripheral neuropathy had striking Magnetic Resonance Imaging (MRI) brain changes that revealed hyper-intensities on T2-weighted images in the cerebral and cerebellar hemispheres [28]. Magnetic resonance spectroscopy (MRS) showed a "choline peak" [28].

The PBS finding [Figure 1] seem to be a game changer for CHS, although it has always been for subleukemic leukemia and hemoparasites when screened for bicytopenia or pancytopenia. The study shows bicytopenia in 65% of cases and pancytopenia in 34.5% cases. The PBS were made for CBC correction and for GBP examination; careful microscopic examination is the key

to clinching the diagnosis. The classic finding of single giant inclusion in lymphocytes and multiple in neutrophils, most of which are MPO positive, warrants the diagnosis of CHS. These granules are considered pathognomic and "peripheral blood smear diagnostic criterion" for *Chédiak* Higashi Syndrome. Only 6 out of 29 cases described their RBC picture, i.e., microcytic hypochromic most commonly, followed by macrocytic and normocytic normochromic RBCs.

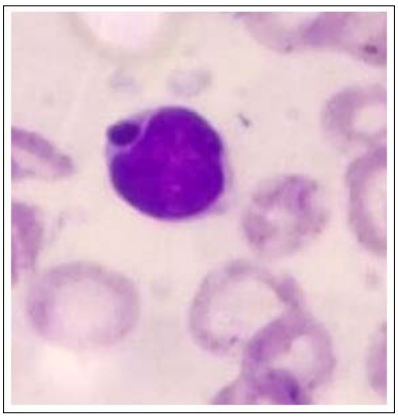

Figure 1: Peripheral blood smear of 7 years male child show single giant cytoplasmic inclusion in lymphocyte (Leishman stain,400x)

Most of the cases are then retrogradely clinically examined and investigated i.e., bone marrow examination, skin biopsy, hair study, etc. The bone marrow examination was performed in 9 of 29 cases, as parents denied the invasive procedure and showed poor compliance. Bone marrow shows evidently increased cellularity for age and increased hemophagocytic activity in 50% of cases (4 of 9), which suggests that further investigations for HLH are doubtful. However, 4 out of 29 found to be associated with HLH, which were properly investigated. In addition, two cases show an association with EBV. The increased bone marrow hemophagocytic activity and reported association with HLH indicate a strong association with HLH. Therefore, once the diagnosis of CHS has been confirmed, the following approach should be considered:

(a) Investigate for accelerated phase [29-30]

Bone marrow examination to see hemophagocytic activity

- Hepatosplenomegaly
- Any history of recurrent pyrexia of unknown origin(PUO)
- Bicytopenia
- Raised serum ferritin levels
- Raised soluble interleukin-2 receptor levels
- Evidence of liver malfunction or disease
- Hypertriglyceridemia or hypofibrinogenemia

(b) Detailed neurological examination, if present then advice MRI brain

(c) If HLH is diagnosed along with CHS, investigate for lymphoma

(d) Genetic study, if available

According to the present study, skin biopsies performed in 4 of 29 cases from abnormal pigmentation areas reveal giant melanosomes in the epidermis' basal layer. A hair study performed in 6 of 29 silver grey hair patients revealed evenly distributed large granular melanin pigment in 2 cases. One case has no melanin pigment, while the other has reduced melanin pigment. The remaining two cases showed normal studies.

It was discovered that these children had gone unnoticed for a long time because they began exhibiting symptoms at a young age (average age 1.5 years). They are frequently suspected of protein-energy malnutrition and have been neglected for simple blood tests. It is recommended to screen the siblings (if any) of reported cases of CHS for early management of this fatal disease. If detected early, it can be prevented from accelerating the disease's course by performing a bone marrow transplant.

Summary

Chédiak Higashi Syndrome is a rare and fatal disease with features of pancytopenia and bicytopenia. If this diagnosis is kept in mind and there is a good practise of screening peripheral smears as much as possible, the hematopathologist's diagnostic approach can make a difference. Because of the strong association with HLH, it is recommended that the patient be screened for it so that early mortality can be reduced. Bone marrow transplantation, if performed early, is the only curative treatment. However, it had only little benefit once the accelerated phase of CHS began. Genetic testing for the *CHS1*/*LYST* gene mutation is not easily available in developing countries, and it is also not affordable by the general population. Therefore, peripheral blood smear screening and bone marrow aspiration studies are utterly needed for early diagnosis and management. Henceforth, a determined peripheral blood smear examination is the key to arresting the diagnosis of *Chédiak* Higashi syndrome in a developing country, defining it as the easiest, quickest, cheapest, and easily available investigation.

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