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CASE REPORT

Chediak-Higashi Syndrome: a Comprehensive Case Report and Literature Review

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SUMMARY

Background: **Chediak-Higashi Syndrome (CHS) is a rare autosomal recessive disorder characterized by oculocutaneous albinism, immune dysfunction, and neurologic abnormalities.**
Methods: **This paper aims to provide a detailed understanding of the clinical presentation, laboratory examination, genetic basis, EEG/MRI, diagnostic challenges, and current management strategies for CHS through a new case report and a analysis of the current literature.**
Results: **The analysis of the case report and literature indicates that CHS requires vigilant clinical observation for early diagnosis and effective treatment. The analysis highlights the necessity for advanced therapies that are both more efficient and cost-effective, given the current limitations in treatment options.**
Conclusions: **The study concludes that further research is needed to develop more efficient and economical therapies for CHS that can enhance patient outcomes. The development of such therapies will be crucial in addressing the unmet needs of patients with this rare genetic disorder.**
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KEYWORDS

Chediak-Higashi Syndrome, LYST gene, skin hyperpigmentation, silvery hair syndrome, immunodeficiency disorder

INTRODUCTION

Chediak-Higashi Syndrome (CHS), first described by Chediak in 1952 and Higashi in 1954, is a rare genetic disorder with an estimated prevalence of 1 in 1,000,000 live births, and about 500 cases reported in the literature [1,2]. The syndrome is caused by mutations in the *LYST* gene, leading to defects in lysosomal-related organelles and causing a spectrum of clinical manifestations including hypopigmentation, immunodeficiency, and neurological impairments [2-4]. This report synthesizes findings from a recent case presentation and a summary of published cases to enhance clinical understanding and management of CHS.

CASE REPORT

Clinical Presentation

We present a case of a 4-year-old girl transferred to our hospital due to sudden convulsions and altered consciousness. On admission, she exhibited recurrent fever, cough, and dyspnea. Clinical examination revealed dyskinesia, muscle weakness, and negative meningeal stimulation. Notable features included pigmentation of extremities and silvery gray hair with a metallic sheen (Figure 1A - D). Past medical history indicated recurrent convulsions and skin hyperpigmentation since the age of 4 months, along with motor difficulties and speech weakness. Family history was significant for consanguineous parents and a sibling with a similar condition who died at the age of four from hemophagocytic syndrome. Treatment for unexplained infection for more than one month.

Laboratory Investigations

Laboratory findings included leukocytosis, elevated serum amyloid A, and C-reactive protein. Coagulation tests revealed prolonged prothrombin time and elevated D-dimer levels. Lymphocyte subset analysis showed high total B lymphocytes and low percentages of helper/induced T cells and total T lymphocytes. The serum test indicated high levels of interleukin-6, calcitoninogen, and ultrasensitive troponin T. Pathogen tests confirmed the presence of multiple infections including streptococcus pneumoniae and influenza A virus.

Peripheral Blood Smear (PBS) Findings

Neutrophils: 20.0% of neutrophils displayed abnormal round or round-like purplish-red granules of varying sizes and numbers in their cytoplasm. Peroxidase staining highlighted multiple sizable aberrant positive granules within the cytoplasm of these neutrophils.
Lymphocytes: 17.0% of lymphocytes contained a single large round or round-like dark purplish-red abnormal granule in their cytoplasm.
Monocytes: Occasional monocytes exhibited a single pink round or round-like granule in their cytoplasm.
Eosinophils and Basophils: Eosinophils were rare, and basophils were not visible in the PBS analysis.
These PBS findings are characteristic of the granule abnormalities seen in Chediak-Higashi Syndrome, with the presence of atypical granules in neutrophils, lymphocytes, and monocytes, and the absence of basophils (Figure 1E - L).

EEG and MRI investigations

EEG Findings: The 5-hour video EEG revealed continuous fast-wave rhythms across all leads, with asymmetry between the left and right hemispheres, notably in the left anterior head region. Sharp slow waves were noted discharging in the anterior heads, occipital, and temporal regions, with the potential to spread to the left posterior head. In the right hemisphere, waves occasionally exhibited a distinct orthophase component and a tendency towards partial evolution. An initial focal electrical seizure in the right posterior head was detected.
MRI Findings: Abnormal signal shadows were observed in several brain regions, including the bilateral hippocampus, amygdala, thalamus, brainstem, and cerebellar hemispheres. Cerebral edema was present in the bilateral frontal lobes and the left parieto-occipital lobe. Effusion was noted in the maxillary, ethmoidal (sieve), and pterygoid sinuses on both sides, as well as in the bilateral mastoid processes.
These findings suggest significant neurological involvement in the patient, with evidence of seizures, cerebral edema, and effusions, which are critical for informing further diagnostic and treatment strategies. (Figure 2A - D).

Genetic Findings

Exome sequencing identified a nonsense mutation (c.1507C>T/p.Arg503) in the LYST gene, confirmed as pathogenic in the ClinVar database (RCV001855924). Both parents were heterozygous carriers of this variant (Figure 3).

Management and Outcome

The patient's condition was complicated by recurrent severe pneumonia, respiratory failure, viral encephalitis, and epilepsy. Hematopoietic stem cell transplantation, the only available treatment, was not pursued due to financial constraints, and the parents withdrew treatment.

Literature Review - Summary of Published Cases

A comprehensive summary of published cases since 2019 is presented in Table 1 [Supplemental material]. The cases highlight the variability in age of onset, clinical features, and outcomes. Skin hypopigmentation, silvery gray hair, neurological impairment, and immunodeficiency are consistent features across cases. Genetic mutations in the LYST gene are confirmed in the majority of cases, with varying mutations leading to the disease phenotype.

Diagnostic Challenges

Early diagnosis of CHS remains a challenge due to its rarity and variable presentation. Peripheral blood smear (PBS) analysis is emphasized as a simple, yet effective, diagnostic tool for recognizing characteristic morphological granules [5].

Management Strategies

Hematopoietic stem cell transplantation (HSCT) is the cornerstone of treatment, with potential to improve immune complications and prolong life [6]. Supportive care includes anti-infective treatments and symptomatic management. The role of novel therapies, such as emapalumab, is emerging in the management of refractory hemophagocytic lymphohistiocytosis associated with CHS [7].

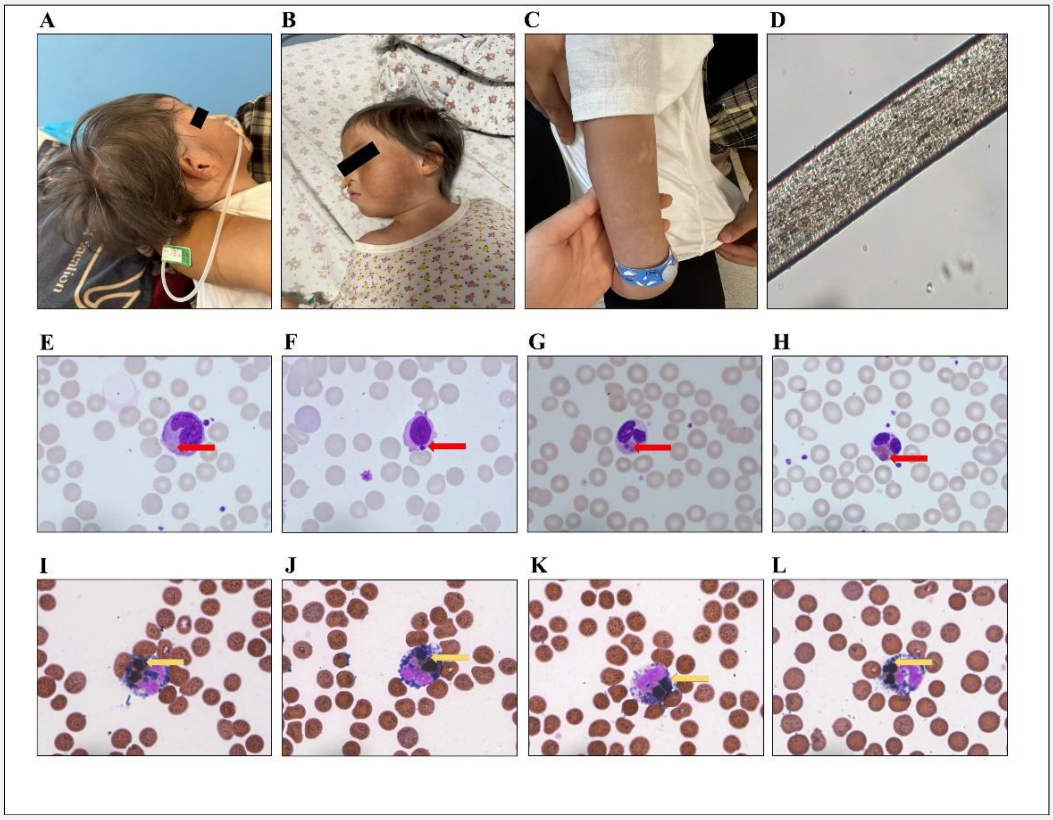

Figure 1. Clinical characteristics and peripheral blood morphology (original magnification x 1,000) in patients with Chediak-Higashi syndrome.

(A) The patient presents with light or silvery hair, which may have a metallic sheen; (B) the patient has facial pigmentation; (C) the patient has scattered milky-café au lait spots on the extremities; and (D) under light microscopy, aggregates of pigment are seen in the hair shafts. Rachel's staining of peripheral blood smear shows one to several abnormal purplish-red or bluish-purple granules (red arrows) in the cytoplasm of some WBCs, (E) monocytes, (F) lymphocytes, (G) neutrophils, and (H) eosinophils. Peroxidase staining of peripheral blood smear: peroxidase-positive large brown granules (yellow arrows) in neutrophils Figure I - L.

DISCUSSION

CHS presents a complex clinical picture with significant morbidity and mortality. The rarity of the condition contributes to delayed diagnosis and challenges in management. In this Case, despite the manifestation of characteristic symptoms, the diagnosis was delayed for more than a month as the condition was initially treated as an unexplained infection. The accurate identification of CHS was ultimately achieved by an experienced laboratory technician through the analysis of PBS. The PBS is a simple, cost-effective, and accessible diagnostic tool that is crucial for recognizing the characteristic morphological granules indicative of CHS [5], which can help to rapidly diagnose the patient as illustrated in this case.

Our case, along with the literature review, underscores the importance of heightened clinical vigilance, early diagnosis, and prompt initiation of therapy, which can significantly impact patient outcomes in CHS. Currently, the treatment of CHS mainly focuses on three aspects: supportive management of disease-related complications, treatment for the "accelerated phase" or hemophagocytic lymphohistiocytosis (HLH), and HSCT [8]. The most effective treatment method is HSCT, but it does not address the progressive neurological damage that CHS patients may experience [8,9]. Research has indicated that the protein encoded by LYST is a lysosomal trafficking regulator, and the main cellular defect in CHS is the disturbance in the biogenesis of lysosomes and LROs, ultimately leading to mislocalization of membrane proteins across the trans-Golgi network, endosomes, lysosomes, and the plasma membrane. Therefore, gene therapy and immunotherapy centered around

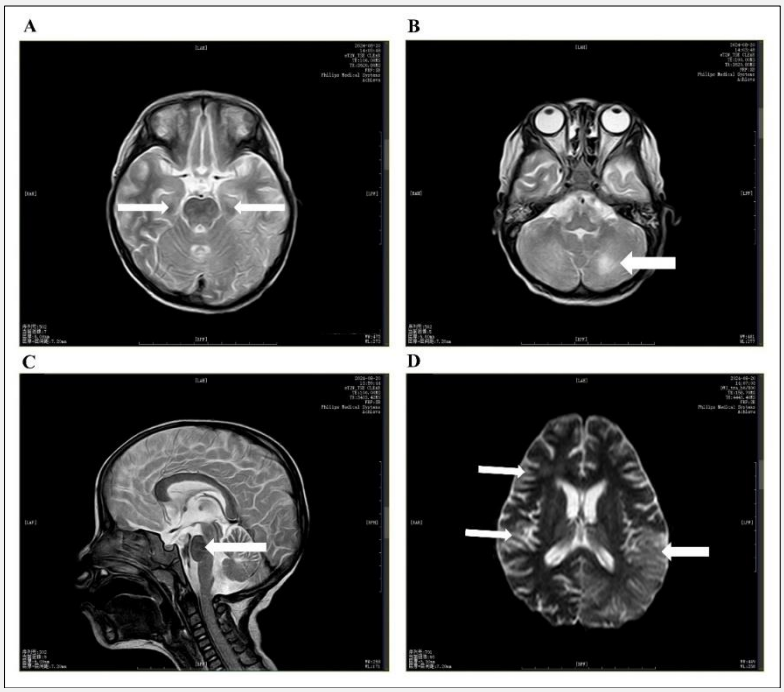

Figure 2. Clinical ancillary findings in patients with Chedik-Higashi syndrome.

(A) Abnormal signal shadows in the cerebellar hemispheres, (B) hippocampus, and (C) brainstem (D) DWI cerebral edema manifestation.

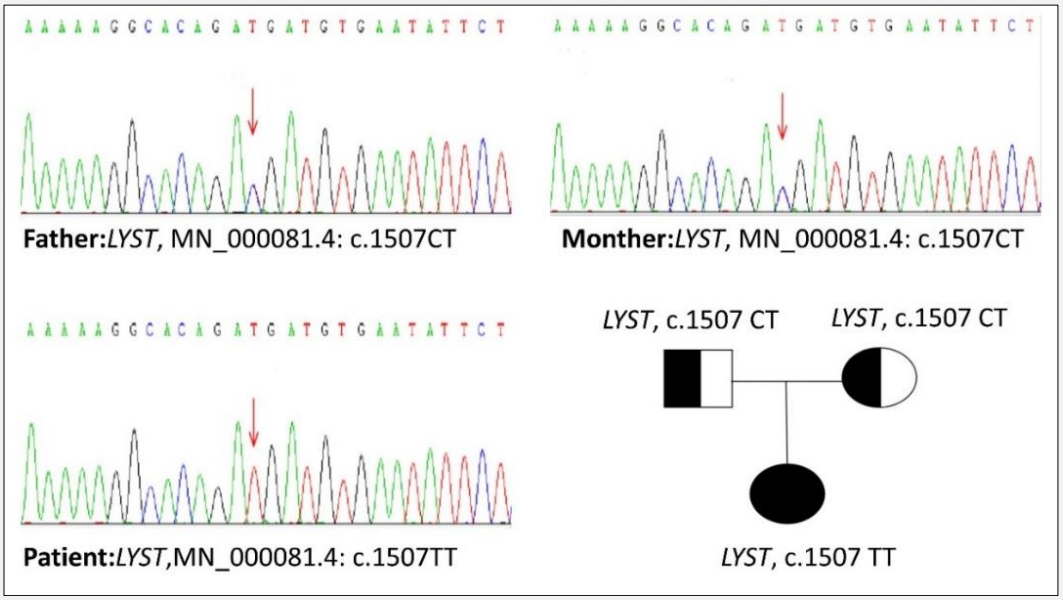

Figure 3. High-throughput sequencing (NGS) test reported that the patient's peripheral blood DNA had a pure nonsense mutation (c.1507C>T / p.Arg503) located on exon 5 (53 exons in total) of the *LYST* (NM_000081.4) gene.

Heterozygous carriage of this variant was detected in both parents and the family line.

the LYST gene are currently trending research directions [4,10].

Chediak-Higashi Syndrome is a multisystem disorder requiring a multidisciplinary approach to management. Additionally, the genetic heterogeneity of CHS demands a comprehensive genetic evaluation and family counseling for accurate diagnosis. Advances in genetic diagnosis and therapeutic options offer hope for improved outcomes. Further research is warranted to elucidate the molecular mechanisms of LYST and develop more economical and efficient therapies.

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Data Availability Statement:
The original data for this study are available from the corresponding authors upon reasonable request.

Human Ethics and Consent to Participate:
The study was approved by the Medical Ethics Committee of Maternal and Child Health Hospital of Guangxi Zhuang Autonomous Region. Informed consent was obtained from the parents of the child patient.

Declaration of Interest:
All authors declare no conflicts of interest.

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http://supplementary.clin-lab-publications.com/250224/