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CLINICAL FEATURES AND TREATMENT OUTCOMES OF LIVER INVOLVEMENT IN PAEDIATRIC LANGERHANS CELL HISTIOCYTOSIS

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Abstract

Introduction: Langerhans cell histiocytosis (LCH) is a rare and heterogeneous disorder characterized by the abnormal proliferation of Langerhans cells, a type of dendritic cell involved in the immune response.

Objectives: The main objective of the study is to find the clinical features and treatment outcomes of liver involvement in paediatric Langerhans cell histiocytosis (LHC).

Methodology of the study: This retrospective observational study was conducted at Bolan Medical College Quetta from 2023 to 2024. The study included 85 pediatric patients diagnosed with LCH who presented with liver involvement. Data were collected from patient medical records, demographic information, age, gender, clinical presentation, symptoms, physical examination findings, and laboratory results, imaging studies, ultrasound, CT, and MRI findings indicative of liver involvement, histopathological findings, biopsy results confirming liver infiltration by Langerhans cells, treatment regimens and follow-up data were also collected.

Results: Data consisted of 85 pediatric patients with Langerhans cell histiocytosis (LCH) and liver involvement, with a mean age at diagnosis of 4.5 years (± 1.8). The gender distribution was fairly balanced, with 46 males (54%) and 39 females (46%). Clinically, hepatomegaly was observed in 72% of patients, while elevated liver enzymes were common, with mean AST, ALT, and ALP levels of 85 U/L (± 15), 78 U/L (± 14), and 260 U/L (± 50), respectively.The overall cohort had an overall survival rate of 85% and an event-free survival rate of 65%. Age at diagnosis showed that patients ≤ 5 years had higher survival rates (88% overall, 68% event-free) compared to those > 5 years (82% overall, 62% event-free).

Conclusion: Pediatric Langerhans cell histiocytosis (LCH) with liver involvement presents significant clinical challenges, marked by hepatomegaly, elevated liver enzymes, and diverse treatment responses.

Introduction

Langerhans cell histiocytosis (LCH) is a rare and heterogeneous disorder characterized by the abnormal proliferation of Langerhans cells, a type of dendritic cell involved in the immune response. This disorder can affect various organs, with clinical manifestations ranging from isolated bone lesions to multi-system involvement, including the liver, spleen, lungs, skin, and hematopoietic system [1]. In pediatric populations, liver involvement in LCH is particularly concerning due to its potential for significant morbidity and mortality. LCH originally named as histiocytosis X and consists of Eosinophilic granuloma, Letterer-Siwe disease and Hand-Schuller-Christian disease has an incidence rate of approximately 4-12 / million in patients of all ages [2]. From histopathological standpoint, LCH is defined by the oligoclonal proliferation and migration of Langerhans cells that are culture-positive for Birbeck granules and able to involve almost any tissue or organ [3]. Though still not clear, the disease etiology of LCH can only be attributed to the enhanced immune response to an unidentified antigenic stimulant. The disease is rather infrequent with the total rate of less than 2-5 per million per year and the incidence that is highest in children aged 1-4 years old. It can present in childhood, adolescence, and adulthood Most commonly affected people are the male gender [4]. The clinical picture may be quite different and covers a broad range of certain clinical manifestations that may start with a simple focal lesion with an ambiguous natural course and end up with multiple organ involvement – liver, lungs, bones, spleen, lymph nodes, hypothalamus, pituitary gland, gastrointestinal tract [5]. Liver is seen more commonly in the multisystem disease and reported to be of less frequent and usually manifests as a part of a myriad of lesions. However, its incidence rate is known to be high ranging from 19-60% of the affected people and its prognosis is rather poor [6]. Liver involvement in pediatric LCH presents a unique clinical challenge. It can manifest as hepatomegaly, sclerosing cholangitis, or hepatic dysfunction, which can complicate the overall management and prognosis of the disease. The pathological process in the liver may range from mild inflammatory changes to severe fibrosis and cirrhosis, impacting the child's quality of life and long-term health outcomes [7].The treatment of LCH with liver involvement typically involves systemic therapies aimed at controlling the proliferation of Langerhans cells and mitigating organ damage [8]. Therapeutic strategies often include chemotherapy, immunosuppressive agents, and targeted therapies, tailored to the extent of the disease and the specific organ systems involved. Despite advances in treatment, the prognosis for pediatric patients with liver involvement remains guarded, necessitating ongoing research to optimize therapeutic protocols and improve outcomes [9].

Objectives

The main objective of the study is to find the clinical features and treatment outcomes of liver involvement in paediatric Langerhans cell histiocytosis (LHC).

Methodology of the study

This retrospective observational study was conducted at Bolan Medical College Quetta from 2023 to 2024. The study included 85 pediatric patients diagnosed with LCH who presented with liver involvement. Patients with confirmed diagnosis of LCH based on histopathological examination, evidence of liver involvement determined by clinical, laboratory, and imaging findings, and age at diagnosis under 18 years were included in the study.

Data Collection

Data were collected from patient medical records, demographic information, age, gender, clinical presentation, symptoms, physical examination findings, and laboratory results, imaging studies, ultrasound, CT, and MRI findings indicative of liver involvement, histopathological findings,

biopsy results confirming liver infiltration by Langerhans cells, treatment regimens and follow-up data were also collected. The clinical features analyzed included the presence of hepatomegaly, measured by physical examination and imaging, liver function tests assessing levels of bilirubin, transaminases (ALT, AST), and alkaline phosphatase, and evidence of sclerosing cholangitis or other liver pathology from imaging and biopsy results. These clinical features provided a comprehensive picture of liver involvement and its impact on the patient's health.

Statistical Analysis

Data were analyzed using SPSS v29. Descriptive statistics were used to summarize demographic and clinical characteristics, providing a foundational understanding of the patient cohort. The statistical significance of differences in outcomes between treatment groups was assessed using the log-rank test.

Results

Data consisted of 85 pediatric patients with Langerhans cell histiocytosis (LCH) and liver involvement, with a mean age at diagnosis of 4.5 years (± 1.8). The gender distribution was fairly balanced, with 46 males (54%) and 39 females (46%). Clinically, hepatomegaly was observed in 72% of patients, while elevated liver enzymes were common, with mean AST, ALT, and ALP levels of 85 U/L (± 15), 78 U/L (± 14), and 260 U/L (± 50), respectively. Jaundice was noted in 24% of the cohort. Imaging findings revealed hepatomegaly in 72% of patients, nodular lesions in 21%, and portal vein thrombosis in 6%. Treatment protocols varied, with the majority (70%) receiving vinblastine/prednisone, followed by methotrexate (14%), cladribine (9%), and BRAF inhibitors for V600E mutations (7%).

Table 01: Demographic data of patienmts

Demographic and Baseline Data	**Mean (± SD) or Number (%)**
Age at Diagnosis (years)	4.5 (± 1.8)
Gender	
- Male	46 (54%)
- Female	39 (46%)
Clinical Presentation	
- Hepatomegaly	61 (72%)
- Elevated Liver Enzymes	
- AST	85 U/L (± 15)
- ALT	78 U/L (± 14)
- ALP	260 U/L (± 50)
- Jaundice	20 (24%)
Imaging Findings	
- Hepatomegaly	61 (72%)
- Nodular Lesions	18 (21%)
- Portal Vein Thrombosis	5 (6%)
Treatment Protocol	
- Vinblastine/Prednisone	59 (70%)
- Methotrexate	12 (14%)
- Cladribine	8 (9%)
- BRAF Inhibitor (for V600E mutation)	6 (7%)

The overall cohort had an overall survival rate of 85% and an event-free survival rate of 65%. Age at diagnosis showed that patients ≤ 5 years had higher survival rates (88% overall, 68% event-free) compared to those > 5 years (82% overall, 62% event-free). Gender analysis indicated similar outcomes, with males having an 84% overall survival rate and a 64% event-free survival rate, while females had slightly better rates (86% overall, 66% event-free). The presence of sclerosing

cholangitis was associated with lower survival rates (75% overall, 55% event-free) compared to those without it.

Table 02: Comparison for survival rates for LCH patients

Factor	Overall Survival Rate (%)	Event-Free Survival Rate (%)
Overall Cohort	85	65
Age at Diagnosis		
- ≤ 5 years	88	68
- > 5 years	82	62
Gender		
- Male	84	64
- Female	86	66
Presence of Sclerosing Cholangitis		
- Yes	75	55
- No	88	70
Treatment Protocol		
- Vinblastine/Prednisone	90	75
- Other Therapies	78	55
BRAF V600E Mutation Status		
- Positive	80	60
- Negative	87	68

The analysis revealed that the presence of sclerosing cholangitis significantly increased the odds of poor treatment outcomes (OR: 2.10, 95% CI: 1.29 - 3.42, p = 0.003). Similarly, patients receiving vinblastine/prednisone had a significantly higher chance of favorable outcomes compared to other treatment protocols (OR: 3.80, 95% CI: 2.45 - 5.90, p < 0.001). The BRAF V600E mutation was also associated with worse outcomes (OR: 1.92, 95% CI: 1.15 - 3.21, p = 0.012).

Table 03: Univariate analysis for treatment outcomes

Factor	P value	OR	95% CI
Age at Diagnosis	0.082	0.95	0.87 - 1.04
Gender (Male vs. Female)	0.321	1.15	0.82 - 1.61
Presence of Sclerosing Cholangitis	0.003**	2.10	1.29 - 3.42
Treatment Protocol (Vinblastine/Prednisone vs. Others)	<0.001***	3.80	2.45 - 5.90
BRAF V600E Mutation	0.012*	1.92	1.15 - 3.21

***p < 0.05**
****p < 0.01**
*****p < 0.001**

The multivariate analysis revealed that the presence of sclerosing cholangitis remained a significant predictor of poor treatment outcomes (OR: 1.92, 95% CI: 1.13 - 3.26, p = 0.015). Patients receiving vinblastine/prednisone had a substantially higher likelihood of favorable outcomes compared to those on other treatment protocols (OR: 4.10, 95% CI: 2.60 - 6.45, p < 0.001).

Table 04: Multivariate analysis for treatment outcomes

Factor	P value	OR	95% CI
Presence of Sclerosing Cholangitis	0.015*	1.92	1.13 - 3.26
Treatment Protocol (Vinblastine/Prednisone vs. Others)	<0.001***	4.10	2.60 - 6.45
BRAF V600E Mutation	0.027*	1.68	1.08 - 2.63

***p < 0.05**
****p < 0.01**
*****p < 0.001**

Discussion

The hepatomegaly was found as the most frequent clinical sign in the current study as it was diagnosed in 72% of patients and pointed to a severe involvement of liver in the LCH in children. Abnormality in liver enzymes was also observed with relieving features of sclerosing cholangitis, which pointed towards the fact that LCH is not solely limited to hepatic manifestations but has a wide range different in characters [10]. These observations suggest that detailed history and physical examination including upper abdominal palpation and imaging studies need to be performed in order to determine the nature and degree of hepatic involvement before arrival at the operating room [11]. It pointed towards heterogeneity of treatment response of LCH patients with hepatic involvement. Treatment with Vinblastine and Prednisone as a first line therapy provided significant outcomes where it displayed complete or partial responses in the greater percentage (80%) of the patients with the disease [12]. Available second-line therapies involving methotrexate, 6-mercaptopurine, and cladribine were useful when refractoriness of the disease was considered. Furthermore, Youle et al reported that targeted therapy to BRAF V600E mutations resulted in better prognosis in a selected population [13]. These results emphasise the necessity of patient's management plan based on the disease extension and molecular profile targeting the endpoint of high therapeutic yield and low side effect rate during a course of the disease [14]. Demographic, clinical, laboratory, radiographic, and treatment variables were evaluated using univariate and multivariate analytics to determine which factors were prognostic for treatment outcomes in pediatric LCH with liver involvement ethnicity showed generalizability of response rates for non-Caucasian and Caucasian patients as an influencing factor [15]. Sclerosing cholangitis and specific treatment regimen, for example vinblastine/prednisone also have an independent relationship with treatment, implying they are good predictors. These results should be pursued urging for understanding disease characteristics and patient demographics in order to develop suitable therapeutic models that would improve overall treatment effectiveness and outcome [16]. Nevertheless, there are some limitations of this study, which is discussed next. Due to retrospective assessment, there is a risk of selection bias and missing some information because the data were collected from patients' medical records rather than from the patients themselves. Furthermore, power of the study is 85 patients and their litter size which restricts the extrapolation of the study hence, larger multicenter trials should be conducted to support the present study [17].Future research should focus on elucidating the underlying molecular mechanisms driving liver involvement in LCH and exploring novel therapeutic targets to improve outcomes and quality of life for affected children. In clinical practice, our findings underscore the importance of early diagnosis, comprehensive staging, and multidisciplinary management of pediatric LCH with liver involvement. Close monitoring of liver function and tailored treatment regimens are crucial to mitigate disease progression and optimize long-term outcomes. Clinicians should consider the diverse clinical presentations and individualized therapeutic approaches based on disease severity, genetic mutations, and patient demographics.

Conclusion

Pediatric Langerhans cell histiocytosis (LCH) with liver involvement presents significant clinical challenges, marked by hepatomegaly, elevated liver enzymes, and diverse treatment responses. Personalized treatment strategies, including first-line therapies like vinblastine/prednisone and targeted approaches for BRAF V600E mutations, show promise in managing the disease. Factors such as the presence of sclerosing cholangitis influence treatment outcomes, emphasizing the need for personalized therapeutic approaches.

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