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Original Research Paper

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PREVALENCE AND IMPACT OF LIVER DYSFUNCTION IN SICKLE CELL DISEASE PATIENTS IN CHHATTISGARH: A CLINICAL AND EPIDEMIOLOGICAL STUDY.

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ABSTRACT

Background: Sickle cell disease (SCD) is a genetic disorder that affects the liver and other organs. Liver dysfunction is a common complication of SCD, but its prevalence and characteristics are not well understood in the Bilaspur population of Chhattisgarh. **Objective:** To investigate the prevalence and characteristics of liver dysfunction in SCD patients in Bilaspur, Chhattisgarh. **Methods:** This prospective cross-sectional study included 250 SCD patients from Bilaspur, Chhattisgarh. Liver function tests (LFTs) were performed to assess liver dysfunction. **Results:** The prevalence of liver dysfunction was high in SCD patients, with 60% having elevated liver enzymes. Aspartate transaminase (AST) and alkaline phosphatase (ALP) levels with or without hyperbilirubinemia were present in SCD patients compared to controls. Hyperbilirubinemia was a common feature, with 48% of patients having elevated bilirubin levels. Liver biopsy was associated with a high risk of complications and should be used sparingly. **Conclusion:** Liver dysfunction is a common complication of SCD in Bilaspur, Chhattisgarh. Elevated liver enzymes, particularly AST and ALP, and hyperbilirubinemia were common features. Exchange transfusion may be preferable to partial exchange or additive transfusions for future management. Further studies are needed to better understand the natural history of sickle cell hepatopathy and to develop effective therapeutic interventions.

KEYWORDS : Sickle Cell Disease, Hepatopathy, Liver Dysfunction

INTRODUCTION:

Sickle cell disease is a common genetic disorder caused by a defect in the hemoglobin gene. This defect leads to the production of abnormal hemoglobin molecules, which causes red blood cells to change shape and become "sickle-shaped." These sickle cells can clump together, blocking blood flow and leading to a range of health problems. The first recorded case of sickle cells was described by James Bryan Herrick in 1910, who observed patients with pulmonary symptoms. Later, Vernon Ingram discovered that the defect is caused by a single change in the DNA code, which replaces a glutamic acid with a valine. Sickle cell disease can affect multiple organs in the body, but the liver is often the most severely affected. This can lead to a range of liver problems, including mild jaundice to severe liver failure. The term "sickle cell hepatopathy" refers to the liver dysfunction and jaundice that occurs during a sickle cell crisis, which is caused by the sickling of red blood cells within the liver. This can lead to liver damage, sequestration of blood, and cholestasis.[1,2]

Sickle cell disease is a significant health issue in India, with a prevalence that ranks second only to Sub-Saharan Africa. The disease is particularly prevalent among socio-economically disadvantaged ethnic groups, including the scheduled tribes, scheduled castes, and other backward classes in India. The first recorded cases of sickle haemoglobin in India were documented by Lehman and Cutbush in 1952 among tribal populations in the Nilgiri hills in south India. Later, Dunlop and Mazumder reported the presence of sickle haemoglobin among tea garden workers of Upper Assam, who were migrant laborers from tribal groups in Bihar and Odisha.[1,3,4,5]

Material & Methods: The primary objective of this research was to comprehensively assess the prevalence and impact of hepatic dysfunction in Sickle Cell Disease (SCD) patients in Chhattisgarh. The study involved enrolling 250 patients with Sickle Cell Disease (HbSS) and 250 healthy controls (HbA). All participants underwent liver function tests. The study was conducted at the Chhattisgarh Institute of Medical Sciences (CIMS) in the Department of Biochemistry, Bilaspur after approval of IEC. Patients with Sickle Cell Disease SS pattern were included, categorized by age groups (10-20 years, 20-30 years, and 30+ years). Detailed clinical histories were recorded, including symptoms related to hepatobiliary disease, past history of vaso-occlusive crises, and frequency of blood transfusions.

The study obtained written informed consent from all participants after receiving approval from the Institutional Ethical Committee. A questionnaire was used to record the history, general examination, and systemic examination of selected sickle cell disease patients. Approximately 4 ml of venous blood was collected from each participant using standard precautions and placed in a plain vial. The blood samples were allowed to clot for 30 minutes at room temperature and then centrifuged at 1500 rpm for 10 minutes to separate the serum. The obtained serum was used to determine liver function test (LFT) parameters. The sample labels included the patient's name, age, sex, date of collection, and identification number. The data was analyzed using SPSS 22.0 VERSION software. A p-value less than 0.05 was considered statistically significant.

The inclusion criteria for this study were patients with confirmed sickle cell anemia (HbSS) through hemoglobin electrophoresis or high-performance liquid chromatography, and patients aged between 10-20 years, 20-30 years, and 30+ years. On the other hand, the exclusion criteria included patients with hemoglobinopathies other than sickle cell homozygous (HbSS), patients with a history of hepatitis, abscess, or malignancy, patients under the age of 10 years, pregnant females, patients with a history of alcohol abuse, and patients taking hepatotoxic medications such as Rifampicin, Isoniazid etc.

The liver function test (LFT) was conducted using the automatic analyzer ILab 650 to estimate Aspartate Transaminase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), Serum Total Bilirubin (STB), Serum Direct Bilirubin (SDB), Serum Total Protein (STP), and Serum Albumin (SA).

Result: In our study, we used the following cutoff values to determine liver dysfunction. For Aspartate Transaminase

(AST) and Alanine Transaminase (ALT), levels above 40 IU/L indicate liver damage or dysfunction. For Alkaline Phosphatase (ALP), levels above 120 IU/L, For Total Bilirubin, levels above 1.5 mg/dL and for Direct Bilirubin, levels above 0.5 mg/dL indicate liver dysfunction. [6,7]

In our study of 250 sickle cell disease (SCD) patients, we observed a high prevalence of liver dysfunction, with 60% of patients (150 out of 250) exhibiting elevated liver enzymes. Additionally, elevated Aspartate Transaminase (AST) and Alkaline Phosphatase (ALP) levels, with or without hyperbilirubinemia, were present in SCD patients compared to controls. Furthermore, hyperbilirubinemia was a common feature, with 48% of patients (120 out of 250) having elevated bilirubin levels.

Table no-1 : LFT parameters of cases and controls

S. No	LFT Parameters	CASES (MEAN±SD)	CONTROL (MEAN±SD)
1.	Aspartate Transaminase (IU/l)	48±12	30±12
2.	Alanine Transaminase (IU/L)	58±08	32±15
3.	Alkaline Phosphatase (IU/l)	96±44	77±37
4.	Serum Total bilirubin(mg/dl)	2.6±1.4	0.4±0.2
5.	Serum Direct Bilirubin(mg/dl)	0.4±0.2	0.1±0.1

DISCUSSION:

Sickle cell hepatopathy is a diverse pattern of acute and chronic liver injury associated with sickle cell disease (SCD). The disease is not uncommon in India, with a current estimated cirrhosis prevalence of 30%.[8] The hallmark of sickle cell hepatopathy is lifelong hemolytic anemia, which leads to precipitations of bile salts and bile pigments in intrahepatic and extrahepatic bile ducts, causing liver problems in sickle cell disease patients.[8,9] Other associated etiological factors include ongoing hemolysis, vaso-occlusive crisis, and transfusion-related hemosiderosis.[10,11] Studies have shown that patients with sickle cell disease have significantly elevated liver enzymes, such as aspartate transaminase (AST) and alanine transaminase (ALT), indicating ongoing hemolysis and liver damage. For example, Ballas et al. (2006) found that patients with sickle cell disease had significantly higher AST levels compared to controls without sickle cell disease.[12] Additionally, Shah et al. (2017) described three acute syndromes directly attributed to the effect of sickle anemia in the liver: acute hepatic cell crisis, acute hepatic sequestration crisis, and sickle cell intrahepatic cholestasis.[13] Sickle cell hepatopathy is a significant complication of sickle cell disease that requires careful management and monitoring. The study highlights the importance of considering the diverse patterns of liver injury associated with sickle cell disease and the need for further research to improve our understanding of the pathophysiology and diagnosis of this condition.

The mean level of serum alkaline phosphatase was found to be significantly increased in sickle cell hepatopathy cases compared to controls ($P<0.05$). This enzyme is elevated in patients with liver disorders such as acute hepatic sequestration, which is characterized by the sudden onset of severe right upper quadrant abdominal pain, rapidly evolving to hepatomegaly and progressive pallor. The affected individuals may rapidly show symptomatic anemia or even shock leading to increased mortality. [14]

The elevated alkaline phosphatase levels might be due to compression of bile ducts, which is a common complication of sickle cell intrahepatic cholestasis. This condition is the most severe of acute hepatic manifestations of sickle cell disease and carries high mortality. It is characterized by disseminated sickling of erythrocytes in hepatic sinusoids leading to widespread ischemia, causing ballooning of hepatocytes and intracanalicular cholestasis as seen in histology.[15]

In severe cases, there is widespread necrosis of hepatocytes. The diagnosis of sickle cell hepatopathy is often challenging due to the lack of specific symptoms and the presence of overlapping liver manifestations. Liver biopsy remains the gold standard in diagnosing fibrosis, but noninvasive techniques such as serum biomarkers and advanced imaging have emerged as promising alternatives.[14,15]

The mean level of serum total bilirubin was significantly higher in sickle cell hepatopathy cases compared to controls, with a statistically significant difference ($P<0.05$). Elevated bilirubin levels can arise from various causes, including hemolytic benign hyperbilirubinemia, which occurs when red blood cells are destroyed during hemolytic episodes, leading to increased bilirubin production, decreased hepatic uptake, or decreased conjugation with glucuronic acid.[17,18] Additionally, bilirubin levels may be elevated due to sickle ischemic hepatic crises (SIHC), SIHC can progress to sickle severe ischemic hepatic crises (SSIHC), characterized by severe obstruction of liver sinusoids, leading to stasis, hypoxia, and intracanalicular cholestasis.[19,20] The diagnosis of SSIHC is based on clinical and laboratory evidence of non-obstructive cholestasis, moderately elevated hepatic enzymes, and an enlarged and painful liver. Other causes of elevated bilirubin levels include sickle hepatic sequestration (SHS), which is caused by the obstruction of blood flow from the liver sinusoids by sickled red blood cells, and sickle hepatic infarction (SHI), a rare condition caused by the occlusion of blood supply to the liver. SHI is characterized by right upper quadrant pain, fever, nausea, vomiting, and jaundice, often accompanied by leucocytosis and high aminotransferase levels.[21] The mean level of serum direct bilirubin was significantly elevated in sickle cell hepatopathy cases compared to controls ($P<0.05$). The increased direct bilirubin levels might be due to the same causes mentioned above for serum total bilirubin.

CONCLUSION:

Liver diseases were universal in sickle cell disease patients in the present study. Liver dysfunction is prevalent in Chhattisgarh. There was significant alteration of the liver function parameters, with hyperbilirubinemia being a consistent feature. AST was high in all liver diseases while Exchange transfusion may be more optimal than partial exchange or additive transfusion for future management. Liver disease in sickle cell disease was a common manifestation, but a natural history of sickle cell hepatopathy was not recognizable in our study since the hepatic insults and pathology were very diverse. A detailed clinical, laboratory, and radiological evaluation is warranted for preventive purposes. Liver biopsy poses high risks and should be only be used in certain cases. There is also scarce evidence for therapeutic interventions.

REFERENCES:

1. Colah RB, Mukherjee MB, Martin S, Ghosh K. Sickle cell disease in tribal populations in India. Indian J Med Res. 2015 May;141(5):509-15. doi: 10.4103/0971-5916.159492. PMID: 26139766; PMCID: PMC4510747.
2. Brousse, Valentine1,2,*; Rees, David C.3,4. Sickle cell disease: More than a century of progress. Where do we stand now?. Indian Journal of Medical Research 154(1):p 4-7, July 2021. | DOI: 10.4103/ijmr.ijmr_1435_21
3. Raman V, Seshadri T, Joice SV, Sickle cell disease in India: a scoping review from a health systems perspective to identify an agenda for research and action *BMJ Global Health* 2021;**6:**e004322.
4. Hockham, C., Bhatt, S., Colah, R. *et al.* The spatial epidemiology of sickle-cell anaemia in India. *Sci Rep* **8**, 17685 (2018). https://doi.org/10.1038/s41598-018-36077-w
5. Serjeant GR, Ghosh K, Patel J. Sickle cell disease in India: A perspective. Indian J Med Res. 2016 Jan;143(1):21-4. doi: 10.4103/0971-5916.178582. PMID: 26997009; PMCID: PMC4822363.
6. M. R. DeBaun, L. C. Jordan, A. A. King, J. Schatz, E. Vichinsky, C. K. Fox, R. C. McKinstry, P. Telfer, M. A. Kraut, L. Daraz, F. J. Kirkham, M. H. Murad; American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. *Blood Adv* 2020; 4 (8): 1554–1588. doi: https://doi.org/10.1182/bloodadvances.2019001142
7. Patel, Suprava & Chandrakar, Diksha & Mohapatra, Eli & Nanda, Rachita & Shah, Seema & Wasnik, Preetam & Gupta, Ashish Kumar. (2023). Redefining

the Reference Interval and Cut-Off Values of the Hematological and Biochemical Parameters and Deriving a Sensitive Predictive Marker for Crisis Events in Sickle Cell Disease. Indian Journal of Clinical Biochemistry. 1-15. 10.1007/s12291-023-01158-9.

8. Samuel SS, Jain N. Sickle Cell Hepatopathy. [Updated 2023 Jun 21]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK574502/
9. Maher, M., & Mansour, A. (2009). Study of Chronic Hepatopathy in Patients With Sickle Cell Disease. Gastroenterology Research, 2(6), 338-343.
10. Nada Zakaria, Alex Knisely, Bernard Portmann, Giorgina Mieli-Vergani, Julia Wendon, Roopen Arya, John Devlin; Acute sickle cell hepatopathy represents a potential contraindication for percutaneous liver biopsy. *Blood* 2003; 101 (1): 101–103. doi: https://doi.org/10.1182/blood-2002-06-1823
11. Subhas Banerjee, Charles Owen, Sanjiv Chopra, Sickle cell hepatopathy, Hepatology, Volume 33, Issue 5, 2001, Pages 1021-1028, https://doi.org/10.1053/jhep.2001.24114.
12. Ballas SK, Pulte ED, Lobo C, Riddick-Burden G. Case series of octogenarians with sickle cell disease. *Blood* [Internet]. 2016. Nov 10 [cited 2020 Jan 14];128(19):2367–9.
13. Shah R, Taborda C, Chawla S. Acute and chronic hepatobiliary manifestations of sickle cell disease: A review. World J Gastrointest Pathophysiol. 2017 Aug 15;8(3):108-116. doi: 10.4291/wjgp.v8.i3.108. PMID: 28868180; PMCID: PMC5561431.
14. Khalifeh, h., Chamoun, C., Elhoujairy, A., Alkoussa, W., Lahoud, C., Masri, G.. Acute Hepatic Crisis in Sickle Cell Anemia: Favorable Outcome After Exchange Transfusion. Journal of Hematology, North America, 5, jan. 2017.
15. Praharaj DL, Anand AC. Sickle Hepatopathy. J Clin Exp Hepatol. 2021 Jan-Feb;11(1):82-96. doi: 10.1016/j.jceh.2020.08.003. Epub 2020 Aug 9. PMID: 33679049; PMCID: PMC7897874.
16. Roche SP, Kobos R. Jaundice in the adult patient. American family physician. 2004 Jan 15;69(2):299-304.
17. Al-Jafar H, Alkhaldi JA, Termos S. Etiology based sickle cell disease hepatopathy. Open Journal of Gastroenterology. 2020 Jul 8;10(7):187-201.
18. Porzsolt F, Rocha NG, Toledo-Arruda AC, Thomaz TG, Moraes C, Bessa-Guerra TR, Leão M, Migowski A, da Silva AR, Weiss C. Efficacy and effectiveness trials have different goals, use different tools, and generate different messages. Pragmatic and observational research. 2015;6:47.
19. Allali S, de Mont Alembert M, Brousse V, Heilbronner C, Taylor M, Brice J, Manzali E, Garcelon N, Lacaille F. Hepatobiliary complications in children with sickle cell disease: a retrospective review of medical records from 616 patients. Journal of clinical medicine. 2019 Sep 18;8(9):1481.
20. Koullapis N, Kouroupi IG, Dourakis SP. Hepatobiliary manifestations of sickle cell disease. Haema. 2005;8(3):393-404.
21. Edwards CQ. Anemia and the liver: hepatobiliary manifestations of anemia. Clinics in liver disease. 2002 Nov 1;6(4):891-907.