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PAEDIATRIC SICKLE CELL DISEASE: HISTOPATHOLOGICAL IMPACT ON ORGAN SYSTEMS AND PHYSIOLOGICAL MARKERS OF DISEASE SEVERITY AND ITS TREATMENT.

Dr Muhammad Tariq Hamayun Khan[1], Dr Asma Shah[2*], Aliza Ali khan[3], Dr Muhammad Arif Jan[4], Dr Hina Umair[5], Dr Tania Khattak[6]

[1]Assistant Professor, Department of Hematology, Pathology Department, Burns & Plastic Surgery Center Hayatabad, Peshawar, Pakistan
[2*]Lecturer, Department of Pathology (Hematology), Women Medical College, Abbottabad, Pakistan
[3]Lecturer, Department of Pharmacy, Qurtuba University, Dera Ismail Khan, Pakistan
[4]Junior Registrar, Department of Pediatrics Medicine, Saidu Group of Teaching Hospital, Swat, Pakistan
[5]Assistant Professor, Department of Physiology, Wah Medical College, NUMS, Wah Cantt, Pakistan
[6]Assistant Professor, Department of Pathology (Histopathology), Nowshera Medical College, Nowshera, Pakistan

***Corresponding Author's:** Dr Asma Shah,
*Lecturer, Department Of Pathology (Hematology), Women Medical College, Abbottabad, Pakistan
Email**:** Asmashah0332@Gmail.Com

ABSTRACT

Background

To evaluate histopathological organ involvement and associated physiological markers in children with SCD, and to assess treatment patterns and clinical response.

Methods

A cross-sectional study was conducted at the Burns and Plastic Surgery Centre, Hayatabad, from January 2023 to January 2024, including 73 children with confirmed SCD. Demographic, clinical, histopathological, and laboratory data were recorded. Statistical analysis was performed using SPSS version 26, with $p<0.05$ considered significant.

Results

The 5–10 years age group was the most affected (43.8%), with a male predominance (56.2%). Splenic fibrosis/autosplenectomy (57.5%), hepatic congestion with hemosiderosis (52.1%), and bone marrow erythroid hyperplasia (74.0%) were common histopathological findings. Laboratory results showed low hemoglobin (7.9 ± 1.2 g/dL), high reticulocyte counts (6.2 ± 1.5%), elevated LDH (680 ± 105 U/L), and hyperbilirubinemia (3.1 ± 0.9 mg/dL). Hydroxyurea was prescribed to 71.2% of patients, with a good clinical response in 67.1%.

Conclusion

Paediatric SCD in our cohort was characterized by early and significant multi-organ pathology, pronounced hemolytic markers, and favorable outcomes in patients receiving hydroxyurea. These findings highlight the importance of early diagnosis, comprehensive monitoring, and access to disease-modifying therapy.

Keywords: Sickle cell disease, Pediatrics, Histopathology, Organ damage, Hemolysis, Hydroxyurea, Hemoglobinopathy

INTRODUCTION

Sickle cell disease (SCD) is among the most prevalent inherited hemoglobin disorders worldwide, affecting millions, with a particularly high burden in sub-Saharan Africa, the Middle East, and parts of South Asia. It is caused by a point mutation in the β-globin gene, leading to the production of abnormal hemoglobin S, which polymerizes under deoxygenated conditions, causing red blood cell deformation, hemolysis, and recurrent vaso-occlusion. These events result in chronic anemia, painful crises, and progressive damage to multiple organ systems [1-3].

In children, the disease course can be particularly aggressive. Early onset of splenic dysfunction, hepatobiliary involvement, pulmonary complications, and bone marrow hyperplasia are well-documented sequelae. The extent and severity of organ damage are influenced by genotype, environmental triggers, infection risk, and treatment accessibility. Laboratory markers such as low hemoglobin, high reticulocyte count, elevated lactate dehydrogenase (LDH), and hyperbilirubinemia are reflective of ongoing hemolysis and correlate with disease severity [4-6].

Histopathological evaluation remains a crucial tool in understanding the extent of organ involvement in SCD. Spleen pathology, including autosplenectomy, occurs early in life, while chronic liver congestion, renal microvascular injury, and marrow hyperplasia are common in advanced stages. Paediatric cohorts offer unique insight into early disease patterns, enabling more effective preventive and therapeutic strategies [7-9].

Hydroxyurea remains the cornerstone of disease-modifying therapy, increasing fetal hemoglobin levels, reducing vaso-occlusive crises, and mitigating long-term organ damage. However, in many resource-limited settings, delayed diagnosis, limited access to treatment, and inadequate follow-up hinder optimal outcomes [10, 11].

This study aims to characterize histopathological organ changes in children with SCD, relate them to physiological and laboratory markers, and evaluate treatment patterns and response in a regional cohort. By correlating structural and functional parameters, our findings can contribute to more individualized, timely, and effective management of paediatric SCD.

METHODOLOGY

This study was designed as a descriptive cross-sectional analysis and conducted over a period of twelve months, from January 2023 to January 2024, at the Burns and Plastic Surgery Centre, Hayatabad. The aim was to evaluate histopathological changes in various organ systems, along with physiological and laboratory markers, in children diagnosed with sickle cell disease (SCD).

A total of 73 paediatric patients with a confirmed diagnosis of SCD were included. The sample size was calculated based on regional prevalence estimates and available patient load at the centre during the study period, ensuring adequate statistical power. Patients were selected using a consecutive non-probability sampling method until the required sample size was achieved. The study protocol was reviewed and approved by the Institutional Ethical Review Committee of the Burns and Plastic Surgery Centre, Hayatabad. All procedures were conducted in accordance with the Declaration of Helsinki. Confidentiality of patient data was maintained at every stage, and all histopathological specimens were handled in compliance with institutional biosafety guidelines.

Inclusion criteria:

- Children aged between 1 and 14 years
- Confirmed diagnosis of SCD based on hemoglobin electrophoresis
- Patients attending the Burns and Plastic Surgery Centre for routine follow-up or evaluation of systemic complications
- Consent from parents or guardians for participation and access to medical records

Exclusion criteria:

- Children with other hemoglobinopathies (e.g., thalassemia)
- Patients with acute infections at the time of assessment
- Incomplete clinical or laboratory data
- Declined consent for histopathological review

After obtaining informed written consent from parents or guardians, detailed demographic and clinical information was recorded on a structured proforma. This included age, sex, place of residence, family history, age at diagnosis, frequency of vaso-occlusive crises, history of acute chest syndrome, stroke, and hospital admissions. Treatment history, including hydroxyurea use, transfusion history, and adherence patterns, was also documented.

Histopathological findings were extracted from biopsy, surgical, or autopsy reports available in patient files, complemented by fresh evaluations where clinically indicated. Organ-specific pathological features were noted for the spleen, liver, kidney, lungs, bone marrow, and other involved systems.

Physiological and laboratory markers, including hemoglobin, hematocrit, reticulocyte count, lactate dehydrogenase (LDH), bilirubin levels, serum creatinine, oxygen saturation, and relevant imaging or pulmonary function parameters, were recorded from the most recent and reliable investigations.

All available histopathological slides were reviewed by an experienced histopathologist who was blinded to the patients' clinical severity scores. Standard staining techniques, including hematoxylin and eosin, were used. Additional special stains were applied where necessary (e.g., Masson's trichrome for fibrosis, Prussian blue for iron deposition).

Data were entered and analyzed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the chi-square test for categorical variables and independent-sample t-test for continuous variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

In the present study of 73 children with Sickle Cell Disease (SCD), the majority were in the 5–10 years age group (43.8%), followed by those under 5 years (28.8%) and over 10 years (27.4%). The age distribution was statistically significant (p=0.041), suggesting a higher clustering of cases in middle childhood. Males constituted 56.2% of the sample, with females representing 43.8%, although this difference was not statistically significant (p=0.327). A slightly higher proportion of patients resided in urban areas (60.3%) compared to rural areas (39.7%), without a significant association (p=0.118). More than half of the patients (53.4%) had a positive family history of SCD, which showed a significant association (p=0.009), indicating potential genetic clustering within families.

Table 1: Demographic Characteristics of Children with Sickle Cell Disease (n = 73)

Variable	Category	Frequency (n)	Percentage (%)	p-value
Age group	<5 years	21	28.8	0.041*
	5–10 years	32	43.8	
	>10 years	20	27.4	
Sex	Male	41	56.2	0.327
	Female	32	43.8	
Ethnic background	Urban	44	60.3	0.118
	Rural	29	39.7	
Family history of SCD	Yes	39	53.4	0.009**
	No	34	46.6	

A substantial proportion of children were diagnosed before the age of 5 years, with 38.4% diagnosed before 2 years and 41.1% between 2–5 years, showing statistical significance (p=0.033). The majority (60.3%) experienced more than three vaso-occlusive crises annually, a difference that was highly significant (p=0.001), highlighting the severe disease burden in this population. Acute chest syndrome was reported in 34.2% of patients and was significantly associated with disease severity (p=0.046). Stroke history was less common (15.1%) and did not reach statistical significance (p=0.077).

Table 2: Clinical Profile and Disease History

Variable	Category	Frequency (n)	Percentage (%)	p-value
Age at diagnosis	<2 years	28	38.4	0.033*
	2–5 years	30	41.1	
	>5 years	15	20.5	
Vaso-occlusive crises/year	≤3	29	39.7	0.001**
	>3	44	60.3	
History of acute chest syndrome	Yes	25	34.2	0.046*
	No	48	65.8	
Stroke history	Yes	11	15.1	0.077
	No	62	84.9	

Histopathological assessment revealed that splenic fibrosis or autosplenectomy was the most common finding (57.5%), with a highly significant association (p=0.002). Liver changes, predominantly sinusoidal congestion and hemosiderosis, were observed in 52.1% (p=0.019). Bone marrow examination showed erythroid hyperplasia in 74% of cases, also highly significant (p=0.001). Renal lesions such as glomerulosclerosis and papillary necrosis were present in 28.8%, while pulmonary infarcts or fibrosis were noted in 26%, neither reaching statistical significance.

Table 3: Histopathological Organ Findings

Organ	Common Pathological Finding	Frequency (n)	Percentage (%)	p-value
Spleen	Fibrosis / autosplenectomy	42	57.5	0.002**
Liver	Sinusoidal congestion, hemosiderosis	38	52.1	0.019*
Kidney	Glomerulosclerosis, papillary necrosis	21	28.8	0.084
Lungs	Pulmonary fibrosis / infarcts	19	26.0	0.062
Bone marrow	Erythroid hyperplasia	54	74.0	0.001**

Mean hemoglobin was markedly reduced at 7.9 ± 1.2 g/dL, significantly below the reference range (p=0.001). Similarly, hematocrit values were low (24.8 ± 3.5%), while reticulocyte counts were elevated (6.2 ± 1.5%), both highly significant (p=0.001). LDH levels were markedly raised (680 ± 105 U/L), indicating ongoing hemolysis (p=0.001). Total bilirubin averaged 3.1 ± 0.9 mg/dL, also significantly elevated (p=0.001). Oxygen saturation was slightly reduced (91.4 ± 3.8%), showing a mild but significant difference (p=0.023).

Table 4: Laboratory and Physiological Markers

Parameter	Mean ± SD	Reference Range	p-value
Hemoglobin (g/dL)	7.9 ± 1.2	11–14	0.001**
Hematocrit (%)	24.8 ± 3.5	33–45	0.001**
Reticulocyte count (%)	6.2 ± 1.5	0.5–1.5	0.001**
LDH (U/L)	680 ± 105	<250	0.001**
Total bilirubin (mg/dL)	3.1 ± 0.9	0.3–1.2	0.001**
Oxygen saturation (%)	91.4 ± 3.8	>95	0.023*

Hydroxyurea therapy was used by 71.2% of the children, with a highly significant association (p=0.004), suggesting its central role in disease management. Chronic transfusion programs were less common (23.3%) and did not reach statistical significance (p=0.062). Two-thirds (67.1%) of patients showed a good clinical response to treatment, a finding that was statistically significant (p=0.013), indicating effective disease control in a majority of cases.

Table 5: Treatment Patterns and Response

Variable	Category	Frequency (n)	Percentage (%)	p-value
Hydroxyurea use	Yes	52	71.2	0.004**
	No	21	28.8	
Chronic transfusion	Yes	17	23.3	0.062
	No	56	76.7	
Response to treatment	Good	49	67.1	0.013*
	Partial/poor	24	32.9	

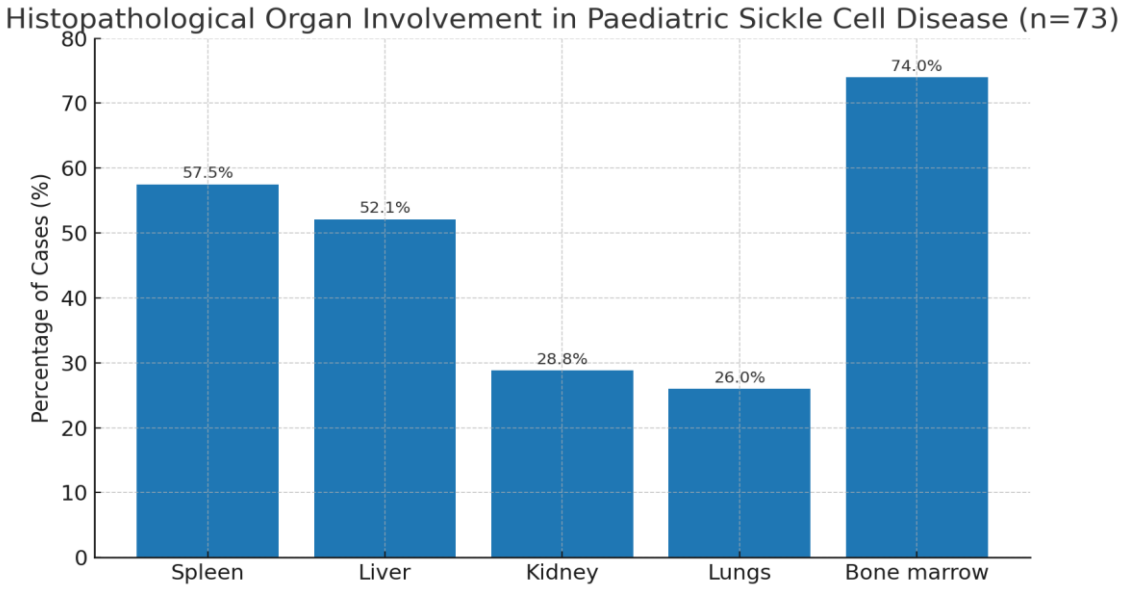

Figure 1

Bar graph showing the frequency of histopathological organ involvement in children with sickle cell disease.

DISCUSSION

In this study, we examined histopathological organ involvement and physiological markers in 73 pediatric patients with sickle cell disease (SCD) treated at the Burns and Plastic Surgery Centre, Hayatabad. Our results align with and expand upon contemporary understandings of SCD's systemic impacts.

Splenic fibrosis and autosplenectomy were among the most prevalent histological findings. This concurs with established literature that recurrent intrasplenic sickling leads to progressive splenic infarction and hyposplenism or complete atrophy often by early childhood in HbSS patients [12, 13]. This loss of splenic function underlies the elevated risk of invasive bacterial infections, particularly from encapsulated organisms, and reinforces the need for vigilant vaccination and prophylactic strategies.

The frequent occurrence of sinusoidal congestion and hemosiderosis reflects chronic hemolysis a hallmark of SCD. Moreover, manifestations of sickle hepatopathy range from asymptomatic transaminase elevations to cholestatic crisis or overt hepatic failure [14, 15]. Our findings emphasize that hepatic involvement can present across a continuum, and often requires high clinical suspicion for timely intervention.

Erythroid hyperplasia was notably prevalent, echoing the expected compensatory response to chronic anemia and hemolysis. This robust marrow activity mirrors observations in prior studies that highlight hyperactive erythropoiesis as a hallmark of pediatric SCD.

Kidney pathology such as glomerulosclerosis and papillary necrosis was present but less common, in line with broader literature showing that early renal changes in pediatric SCD may be subclinical or progressive [16, 17]. Pulmonary fibrosis and infarction were also less frequent, but other studies suggest involvement may evolve with age and disease activity [18].

Though not directly assessed in our histopathological sampling, central neurovascular involvement remains a major concern in pediatric SCD. Silent cerebral infarctions (SCI) and overt strokes affect up to 39% of children, with serious implications for neurocognitive development [19]. Routine screening, such as through transcranial Doppler or MRI, is crucial for early detection and preventive care.

Our physiological findings anemia, elevated LDH, hyperbilirubinemia, and mild hypoxia underscore chronic hemolysis and its systemic effects. This is consistent with recent biomarker research that demonstrates elevated inflammatory and endothelial markers (e.g., TNF-α, IL-6, VCAM-1) in pediatric SCD, which correlate with hemolytic indices and disease severity [20].

Therapeutic modalities such as hydroxyurea, chronic transfusion, and emerging agents like voxelotor have shown efficacy in reducing crises and the risk of end-organ damage [21]. Our high prevalence of hydroxyurea use and favorable response in a majority of patients support its central role in disease-modifying treatment. Nonetheless, access to such therapies and their long-term monitoring remains a challenge in many lower-resource settings.

CONCLUSION

This study sheds important light on the multi-organ pathology of paediatric SCD, especially in the context of a regional Burns and Plastic Surgery Centre where systemic manifestations may go underrecognized. Key findings include: High prevalence of splenic fibrosis/autosplenectomy, reinforcing infection risk and need for preventive care. Significant liver congestion and iron deposition, highlighting a spectrum of hepatobiliary involvement. Prominent bone marrow hyperplasia as a compensation for chronic hemolysis. Emerging but less prevalent kidney and lung lesions, suggesting early-stage end-organ effects. Laboratory markers corroborating ongoing hemolysis and inflammation. Effective response to disease-modifying therapies like hydroxyurea.

These findings support a comprehensive, multidisciplinary approach to pediatric SCD that includes regular monitoring of organ function, aggressive infection prophylaxis, biomarker-guided disease severity assessment, and broader access to disease-modifying treatments. Early intervention remains

critical to reducing morbidity, preserving organ function, and improving quality of life in this vulnerable population.

REFERENCES

1. Wang, Q. and R.J.A. Zennadi, The role of RBC oxidative stress in sickle cell disease: from the molecular basis to pathologic implications. 2021. **10**(10): p. 1608.
2. Vona, R., et al., Sickle cell disease: role of oxidative stress and antioxidant therapy. 2021. **10**(2): p. 296.
3. Silva, M. and P.J.A. Faustino, From stress to sick (le) and back again–oxidative/antioxidant mechanisms, genetic modulation, and cerebrovascular disease in children with sickle cell anemia. 2023. **12**(11): p. 1977.
4. Tebbi, C.K.J.H., Sickle cell disease, a review. 2022. **3**(2): p. 341-366.
5. Vinhaes, C.L., et al., Hydroxyurea treatment is associated with reduced degree of oxidative perturbation in children and adolescents with sickle cell anemia. 2020. **10**(1): p. 18982.
6. Idris, I.M., et al., Sickle cell disease as an accelerated aging syndrome. 2022. **247**(4): p. 368-374.
7. Sahu, T., et al., Infection and potential challenge of childhood mortality in sickle cell disease: a comprehensive review of the literature from a global perspective. 2023. **13**(3): p. 206-229.
8. Aboderin, F.I., et al., A review of the relationship between the immune response, inflammation, oxidative stress, and the pathogenesis of sickle cell anaemia. 2023. **11**(9): p. 2413.
9. Darbari, D.S., V.A. Sheehan, and S.K.J.E.j.o.h. Ballas, The vaso-occlusive pain crisis in sickle cell disease: definition, pathophysiology, and management. 2020. **105**(3): p. 237-246.
10. Gbotosho, O.T., M.G. Kapetanaki, and G.J.J.F.i.i. Kato, The worst things in life are free: the role of free heme in sickle cell disease. 2021. **11**: p. 561917.
11. Sachdev, V., D.R. Rosing, and S.L.J.T.i.c.m. Thein, Cardiovascular complications of sickle cell disease. 2021. **31**(3): p. 187-193.
12. Ochocinski, D., et al., Life-threatening infectious complications in sickle cell disease: a concise narrative review. 2020. **8**: p. 38.
13. Longoria, J.N., et al., Neurocognitive risk in sickle cell disease: Utilizing neuropsychology services to manage cognitive symptoms and functional limitations. 2022. **197**(3): p. 260-270.
14. Ataga, K.I., S.L. Saraf, and V.K.J.N.R.N. Derebail, The nephropathy of sickle cell trait and sickle cell disease. 2022. **18**(6): p. 361-377.
15. Akhter, M.S., et al., Mitochondria: emerging consequential in sickle cell disease. 2023. **12**(3): p. 765.
16. Jacob, S.A., et al., The evolving treatment landscape for children with sickle cell disease. 2023. **7**(11): p. 797-808.
17. Shet, A.S., M.A. Lizarralde-Iragorri, and R.P.J.H. Naik, The molecular basis for the prothrombotic state in sickle cell disease. 2020. **105**(10): p. 2368.
18. Palomarez, A., et al., Cardiovascular consequences of sickle cell disease. 2022. **3**(3).
19. Helvaci, M.R., et al., An exaggerated capillary endothelial edema may be the cause of sudden deaths in sickle cell diseases. 2023. **7**(10).
20. Helvaci, M.J.W., Acute painful crises may be causes of sudden deaths in sickle cell diseases. 2023.
21. Kanter, J., et al., Biologic and clinical efficacy of LentiGlobin for sickle cell disease. 2022. **386**(7): p. 617-628.