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Spleen Histology in Children with Sickle Cell Disease and Long-Term Hematologic and Clinical Outcomes of Splenectomy in Children with Hereditary Spherocytosis and Sickle Cell Disease

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ABSTRACT

Background: Sickle Cell Disease (SCD) and Hereditary Spherocytosis (HS) are hemolytic diseases that produce essential changes in splenic architecture and pathophysiology. The spleen is primarily involved in removing what may be regarded as abnormal red blood cells; in these diseases, the splenic disease may well require splenectomy. Thus, splenectomy and the estimation of the changes in the spleen histopathology and hematologic status can serve as important information from the treatment perspective.

Objective: To determine histopathological features of the spleen and evaluate hematologic and clinical outcomes in children with SCD and HS after splenectomy.

Methodology: The present study is a retrospective cohort analysis conducted at the Histopathology Department of Nowshera Medical College, in collaboration with the Pediatric Surgery Departments of its affiliated hospitals, from January 2023 to January 2024. Altogether 151 PK pediatric patients, 95 with SCD and 56 with HS were enrolled in the study. The spleen's histopathological changes were evaluated with the help of tissue samples, and the pre-and post-splenectomy haematologic features were compared, such as hemoglobin content, levels of reticulocytes, and transfusion rates.

Results: SCD patients had severe splenic disease, where 90 analyzable patient samples had pathologic changes. Atrophy of white pulp was demonstrated in 5% of the cases, while 79% of the patients demonstrated follicular hyperplasia. 9% were recorded to have congestion in the red pulp at sites where agar plates were placed and 48. 4% experiencing autosplenectomy. On the other hand, in HS patients' splenic involvement was relatively mild 45. 6% of patients had signs of white pulp atrophy to different degrees and no patient had autosplenectomy evident. After splenectomy, there were enhancements in the hematologic profiles in both groups, though even greater changes were noted in the SCD patients; mean hemoglobin concentration was raised by 8. 2 g/dL to 9. 8 g/dL among LS patients, and from 9. 6 g/dL to 12. of 3 g/dL in the latter patient groups, reaching significance at $p < 0.05$. Reticulocyte counts and number of transfusions also reduced in the R hu group and the HbA1c group.

Conclusion: SCD and HS induced different histopathological changes in the spleen, however, SCD appears to be more damaging to the spleen. Patients with both diseases exhibit marked hematologic improvement following splenectomy although in HS subjects the rise in hemoglobin is even more dramatic than in the SCD subjects. The results stress early diagnostic workup and the right surgical procedures for the treatment of these problems.

Keywords: Sickle Cell Disease, Hereditary Spherocytosis, Laparoscopic Splenectomy.

Introduction

The spleen is also a very important organ of the human body since it is involved in filtering the blood, recycling old and worn-out red blood cells, and also being involved in the immune system of the human body and fighting any infection.(1) Histologically, the spleen is composed of two main areas: These are the white pulp and the red pulp. The white pulp contains mainly lymphoid tissue, which is the site of immune responses while the red pulp plays a role in the filtration of blood as well as in the elimination of abnormal erythrocytes.(2) The spleen experiences marked pathological changes in patients with some hematologic disorders including SCD and HS and thus their normal function and structure can be affected.(3) Sickle cell disease is a rare heir genetic disease by the hemoglobin S under low oxygen, the red blood cell becomes rigid or has a 'sickle cell' shape.(4) They have the ability to curl up within small blood vessels and cause Ischemic injury over time due to repeated vaso-occlusion, most significantly the spleen.(5) This she stated is a result of the fact that the spleen in children with SCD is usually one of the initial organs to be physically altered. Spleen involvement in early life is characterized by congestion, hyperplasia of red pulp, and infraction caused by the accumulation of sickled erythrocytes.(6) Long-term effects of recurrent infarctions mean auto splenectomy; the spleen atrophies and becomes nonfunctional. Splenic tissue in SCD patients is characteristically abnormally developed and has a fibrotic appearance, is atrophied, and possesses a dysfunctional architecture that compromises the immunologic functions of the spleen and elevation of the profile of infections.(7)

Hereditary spherocytosis is another type of disease in which red blood cells have a spherical shape but do not have the shape of the biconcave disc.(8) These spherocytes are less deformable and can easily be sequestered and lysed by the spleen hence causing hemolytic anemia. For both HS and SCD, splenectomy, the act of removing the spleen, may be carried out to control the Sickel Cell sub complications.(9) HS is characterized by massive splenomegaly, and although splenectomy is only occasionally beneficial to the patient, it is most commonly done in those situations in order to reduce the rate of hemolysis and the degree of anemia that can significantly impair the patient's quality of life. In SCD despite the fully functional asplenia due to autosplenectomy, some patients may develop complications necessitating splenectomy, such as splenic sequestration crises in which large volumes of blood are trapped in the spleen resulting in acute anaemia and hypovolaemic shock.(9)

Despite the positive clinical outcomes and vast advantages of splenectomy, including reduced hemolysis and better hematologic indices, there are long-term effects of splenectomy, much worse in children. Asplenic patients are more prone to infections and are most commonly associated with bacterial infections by encapsulated bacteria such as S. pneumoniae, H. influenzae and N. meningitidis.(10) It is thus important to insist on the use of prophylactic antibiotics and vaccinations to control these risks following splenectomy. Moreover, the frequency of vaso-occlusive crises, the incidence for acute chest syndrome, and survival in children with SCD could also be influenced by splenectomy.(11) Systematic analysis of patients who had undergone splenectomy during childhood is still needed to draw comparative and fuller conclusions over the effect of splenectomy on such important aspects, as the hemoglobin and the reticulocyte counts, the growth, the development, and the quality of life of patients.

This means that there is an improved position of hemoglobin in children suffering from hereditary spherocytosis once splenectomy has been done as the use of blood transfusion also decreases considerably. Nevertheless, one's vulnerability to developing post-splenectomy

sepsis will always be a critical concern that should be dealt with. The benefits of splenectomy in terms of decreasing acute splenic sequestration crises and general hematological attenuation are additionally associated with an increased lifetime threat of serious infections and varied complications in children with SCD. Thus, splenectomy in these patients has to be done selectively and with consideration of the potential complications and benefits for the patient's condition and therapy and always should be followed by careful monitoring and control of possible adverse effects.

It is therefore important to understand the histological alteration that occurs in the spleen in sickle cell disease and the results of splenectomy in children with hereditary spherocytosis and sickle cell disease to enhance management and enhance patient conformity. Based on splenic pathology in hematologic disorders and long-term clinical data presented in this article, it is possible to analyze the relationship between these diseases and splenologic states in children, as well as the impact of splenectomy in childhood and further life.

Materials and Methods

This research work used cross-sectional descriptive survey research to determine the level of histological change in children with SCD and to analyze the hematologic and clinical benefits of splenectomy in children with HS and SCD. The study was a cross-sectional descriptive study that was done over 12 months from January 2023 to January 2024

The present study was conducted at the Histopathology Department of Nowshera Medical College, in collaboration with the Pediatric Surgery Departments of its affiliated hospitals, from January 2023 to January 2024. The sample size for this study was estimated at 95% confidence level, 5% precision level, and splenic histopathological changes prevalence estimate in children with SCD and HS from previous research findings. The patients chosen for this study were 151 pediatric patients who fulfilled the inclusion criteria.

The study sample consisted of the pediatric patients affected with sickle cell disease and hereditary spherocytosis, who have indeed undergone splenectomy or the ones, who were observed for splenic histopathological alterations. Inclusion criteria were based on age, and diagnosis of SCD or HS, and the children had to be between the ages of 2- 18 years old and had to have sought care at Nowshera Medical College over the study period.

The inclusion criteria are patients aged 2-18 years with confirmed sickle cell disease or hereditary spherocytosis, patients who have a history of splenectomy for HS or SCD, patients in whose spleen histopathology can be assessed, and patients with their parents' or guardians' informed consent. The exclusion criteria included children with other haematologic or non-SCD/HS systemic diseases, patients' records that are not complete or splenic tissue not available, and patients who have not had a splenectomy and are not originating from centers under observation for splenic histopathological changes.

The data was collected in two phases and these are as follows. The first phase included a histopathological examination in which splenic tissue biopsy samples were derived from splenectomy patients. These samples have been processed and reviewed by histopathology at the Nowshera Medical College pathology department by the histopathologist. Histopathological assessment involves assessing the organization of splenic tissue, fibrosis and infarction, and other pathological changes that are characteristic of SCD and HS. There are described specific changes that can be revealed on the histopathological examination, namely, white pulp atrophy, red pulp congestion, and fibrosis.

The second phase involved their clinical and hematologic history whereby medical records of the selected patients were reviewed to assess the hematologic characteristics of the patient after splenectomy with special emphasis on pre-and post-splenectomy hematologic profile, complete blood counts, packed cell, reticulocyte count and blood transfusion frequency. Data on clinical events such as frequency of vaso-occlusive crises, infections, and other complications were also recorded and patient's demographic profile, duration of disease and indications for splenectomy were also obtained.

The examination of splenic tissue samples was done systematically in an attempt to assess the pathological changes related to Sickle Cell Disease (SCD) and Hereditary Spherocytosis (HS). This investigation work was conducted on the splenic tissue samples excised from pediatric patients who underwent splenectomy at Nowshera Medical College. Such samples were quickly fixed and cross-linked in 10% neutral-buffered formalin and therefore the tissues did not degrade and reliable cellular features were properly maintained.

After this fixation was over the tissue samples were sent to the pathology department in Nowshera Medical College. The samples were processed through a graded alcohol series and cleared in xylene before being embedded into paraffin wax to form tissue blocks. These blocks were then sectioned into 4-micron thick slices using a microtome Their presentations at the EM included a series of specimen-formalin fixed adhesive strips and arrays of specimen-formalin fixed adhesive tabs and strips. These thin sections were then mounted on the glass slides and left to dry at 37 'C for one night.

For histological examination, the slides were stained using haematoxylin and eosin, periodic acid schiff, reticulin, alcian blue/periodic acid schiff, and giemsa stains. There was also conventional staining which used Hematoxylin and Eosin (H&E) which is widely used in general tissue examination. The cell nuclei were stained blue using hematoxylin, and Eosin gave a pink coloration to the cytoplasm and the extracellular matrix to facilitate the examination of the splenic architecture comprising of the white pulp and red pulp.

On occasion, special stains were used in order to examine specific histopathologic characteristics, over and above the usual H&E staining. Diffused fibrosis was identified by Masson's trichrome stain in which collagen fibers were stained blue, muscle and erythrocytes were stained red and cell nuclei were stained black. This was particularly useful while trying to determine the level of fibrotic replacement with the splenic tissue. Hematoxylin and eosin stains were used to assess the overall morphology of the tissue samples, assessment of immunohistochemistry, and identification of the artery/arteriole at the hilum of the spleen Reticulin stain was used to evaluate the integrity of the splenic framework due to the damage and fibrosis of tissues in some of the specimens. Last, Perl's Prussian Blue stain was employed to see if there was the presence of iron that is characteristic of hemosiderosis which is frequently a feature of chronic hemolytic conditions like SCD.

All the stained slides were reviewed and studied under a light microscope with the assistance of a skilled histopathologist. Major areas of histopathological changes that were examined were white pulp atrophy, red pulp congestion, fibrosis, infarction, and any other pathological changes attributable to SCD and HS. These features were documented in detail for each patient, which helped the study to provide a complete account of splenic involvement in the two types of hemolytic diseases.

The collected data were also as recorded in the data collection tools analyzed using the Statistical Package for Social Sciences (SPSS) version 26. In this study quantitative descriptive

analysis is used to present demographic, clinical and histopathological characteristics using mean, SD, frequencies and percentages. Descriptive statistics such as frequencies and percentages of multiple histopathological characteristics of splenic tissue SN were determined. Cross-sectional comparison was made between the histological alterations in patients with SCD and with HS. Data on hematologic parameters before and after splenectomy were compared using paired t-test where data was normal or Wilcoxon signed rank test if data was not normal.

Written consent was taken from all the participants and ethical approval of the study was sought from the Institutional Review Board (IRB) at Nowshera Medical College. The parents or guardians of all the participating children give their informed consent regarding any BDI. Patients' data are kept confidential throughout the study and all the data are masked before analysis is conducted.

Results

It consisted of 151 subjects, 95 of whom were diagnosed with Sickle Cell Disease (Group 1) and 56 of whom were diagnosed with Hereditary Spherocytosis (Group 2). The experimental group's mean age of the participants was 8. 7 ± 3. Five years and the median age of the children is nine years. 0 years. The gender distribution disparity was not very high; 57% of the students were female. 3% male and 44. 7% female participants. The duration of disease was also different; 41% of the total participants were having the disease from 5 but less than 10 years, 41% of participants had the disease for less than 5 years, and only 18% participants were having the disease for more than 10 years. (Table 1)

These findings are supported by the results of histopathological examination of splenic tissues whereby there was observed a higher degree of differences between the SCD and HS patients. The atrophy of white pulp was also found in 90. and SCD patients was 5%, while that of control subjects was 45%. 6% in HS patients. Hemoglobin levels were significantly different from one another, with SCD patients having a mean and standard deviation of 8. 29 ±1.33, much lower than the 12.74 ±2.12 of HS patients There was also a higher incidence of red pulp congestion in SCD patients with (79. 9% as compared to 27. 8% in the HS group). Fibrosis and infarction were also significantly more frequent in SCD patients and were reported in 72%. 6% and 87. 3% respectively while the remaining 33% belong to the other occupational classifications. 1% and 18. 9% in HS patients. Interestingly, 48% of patients were noted to have autosplenectomy. 4% of SCD patients but was not detected in any HS patient. (Table 2)

In both patients with SCD and HS Splenectomy showed a significant increase in most of the hematologic indices that were assessed in the study. The initial and final mean hemoglobin values in the SCD patients were as follows: 8. 2 ± 1. 3 g/dL in pre-operative to 9. 4 ± 1. Splenectomy was seen to increase ANC from the pre-splenectomy mean of 1625±87 to 2256±86 post-splenectomy (p = 0. 023) to 2 g/dL post-splenectomy (p = = 0. 023). In the same way, HS patients rose slightly from 9. 6 ± 1. 1 g/dL to 12. 3 ± 1. 5 g/dL. The reticulocyte count was reduced in both groups but the level of reduction was higher in the SCD group reducing from a count of 13. 0 ± 3. 5% to 7. 7 ± 2. 15% (p =0. 020) and HS patients from 10%. 4 ± 2. 9% to 3. 0 ± 1. 2%. The use of blood transfusions per year, another measure of the disease activity, was lower after splenectomy, pre-splenectomy = 3. 3 ± 1. 6 to 1. 5 ± 1. 1 in SCD patients (p = 0. 032), and from 1. 9 ± 1. 3 to 0. 4 ± 0. 6 in HS patients. (Table 3)

Table 1: Demographic Characteristics of the Study Population (n = 151)

Variable	SCD (n = 95)	HS (n = 56)	Total (n = 151)

Age (years)			
Mean ± SD	8.3 ± 3.7	9.2 ± 3.2	8.7 ± 3.5
Median (IQR)	8.5 (6.0–12.0)	9.5 (7.0–13.0)	9.0 (6.0–12.0)
Gender			
Male	54 (55.8%)	31 (57.1%)	83 (57.3%)
Female	41 (44.2%)	25 (42.9%)	68 (44.7%)
Duration of Disease			
<5 years	38 (40.0%)	20 (35.7%)	60 (41.1%)
5-10 years	39 (41.0%)	25 (44.6%)	63 (41.1%)
>10 years	18 (18.9%)	11 (19.6%)	28 (17.9%)

Table 2: Histopathological Findings in Splenic Tissue Samples (n = 151)

Histopathological Feature	SCD (n = 95)	HS (n = 56)	Total (n = 151)
White Pulp Atrophy	86 (90.5%)	26 (45.6%)	112 (74.1%)
Red Pulp Congestion	76 (79.9%)	16 (27.8%)	92 (80.0%)
Fibrosis	69 (72.6%)	19 (33.1%)	88 (76.5%)
Infarction	83 (87.3%)	11 (18.9%)	94 (62.2%)
Autosplenectomy	46 (48.4%)	0 (0.0%)	46 (40.0%)

Table 3: Pre- and Post-Splenectomy Hematologic Parameters in HS and SCD Patients (n = 151)

Parameter	Pre-Splenectomy Mean ± SD	Post-Splenectomy Mean ± SD	p-value
Hemoglobin (g/dL)			
SCD (n = 95)	8.2 ± 1.3	9.4 ± 1.2	0.023
HS (n = 56)	9.6 ± 1.1	12.3 ± 1.5	
Reticulocyte Count (%)			
SCD (n = 95)	13.0 ± 3.5	7.7 ± 2.2	0.012
HS (n = 56)	10.4 ± 2.9	3.0 ± 1.2	
Transfusion Frequency (per year)			
SCD (n = 95)	3.3 ± 1.6	1.5 ± 1.1	0.032
HS (n = 56)	1.9 ± 1.3	0.4 ± 0.6	

Discussion

Our study observed that children with Sickle Cell Disease (SCD) and Hereditary Spherocytosis (HS) had significantly different spleen histology and hematologic profiles. Thus, in SCD patients, the frequency of white pulp atrophy were 90. 5%, red pulp congestion – 79. 9% and autosplenectomy – 48. 4%, stressing significant splenic lesions inflicted by recurrent vaso-occlusive episodes. On the other hand, there was relative sparing of histopathological changes in the HS patient; 45. 6% had white pulp atrophy and none of the patients demonstrated autosplenectomy. Patients of both groups showed significant improvement of hematological parameters after splenectomy: the increase of hemoglobin levels and the decrease of reticulocyte counts and frequency of transfusions, however, this improvement was more prominent in HS patients regarding to the level of hemoglobin. Such outcomes reflect the differences in effects of these diseases on spleen shape and the splenectomy efficiency in hematologic disorders treatment.

In the present work, it was possible to identify that white pulp atrophy occurred in 90% of the analyzed cases. As compared to the normal population 5% of SCD patients had global cognitive

impairment, which was significantly higher than 45%. 6% has been observed in the HS patients compared to the normal population. This is in agreement with the recent work of Chekroun et al. (2019) who observed decreased splenic volume and established that SCD patients had considerable white pulp atrophy due to repeated splenic infarctions.(12) Solomon et al (2022) described the same in their study of SCD spleens in which fibrosis and atrophy were observed to be multiple and progressive due to chronic ischemic injury arising from repeated vaso-occlusion..(13) Lenti et al (2022) noted lesser atrophy in the HS spleens which is in good agreement with the results of the present study. They opined that since the pathogenesis of HS differs from that of SCD, they recommended that milder splenic involvement observed in HS can be attributed to relatively lesser severe hemolytic episodes.(14)

In the present study, congestion in red pulp was observed in 79. 9% of SCD patients and similar to Suttorp et al (2021) who also presented the same congestion arising from splint infarction accumulated frequently.(6)These are as follows; Autosplenectomy 48. Of the SCD patients in our sample, 4% had decompensated the disease, which underscores the findings of Ahmed et al. (2023). They noted that autosplenectomy was usually done early in the lifecycle of the SCD patients a scenario that was evident in the current study.(3)

Hemoglobin levels in both the SCD and HS patients of this study also rose; SCD patients enhanced from 8. 2 ± 1. 3 g/dL to 9. 4 ± 1. CAD patients had an increase of 2 g/dL and HS patients from 9. 6 ± 1. 1 g/dL to 12. 3 ± 1. 5 g/dL. This improvement is in line with the study done by EI-Gohary et al. (2020) where the authors also noted the same increase of hemoglobin levels of the SCD patients who had undergone splenectomy.(15) Hemoglobin enhancements, noted by Celik et al. (2023) in the same patients too, were also found to be highly significant.(16) However, AI Ladu et al. (2021) opined that while splenectomy does enhance the hemoglobin level, it elevates the risk of infection, this about SCD patients especially requires cautious postoperative care.(17)

Reduced reticulocyte count and duration on transfusion support post-splenectomy were demonstrable on both SCD and HS in the presented study. This is in tandem with S. Peretz et al. (2021) who observed similar reductions in the reticulocyte counts also implying the reduction in hemolysis among SCD patients following splenectomy.(18) Similar observations were made by Marie et al. (2021) in SCD patients where a significant decrease in transfusion needs was witnessed after splenectomy in this study.(19) Similar findings in the HS patients were reported by S Kumar et al. (2021) who noted that splenectomy reduced the patients' requirement of blood transfusion, confirming the usefulness of splenectomy in the management of severe hemolysis in HS.(20)

Conclusion

This is evidenced by the dissimilarities in splenic pathology in sickle cell disease and hereditary spherocytosis whereby a lot of SCD patients will undergo autosplenectomy promptly. These hematologic gains after splenectomy re-endorse the approach's effectiveness in treating serious instances although the conceivable danger especially in SCD suggests that it needs further investigation.

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