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INSIGHTS INTO UNDIAGNOSED SICKLE CELL DISEASE MORTALITY: A POSTMORTEM INVESTIGATION

Pathology

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ABSTRACT

Introduction: The sickle hemoglobinopathies are hereditary disorders in which the red cells contain Hb-S, which includes homozygous (SS disease) and heterozygous (Sickle cell trait) states. Sickle cell anaemia (SCA) is a hemolytic disease characterized by the production of abnormal hemoglobin chains that tend to polymerize when deoxygenated, distorting the red blood cell (RBC) morphology (sickling) and leading to vascular occlusion and ischemia with multi-organs involvement. Death in clinically asymptomatic patients with sickle cell disease and sickle cell trait is not uncommon. **Materials and Methods:** This is an observational study of 1241 autopsies (January 2019 – June 2020). We received the gross specimen of the lungs, heart, liver, kidney, spleen, and brain for Histopathological examination. The data of clinical history, and gross and microscopical examination of all cases were analyzed. **Results:** Out of a total 1241 autopsy cases, 61 cases showed the presence of sickle-shaped RBCs in any of the above-mentioned organs on Histopathological examination with a Male: Female ratio of 3.7:1, and peak mortality was 2nd to 3rd decade of life. The common causes of death in this study include vaso-occlusive crisis (37%), and infection (18%). The terminal infection was heralded by the upper respiratory tract 45 and by the Central Nervous System (27%). The predominant gross finding is Splenomegaly, observed in 39% of cases. **Conclusion:** This study is to precise analysis of causes of death which is needed to focus on and improve morbidity and mortality in sickle cell disease, especially in highly prevalent areas, which will impact the overall survival of these patients.

KEYWORDS

Sickle Cell Anemia, Sickle Cell Crisis, Sudden unexpected death

INTRODUCTION

Hemoglobinopathies are inherited red blood disorders in which there is decrease in production of hemoglobin (thalassemia) or abnormal form of hemoglobin (variant). The two main groups are structural Hb variants including thalassemia syndromes and HbS, HbE, and HbC (abnormal hemoglobins).[1]

Sickle cell disease (SCD) was first described in 1910 by a Chicago cardiologist, named Herrick, studied West Indian dental students who had presented with pulmonary symptoms. The term "sickle-shaped" was coined by Herrick to describe the peculiar appearance of the RBC of the dental patients. In India, the sickle hemoglobin was first described by Lehman H et al in 1952 in vedeloid tribal population in Nilgiri hills in Tamil Nadu and it was later discovered in other tribes of Orissa and Assam, certain tribes of Marathi.[2] Between 2000 and 2021, the number of people living with sickle cell disease globally increased by 41·4% (38·3–44·9), from 5·46 million (4·62–6·45) in 2000 to 7·74 million (6·51–9·2) in 2021.[3]

In India, Extensive studies performed by the Anthropological Survey of India have documented the frequency and distribution of the sickle cell trait which reaches levels as high as 35 percent in some communities.[4] Among the scheduled tribes, scheduled castes predominantly HbS is seen, and other backward castes, among the central, western, and southern states have a carrier frequency ranging from 5% to 35%.[5] Increased prevalence is reported in the non-tribal communities of these areas as well.

The sickle hemoglobinopathies are hereditary disorders in which the red cells contain Hb-S, they include the homozygous (SS disease) and heterozygous (Sickle cell trait) states for the Hb-S. In deoxygenated state, the solubility of Hb-S is 10% of that of Hb-A. The conformational changes the cells containing the abnormal hemoglobin to become rigid and deformed, assuming a sickle or crescent shape.[6] Clinical features are variable and may be correlated to diverse factors, ranging from socioeconomic condition, climate, hemoglobin level, type of abnormal hemoglobin that accompanies the HBs in heterozygous form, and level of fetal hemoglobin. Sickle cell anaemia (SCA) is a hemolytic disease characterized by the production of abnormal hemoglobin chains that tend to polymerize when deoxygenated, distorting the cell (RBC) morphology – sickling, and leading to vascular occlusion and ischemia with multiple organs involvement.[7]

Death in clinically asymptomatic patients with sickle cell disease and sickle cell trait is not uncommon. Due to unawareness or unavailability of history in prevalent tribal areas with a high prevalence of sickle cell anemia, a smaller number of deaths was reported.

In the present study, we found the presence of sickle red blood cells in Histopathological examination of various organs. The pathological findings seen at autopsy may or may not be directly related to the cause of death. Our main aim is to create awareness among physicians and in the community to minimize unexpected deaths from complications or crisis of sickle cell disease.

Method

This is an observational study of 1241 autopsies (January 2019 – June 2020). Out of which 61 autopsies showed the presence of sickle cell in Histopathological examination of various organs received at tertiary care hospital of South Gujarat.

We received the gross specimen of the lungs, heart, liver, kidney, spleen, and brain for Histopathological examination. The data of clinical history, gross and microscopical examination of all cases were analyzed.

This study is retrograde and patients have not documented cases of sickle cell anemia, and data regarding Hb electrophoresis or HPLC was not available so homozygosity, heterozygosity, or presence of other hemoglobinopathy was not available.

RESULT

Out of a total 1241 autopsy cases, 61 cases showed the presence of sickle-shaped RBCs in any of the above-mentioned organs on Histopathological examination.

Out of 61 cases, 48 cases were male and 13 cases were female, thus reflecting male predominance with a ratio of 3.7:1, which may be due to selection bias as they all are medicolegal cases.

The mode of death was sudden death, observed in 12 cases. The most

common morphological finding observed after the presence of clogged vessels with all organs was splenomegaly, observed in 39% of cases.

The most common organ where we found sickled RBCs was Spleen (62%) cases, followed by kidney (59%), lung (55%), Liver (31%) and Brain (23%).

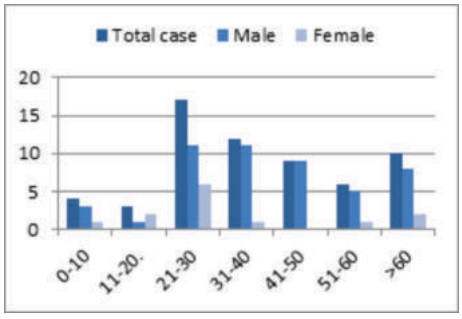

Figure 1: Age and Sex-Wise Distribution

TABLE – 1 Clinical Presentation of Sickle Cell Disease Patients

Clinical presentation	No. Of cases	Percentage
Sudden death	12	19.67
Fever	6	9.83
Acute chest syndrome	5	8.19
CNS Symptoms	5	8.19
Gastrointestinal symptoms	6	9.83
Intra-operative/ Postoperative complication	2	3.27
Chest pain	2	3.27
RTA	3	4.91
Unknown	11	18.03
Bodyache	1	1.63
Cervical carcinoma	1	1.63
Miscellanous	7	11.47
Total	61	100

Table - 2 Morphological Organ Injury in Autopsies of Patients:

Organ	Morphological findings	No of cases	%
Spleen	Presence of sickle	38	62
	Splenomegaly	24	39
	Chronic Venous Congestion	1	1.6
	Gamma gandy bodies	6	9.8
	Capsular fibrosis and subcapsular calcification	1	1.6
Lung	Presence of sickle	34	55.7
	Congestion	15	24.59
	Pneumonia	5	8
	Bone marrow embolism	4	6.5
	Chronic Venous Congestion	2	3.2
	Alveolar hemorrhage	5	8
	Edema	13	21
Liver	Presence of sickle	19	31
	Steatosis	10	16
	Congestion	6	9.8
	Cirrhosis	1	1.6
	Chronic Venous Congestion	1	1.6
	Metastasis	1	1.6
Heart	Advanced atherosclerosis	11	18
	Cardiomegaly	5	8
	Myocardial infarction	7	11
	Rhematic carditis	1	1.6
Kidney	Presence of sickle	36	59
	Chronic glomerulonephritis	2	3.2
	Chronic pyelonephritis	4	6.5
	Metastasis	1	1.6
	Acute GN	1	1.6
	End-stage kidney disease	1	1.6
	Tubulointerstitial nephritis	1	1.6
Brain	Presence of sickle	14	23
	Subdural hemorrhage	1	1.6
	Meningitis	2	3
	Encephalitis	1	1.6
Pancreas	Acute Pancreatitis	2	3
Cervix	Cervical carcinoma	1	1.6

Table 3. Cause of Death in Sickle Cell Disease Patients:

Cause of Death		No
Sickle crisis		23(37.7%)
Infections:		11(18%)
	Respiratory tract	5
	Pancrease	2
	CNS	3
	Genitourinary tract	1
Organ damage		9(14.8%)
Myocardial infarction		7(11.4%)
Subdural hemorrhage		1(1.6%)
Metastais		1(1.6%)

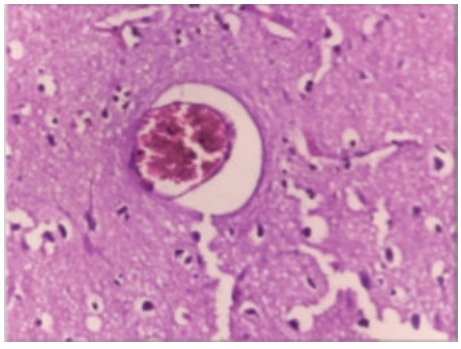

Figure 2. H&E Stain (40x view): Brain Vessels Clogged with Sickled RBCs.

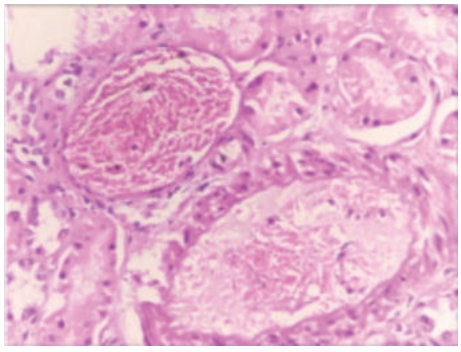

Figure 3. H&E Stain (40x view): Lung Vessels Clogged with Sickled RBCs.

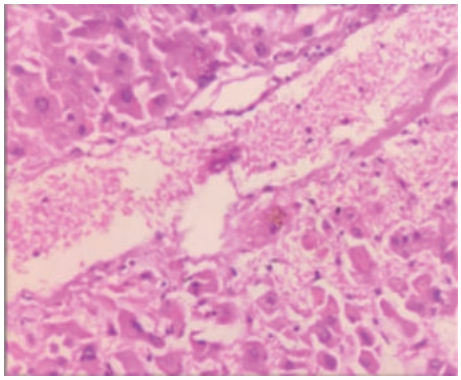

Figure 4. H&E Stain (40x view): Liver Sinusoids and Vessel Clogged with Sickled RBCs.

DISCUSSION

Sickle cell disease is common among people from Arabia, India, and Africa. Research has produced care models for diseases originating in Africa that improve quality of life while preventing serious complications and raising survival rates. In India, the disease is largely undocumented. Thus, there is an urgent need to document the features of Indian disease so that locally appropriate models of care may be evolved.[8]

The mean age of death in our study is 28 years with a peak at 21 to 30 years (3rd decade), while some Nigerian people is 21 years and that of Europe, USA, and Caribbean people is 45 to 55 years, which is shown by a study done in various countries. [9,10] The higher survival in those studies could be attributed to easy access of SCD patients to health care and health education in the locales where these studies were done.[9]

The reported mortality rate's male preponderance (3.7:1) may be explained by the fact that not all deaths are reported, particularly when they happen at home and include a medical condition that is financially and emotionally taxing on the family. This is especially so in early childhood when children will succumb to the illness as a result of infection or anemia before getting to the hospital. [9]

Underlying Causes of Death:

Sudden death is defined as an unexpected death occurring in a relatively healthy patient who suddenly dies either at home or in the hospital, with or without vaso-occlusive crises.[11] The diagnosis of multiorgan failure was assigned if two or more vital organs were involved at the time of death. These organs included the lungs and at least one other vital organ such as the brain, kidney, or liver. Thromboembolism did not include stroke but was defined as the finding of thrombi in the lungs at autopsy.[12]

In our case study, the most common mode of death is Sudden death (19%) followed by Fever (9.8%) and acute chest syndrome (8.19%).

According to Kar BC et al too noted attacks of pain, fever, and anemia were the predominant presenting features.[13] Extensive study by Kate SL et al anemia, intermittent Jaundice, severe Joint pain, and recurrent infection were the common symptoms.[14]

Our first most common cause of death was the sickle cell crisis (37.7%). Other studies conducted in India have shown nearly the same results – Gamti et al (45%), Dhawle et al (50%), Shah et al (4% cases of all sudden death)[1115] [16]. Studies conducted in the USA show painful crisis in 59.6% in Manci et al. and 33% in Platt et al.[17,18]. Each acute painful episode is usually related to inflammation that worsens with recurrent episodes, often resulting in serious complications and organ damage such as multi-organ failure, acute chest syndrome, crisis, and others.[7]

Although artificial postmortem sickling, which is known to result from formalin fixation, can confuse when it comes to sickled erythrocytes (drepanocytes) in the major viscera, it has been suggested that fixation-related sickling should affect a tissue section uniformly, so that the presence of both sickled and unsickled cells in the same section would favor an interpretation of true antemortem sickling.[19]

In our study, the second most common cause of death was infection (18%), which is also seen in other studies in India like Gamit et al (16%). Upper respiratory infections signaled the end of the illness in 5(45.5%) cases and the Central nervous system in 3 (27.2%) cases. Respiratory tract infection was also reported most common portal in the USA with infection being the most common cause of death in a study done by Manci et al with a predominance of Respiratory infection (72.6%) cases which was followed by gastroenteritis in 1.7% of cases[18]. In Nigerian people (in a study done by Ogun et al.) most common system is the respiratory system (53%) followed by cerebral infection (17%) and in a Jamaican study (Thomas et al) infection was the cause of death in 15.6% of cases. [9,20]

Bacterial infections are a first-rate reason for morbidity and mortality in kids with sickle-cell disease. The heightened vulnerability observed in impacted children is probably due to many factors, such as compromised splenic function, abnormalities in complement activation, inadequacies in micronutrient acquisition, and tissue ischaemia.[21]

Additionally, SCD patients have defective alternative pathway of complement activation and reduced ability of neutrophils to kill pathogenic organisms which makes them especially prone to infection by encapsulated organisms.[9]

Other causes of death included End organ damage in 14%, Myocardial infarction in 11% of cases along with 1 case of Metastasis and 1 case of Subdural hemorrhage. 18% cases with chronic organ failure were observed in a study done in the USA (Platt et al.)[17]

Acute chest syndrome is the second common purpose of Hospitalisation in sufferers of sickle-cell disease. It is a form of acute lung injury and is defined as the development of a new alveolar pulmonary infiltrate involving at least one lung segment. This syndrome is caused by a combination of infection, fat embolism, and vaso-occlusion of the pulmonary vasculature.[22]

In our study, 8% of cases presented with Acute Chest syndrome. While in other Indian studies Dhawle et al 78% of cases presented with ACS or Acute Painful episodes.[15] Studies conducted in France have also shown the same results.[23]

The clinical presentation of acute pulmonary pathology in SCD has been termed acute chest syndrome (ACS). Various study describes it differently. In the study by Thomas AN et al, the term encompassed disease due to pneumonia, pulmonary embolism, or both; in the study by Darbari DS et al, it was defined as chest pain, fever, and new pulmonary infiltrate on chest x-ray, and in the study by Gray A et al, it denoted acute pulmonary failure.[12] Infection is the most common identifiable cause of acute chest syndrome and other important triggers for acute chest syndrome are vaso-occlusive crisis (VOC) or pulmonary fat embolism causing pulmonary vascular obstruction resulting in infarction of pulmonary parenchyma.

There are at least 2 pathogenetic and histopathological versions: − type A: severe distension of arterioles, capillaries, and venules by packed sickled red cells (i.e. a pan-lung sickle crisis); there may also be local infarction; if there is no distension by sickled red cells present, it is not the ACS − type B: embolism of necrotic bone marrow to small pulmonary arteries. [24]

The incidence of chronic organ damage was observed in 18% of cases in Platt et al, in which sickle cell disease was thought to be a complicating factor. [17] In our study 9(14%) cases with multiple organ damage was observed.

Death due to non-hemoglobinopathy-related causes such as Road traffic accidents, intra/post-operative complications, and cervical carcinoma in 21% of cases. In the study by Manci EA et al, 8.4% of deaths were non-hemoglobinopathy-related.[18]

Splenomegaly was one of the gross findings found in 39% of cases. Along with Congested vessels and dilated sinusoids, Gamma gandy bodies were found in 9.8% of cases and 1 case of splenic fibrosis and subcapsular calcification. Recurrent intrasplenic vascular crises with minor infarctions and fibrosis with foci of fibrosis with iron and calcium deposits are represented by gamma-Gandy nodules. They may leave behind a small, non-functioning splenic remnant weighing 5 g or less after accumulating over decades. [24] These findings are similar to the study by Chopra R et al.[25 26]

The atheromatous lesion was observed in 18% of cases, cardiomegaly in 8% of cases, changes of Myocardial infarction seen in 11% of cases, and one case with rheumatic heart disease was observed.

Changes of MI were found in 17% of cases in a study done by Mansi et al. [27]

In the kidney after sickled RBC clogged vessels, important findings were Chronic glomerulonephritis in 3.2% cases and chronic pyelonephritis in 6.5% cases. In study done by Ress et al showed that 30% of adults develop chronic renal failure, which is a contributory factor in many deaths.[21]

26% of cases with renal failure observed in a Study Done by Darbari et al. and a study done by Behrens RJ et al observed renal failure in 10.5% of cases.[2812]

Subdural hemorrhage was observed in 1 case of 44-year-old male with a history of sudden death. In a study done by Darbari et al. observed 6% cases of stroke, whereas a in study done by Behrens et al. showed 9.6 % death with stroke.[2812]

The most common finding in lung microscopy was the presence of congested vessels by sickled RBCs, followed by edema (21%), pneumonia (8%), pulmonary hypertension (9%), and Bone marrow embolism (6.5%) in cases. A study done by Grahm et al. has shown the presence of edema in 47.6% of cases, Thromboembolism in 38%, fat

embolism in 33%, and pulmonary hypertension in 33% of cases.[29] An increasingly recognized side effect of sickle-cell disease in adults and teens is pulmonary hypertension.[21]

Numerous investigations have shown that the primary causes of sudden mortality include acute chest syndromes, cerebrovascular events, splenic dysfunction, sequestration, and aplastic crises. However, any presentation of sickling might result in death if one of these more serious complications subsequently develops.[30]

Platt et al studied 3764 patients with SCD and 209 adult patients who died of SCD. Peak incidence of death among children with sickle cell anemia occurred between 1-3 years of age. 18% of deaths in adults were due to chronic organ failure and 33% of deaths occurred in relatively healthy patients who died during a sickle cell crisis. 78% died either due to painful episodes or acute chest syndrome.[17]

CONCLUSION

Histological studies are quintessential to diagnose and understand the pathogenesis of sickle-related death. In susceptible persons sudden unexpected death may occur, when poor physical conditioning, dehydration, heat stresses, or hypoxic states precipitate sickling of abnormal erythrocytes. It is necessary to administer strong care and closely monitor acute episodes, particularly in the first 24 hours after presentation. We share our research to underscore the need for autopsy in situations of sudden unexplained death and to emphasize that sickle cell crisis is one of the reasons. We present this study to emphasize that sickle cell crisis is one of the causes of sudden unexplained death and highlight the role of autopsy in such cases. Within the sickle cell complex of illnesses, gross observation and pathological guessing alone may not be sufficient to determine the cause of mortality. However morphological findings are indicative of the possible mechanism of death, yet they do not prove it. Additionally, the discovery of normal size and enlarged spleen in patients with SCA in post-mortem prompted the need to re-evaluate the common belief that autosplenetomy is the rule among all of them. The presence of sickled RBCs in autopsy examination indicates underlying disease in otherwise patients with no such history. Our primary goal is to generate a new generation of RBCs that are healthy.

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