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Original Research Article

Autopsy Findings & Pattern Of Mortality In Undiagnosed Sickle Cell Disease Patients

Dr. Shantanu Agashe[1] (Asst. Prof.) & Dr. Ranu Gupta[2] (Asst. Prof.)

Dept. of Forensic Medicine, Index Medical College Hospital & Research Centre, Indore, M.P.[1]
Dept. of Pathology, Index Medical College Hospital & Research Centre, Indore, M.P.[2]

Corresponding Author: Dr. Ranu Gupta

Abstract

Background: Sickle Cell Disease has a high mortality rate. The aim of the study is to assess autopsy findings & pattern of mortality in undiagnosed sickle cell disease patients.

Methods: This study is retrospective study. Clinical data like age, gender, symptoms and major autopsy findings including cause of death & histopathology are documented.

Results: Out of 1200 autopsies observed sickled erythrocytes were detected in 100 cases. The mean age of death was 21-30 years and peak mortality was in the 2nd and 3rd decades of life. The common causes of death in this study include vaso-occlusive crisis (51%), infection (36%). The terminal infection was heralded by upper respiratory tract (13%) and by gastroenteritis (12%). Other causes of death included intracranial haemorrhage (2%) and cirrhosis (3%)

Conclusion: Early diagnosis, prompt treatment & extended screening programme are necessary in prevalent tribal belt of western India to reduce morbidity & mortality. We should also introduce awareness programmes in India.

Keywords: Autopsy, mortality, undiagnosed & sickle cell.

Study Design: Retrospective Study.

1. Introduction

Sickle cell disease (SCD) is genetic disease with mutation result in substitution of valine in place of glutamic acid in the 6th position of β chain, which import sickle shape to red cells in a state of reduced oxygen tension[1-4]. Sickle haemoglobin is highly prevalent among the tribal of central, southern and western India. The homozygote state also known as sickle cell anemia (SCA) is the commonest variant & has the severest clinical manifestations of any of the SCD variants. The heterozygote state (sickle cell trait or HbAS) is usually normal phenotypically. Autopsies are performed at the request of the treating physician after the demise of a patient in the hospital after obtaining consent from the relatives & when a patient is brought dead at hospital[5-8].

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Sickle cell disease (SCD) is the generic term for the group of haemoglobinopathies caused by the occurrence of haemoglobin S (Hbs) in the homozygous form sickle cell anaemia (Hbss) or as the heterozygous combination of Hbs with another abnormal haemoglobin such as Hbsc or beta –thalassaemia's (Hbsb-thal). Haemoglobinopathies are the commonest inherited disorders worldwide & SCD shows an important proportion of these[9-11]. The clinical features are variable & relate to diverse factors, ranging from climate, socioeconomic condition, haemoglobin level, level of fetal haemoglobin & the type of abnormal haemoglobin that accompanies the Hbs in the heterozygous form. In spite of much improvement in treatment, disease is still associated with high morbidity & mortality[12]. This study is to evaluate the autopsy findings at our centre & compare them with that of other places as to create awareness among the physicians & relatives/public & to minimize future unexpected death from complications or crisis from SCD[13].

The aim of present is to evaluate morphological evidence of cause of death with special emphasis on gross and microscopic findings of various organs.

2. Material & Methods

Present study was conducted at Medical College, Dhule, Maharashtra for 01 Year (2018-2019). We analyse clinical presentation, morphological (gross & microscopic) examination of heart, liver, lung, kidney, brain & spleen & cause of death.

This study is retrograde & patients were not documented cases of sickle cell anaemia & data regarding Hb electrophoresis or HPLC was not available so homozygosity, heterozygosity or presence of other haemoglobinopathy was not available.

Inclusion criteria:

1. Presence of sickled RBC on histopathological examination.

3. Results

A total 1200 autopsies were seen in one-year period (July 2018-July 2019) out of which 100 cases show presence of sickled RBC on histopathological examination of various organs.

Peak age group of mortality in our study was seen between 21-30 years male grp.

Out of 100 SCD studied 70% were seen in males and 30% in females.

Table No. 1: Various clinical presentations in death due to SCD.

S. No.	Clinical presentation	No.	Percentage
1	Sudden death	37	37
2	Fever	25	25
3	Gastrointestinal symptoms	12	12
4	Respiratory symptoms	13	13
5	Intra operative	03	03
6	Miscellaneous	10	10
	Total	**100**	**100**

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In our study mode of death was sudden (37%), followed by fever (25%), gastrointestinal symptoms (12%) and respiratory (13%) which includes breathlessness and chest pain.
Rest cases were natural deaths during treatment of existing illness such as tuberculosis or acute misc. event like snake bite, intra-operative or accidental fall from height. Other nonspecific findings are chronic venous congestion of lung as well as liver and red pulp as well as sinusoidal dilatation of spleen.
The morphological findings mentioned were as a result of chronic haemolysis and vascular occlusion on presence of sickled erythrocyte and also due to other underlying pathology. Marked congestion of internal organ with presence of sickle cell in dilated blood vessels found in all cases as it is an inclusion criterion of this study. Most common morphological finding in our study is splenomegaly.
Most common cause of death is vaso-occlusive crisis (51%) followed by infection in (36)% of cases. Other causes of death are intracerebral hemorrhage (2%), cirrhosis of liver (3%).
Most common portal of entry is respiratory tract followed by gastrointestinal tract.

Table No. 2: Age group and gender distribution of patients

		Male		**Female**	
S. No.	**Parameter**	**No.**	**Percentage**	**No.**	**Percentage**
1	00-10	02	2.8	01	3.3
2	11-20	18	25.7	06	20
3	21-30	23	32.8	08	26.6
4	31-40	15	21.4	09	30
5	41-50	07	10	04	13.3
6	51-60	05	7.1	02	6.6
	Total	**70**		**30**	

Table No. 3: Morphological organ injury in autopsies of patients.

S. No.	**Organ**	**Morphological finding**	**No.(cases)**
1	**Spleen**	Splenomegaly	47
		Gamma gandy bodies	03
2	**Lung**	Pulmonary edema	21
		Pneumonia	11
		Tuberculosis	04
		Invasive differentiated squamous cell Ca	01
3	**Liver and gall bladder**	Steatosis	11
		Cirrhosis	02
		Gall stone	02
4	**Heart**	Atherosclerosis	06

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		Myocardial infarction	04
		Acute carditis	02
5	**Kidney**	Papillary and interstitial fibrosis	07
		Acute tubular necrosis	05
		Focal glomerulosclerosis	03
6	**Brain**	Intracerebral haemorrhage	02
7	**Uterus**	Pyometra (pus in uterus)	01

Table No. 4: Causes of death in sickle cell disease patients.

S. No.	Cause of death	No.	Percentage
1	**Vaso-occlusive crisis**	51	37
2	**Infections**	36	33
	Pneumonia	11	11
	Gastroenteritis	10	10
	Tuberculosis	06	06
	Pyometra	02	02
	Acute nonspecific carditis	02	02
	Septicaemia	03	03
	Cholecystitis & cholelithiasis	02	02
3	**Intracerebral haemorrhage**	02	02
4	**Cirrhosis**	03	03
5	**Trauma/suicide**	05	05
6	**Complications of therapy**	02	02
7	**Snake bite**	01	01

4. Discussion

Sickle cell anemia is the structural disorder of hemoglobin. Sickle gene frequency is between 5% to 40% distributed in three different geographic zone, mainly in tribal population of central and southern part of India.[14]

In our study, male predominance and peak age group of death (21-30 Years) is similar to the mean age of death reported between 32 to 45 years in other study series.[15-18]

Sudden death is defined as an unexpected death occurring in relatively healthy patient who suddenly died either at home or in the hospital with or without vaso-occlusive crises.[16,19]

Most common mode of death in our study is sudden unexpected death. Terminal event were fainting and convulsion, chest pain, dyspnea and sudden collapse without any prior symptoms or sudden death after short illness. The exact pathogenesis leading to sudden death is

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multifactorial. In our study, 37 cases were of sudden death and sickle-related vaso-occlusion was the primary cause of death in about half of the patients. Similar results suggest that pain episode is the main circumstance of death in adults with SCD.[15]

In many cases, precipitated factor for vaso-occlusive crisis is not known and patients are collapsed on duty, or with complain of dyspnea and chest pain of short duration, which is a sign of vaso-occlusion followed by death. Few cases are brought dead and history was not available. Knowledge of disease was only after autopsy.

Second most common cause of death in our study is infection which is comparable to the study by Perronne V et al.[18] The most common route of infection was respiratory tract (13%), followed by gastrointestinal tract (12%) and genitourinary which is similar to various studies.[20,21] The portal of entry appeared to be dictated by the sites of underlying chronic organ injury, suggesting that measures to prevent chronic organ injury may also prevent some infections and therefore improve long-term survival. As the portal of entry for infectious agents was predominantly the respiratory tract, early treatment of respiratory infections and its preventative measures like vaccination program, are important especially in childhood. Infection and dehydration were the precipitated factors for vaso-occlusive crisis especially in the cases of gastroenteritis. So, for knowledge of disease and to prevent complications, screening is essential.

In present study, there were (11%) cases reported as pneumonia and (10%) cases of gastroenteritis which is comparable with the study by Thomas AN et al and Manci EA et al.[17,20] The clinical presentation of acute pulmonary pathology in SCD has been termed as acute chest syndrome (ACS). In the study by Thomas AN et al the term encompassed disease due to pneumonia, pulmonary embolism or both; in the study by Gray A et al, it denoted acute pulmonary failure and in the study by Darbari DS et al, it defined as chest pain, fever and new pulmonary infiltrate on chest x-ray.[16,17,22] Infection is the most common identifiable cause for acute chest syndrome and other important triggers for acute chest syndrome are asthma, pulmonary fat embolism, vaso-occlusive crisis (VOC) causing pulmonary vascular obstruction resulting in infarction of pulmonary parenchyma.[23-26]

Intracerebral hemorrhage was recognized in (2%) cases in this study. Cerebrovascular accidents (CVA) in SCD may be due to intracerebral hemorrhage, subarachnoid hemorrhage due to (berry) aneurysm and infarction. Its incidence/ prevalence are range from 2% to 26% in various studies[16,17,21,22].

The incidence of death from chronic organ failure related to SCD was very low in our study (3%), the primary cause being cirrhosis[18]. This result contrasts with the pattern of chronic organ involvement identified in the study by Darbari DS et al and Thomas AN et al, where renal failure is the predominant cause.[16,17] Intra operative complications and collapse during surgery is likely due to factors such as hypoxia, acidosis, or hypothermia promotes erythrocyte sickling and it causes acute tissue injury by vaso-occlusion. The pre-operative prophylaxis by blood transfusion is the assumption that the dilution of sickle cells with normal erythrocytes will decrease the incidence of perioperative SCD-specific complications.

In study by Behrens RJ et al, circumstance of death is acute pain episode (21.5%), unknown (17.7%), renal failure (10.5%), stroke (9.6%), post-operative (6.7%) and infection (6.2%).[30]

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One striking gross morphological finding of our autopsy study was splenomegaly in adult patient. Splenomegaly was found in 47 cases. In the study by Manci EA et al, 25.4 % cases of splenomegaly were reported.[20] In acute splenic sequestration the spleen is markedly congested and enlarged, sometimes massively. Late persistent and gross splenomegaly is peculiarity of Indian SCD patients while in African or American patients have nonfunctional small spleens due to repeated infarcts and is associated with increased levels of fetal hemoglobin level.[28,29-35]

Most common microscopic morphological finding were marked congestion of all internal organ with disseminated intravascular sickling. Most of the death mechanisms are related to the biological consequences of diffuse microvascular occlusion due to sickling.

The chief histological change present is congestion involving the sinusoids mainly and extensive fibrosis of capsule, septa and splenic parenchyma with foci of hemosiderin deposit, calcification and gamna-gandy body. These findings are similar to the study by Chopra R et al.[35]

The spectrum of microscopic findings in lung ranges from pulmonary edema (21 cases), pneumonia (11cases), tuberculosis (4 cases), well differentiated invasive squamous cell carcinoma (1case) to chronic venous congestion and fibrosis. In a study reported pulmonary edema in 30.8% and pneumonia in 15.4% of cases which is comparable to our study.[15] In the past, the term sickle cell chronic lung disease (SCCLD) was used to show the association of pulmonary fibrosis and pulmonary hypertension in SCD, but now these processes are considered individually and clinically it is manifested as dyspnea.

The prominent lesions found in the kidney consist of papillary and interstitial fibrosis (7cases), acute tubular necrosis (5 cases), focal glomerulosclerosis (3 cases) and infiltration with lymphoid cells. In the study by Manci EA et al, papillary necrosis was found in 14.5% of cases.15 The distinctive abnormality of the renal papillae is due to occlusion of blood flow in the vasa recta, which may lead to papillary necrosis and fibrosis.[27,36]

SCD patients are more prone to infections because of auto-splenectomy that occurs as a result of repeated infarction of the organ thus leading to the loss & inability to fight infection. Additionally, SCD patients have defective alternative pathway of complement activation & reduced ability of neutrophils to kill pathogenic organisms which makes them especially prone to infection by encapsulated organisms. Common bacterial organisms that have been documented to cause infection in SCD patients in our environment include Salmonella typhi, E. coli, Staphylococcus Aureus, Haemophillus influenza & Klebsiella species, while Infection caused by Streptococcus pneumonia which have been reported by others have not been reported among SCD patients in our locale. The high prevalence of infections by Haemophilus Influenza & Pneumococcus species in patients with SCD, is the reason why patients in the UK & USA are placed on prophylaxis & vaccinated against these organisms. The introduction of bacterial prophylaxis for SCD patients in Nigeria may therefore reduce the mortality rate especially in early childhood due to infections.

Another important cause of death is severe anaemia associated with cardiac failure, playing a significant role as cause of death.

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5. Conclusion

Early diagnosis, prompt treatment & extended screening programme are necessary in prevalent tribal belt of western India to reduce morbidity & mortality. We should also introduce awareness programmes in India.

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