Research Article

**Autopsy findings and pattern of mortality in undiagnosed sickle cell disease patients**

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**ABSTRACT**

**Background:** Sickle cell disease (SCD) has a high mortality rate with unexpected sudden death. So, the purpose of the study was to analyze clinical and/or autopsy findings at the time of death among sickle cell disease (SCD) patients.

**Methods:** This is a retrospective study of SCD patients who died between January 2011 to December 2011 and the morphological evidence of the cause of death was studied in a tertiary care hospital of south Gujarat. The clinical data, including the age, gender, symptoms and the major autopsy findings and cause of death were obtained for each patient that included histopathological examination.

**Results:** A total of 472 autopsies were performed, out of which sickled erythrocytes were detected in 40 cases. The mean age at death was 30 years and a male/female ratio of 3:1 and peak mortality was in the 2nd and 3rd decades of life. The common causes of death in this study include vaso-occlusive crisis (45%), infection (40%). The terminal infection was heralded by upper respiratory tract (43.7%) and by gastroenteritis (31.2%). Other causes of death included intracranial haemorrhage (2.5%) and cirrhosis (2.5%). Among the cases of SCD, 10% of deaths were non-haemoglobinopathy related such as fall (accidental), organophosphorus poisoning and snake bite.

**Conclusion:** This study is to precise analysis of causes of death is needed to focus and improve morbidity and mortality in sickle cell disease especially in highly prevalent area and will impact on the overall survival of these patients.

**Key words:** Sickle cell disease, Sudden and unexpected death, Vaso-occlusive crisis, Autopsy

**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. Sickle haemoglobin is highly prevalent among the tribal of central, southern and western India. The sickle haemoglobin in India was first described by Lehman H et al. in 1952 in the tribal populations in the Nilgiri hills in south India. Gujarati have a high prevalence of HbS (13-31 %) in tribal area. The morbidity and mortality of sickle cell disease is very high. Depending upon sickle cell trait (SCT), SCD or sickle cell heterozygosity with other haemoglobinopathy like thalassemia, HbE, HbD, clinical course is very heterozygous from asymptomatic to repeated painful episode to sudden death in relatively healthy person.

In present study, we review morphological evidence of cause of death in autopsy which show presence of sickle cell in histopathological examination, with an emphasis of gross and microscopic finding of various organs; importance and frequency of those lesions that possibly lead to death.
The pathological finding seen at autopsy may or may not be directly related to the cause of death. Sickling of RBC may be seen even in trait person due to terminal hypoxic event which may not be responsible for death. Such problems include increased urinary tract infection in women, gross hematuria, splenic infarction with altitude hypoxia, life-threatening complications of exercise or idiopathic sudden death.

Despite high prevalence of SCD in India, relatively few autopsy studies have analyzed death in adult with SCD. Aim of this study to provide information which may be useful for reducing mortality and morbidity.

METHODS

During year January to December 2011, we review 472 autopsies. Out of which 40 autopsies showed presence of sickle cell in histopathological examination of various organ.

We analyze clinical presentation, morphological (gross and microscopic) examination of heart, liver, lung, kidney, brain and spleen and cause of death.

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

Inclusion criteria are presence of sickled RBC on histopathological examination.

RESULTS

A total 472 autopsies were seen in one year period (January-December 2011) out of which 40 cases (8.5%) show presence of sickled RBC on histopathological examination of various organs.

Peak age of mortality in our study was between 2nd and 3rd decades of life and mean age was 30 year. In our study male: female ratio was 3:1, reflects bias in case selection as these are all medico legal cases (Figure 1).

Mode of death was sudden and unexpected in 15 cases (37.5%) followed by fever (25%), gastrointestinal symptoms (12.5%) like acute gastroenteritis, diarrhea and vomiting and respiratory symptoms (12.5%) which includes breathless ness, chest pain, gabharaman and respiratory failure.

Four cases (10%) were natural death during treatment of their existing illness such as tuberculosis or following acute miscellaneous event such as snake bite, suicidal organophosphorus poisoning or accidental fall from height. One 3 year boy collapsed during surgery (herniorrhaphy) (Table 1).
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 in Table 2 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 criteria of this study. (Figure 2-6) Most common morphological finding in our study is splenomegaly.

Table 2: Morphological organ injury in autopsies of patients.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Morphological findings</th>
<th>No. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>Splenomegaly</td>
<td>21 (52.5)</td>
</tr>
<tr>
<td></td>
<td>Gamma gandy bodies</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Lung</td>
<td>Pulmonary edema</td>
<td>10 (25)</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>2 (5)</td>
</tr>
<tr>
<td></td>
<td>Invasive well differentiated squamous cell carcinoma</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Liver and gall bladder</td>
<td>Steatosis</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td></td>
<td>Cirrhosis</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Gall stone</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Heart</td>
<td>Atherosclerosis</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
<td>2 (5)</td>
</tr>
<tr>
<td></td>
<td>Acute nonspecific carditis</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Papillary and interstitial fibrosis</td>
<td>4 (10)</td>
</tr>
<tr>
<td></td>
<td>Acute tubular necrosis</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td></td>
<td>Focal glomerulosclerosis</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Brain</td>
<td>Intracerebral hemorrhage</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Uterus</td>
<td>Pyometra (pus in uterus)</td>
<td>1 (2.5)</td>
</tr>
</tbody>
</table>

Table 3: Causes of death in sickle cell disease patients.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaso-occlusive crisis</td>
<td>18 (45 %)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>• Pneumonia</td>
<td>5 (31.25%)</td>
</tr>
<tr>
<td>• Gastroenteritis</td>
<td>5 (31.25%)</td>
</tr>
<tr>
<td>• Tuberculosis</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>• Pyometra</td>
<td>1 (6.25%)</td>
</tr>
<tr>
<td>• Acute nonspecific carditis</td>
<td>1 (6.25%)</td>
</tr>
<tr>
<td>• Septicemia</td>
<td>1 (6.25%)</td>
</tr>
<tr>
<td>• Cholecystitis with cholelithiasis</td>
<td>1 (6.25%)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Trauma/suicide</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Complications of therapy</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Snake bite</td>
<td>1 (2.5%)</td>
</tr>
</tbody>
</table>

Most common cause of death is vaso-occlusive crisis (45%) followed by infection in 49% of cases. Other causes of death are intracerebral hemorrhage (2.5%), cirrhosis of liver (2.5%). (Table 3) Most common portal of entry is respiratory tract (43.7%), followed by gastrointestinal tract (31%) and lastly genitourinary tract (6.2%) (Table 4).
In our study, male predominance and peak age group of death (11-30 Years) and the mean age at death of 30 years is similar to the mean age of death reported between 32 to 45 years in other study series.10,12,16,17 In our study, 15% cases of sudden death is reflect bias in case selection as these were all medico legal cases and sudden unexpected death is reason for medico legal case.

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.11,14 Most common mode of death in our study is sudden unexpected death. Terminal event were fainting and convulsion, chest pain and gabharaman and sudden collapse without any prior symptoms or sudden death after short illness. The exact pathogenesis leading to sudden death is multifactorial. In our study, 15 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.10

In many cases, precipitated factor for vaso-occlusive crisis is not known and patients are collapsed on duty, or with complain of gabharaman 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.

2nd most common cause of death in our study is infection which is comparable to the study by Perronne V et al.13 The most common route of infection was respiratory tract (43.7%), followed by gastrointestinal tract (31.2%) and genitourinary tract (6.2%) which is similar to various studies.15,16 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 5 cases (12.5%) reported as pneumonia and 5 cases (12.5%) of gastroenteritis which is comparable with the study by Thomas AN et al and Manci EA et al.12,15 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.11,12,17 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.18-21

One case (2.5%) of Cholecystitis with cholelithiasis was reported as we have not received gall bladder in all cases. In the study by Manci EA et al, cholelithiasis was reported in 29% of cases.15 Cholelithiasis is one of the common complications of SCD and it is usually result from chronic hemolysis leading to continuous increased bilirubin production. A frequency however is variable depending on the age of the patients ranging from 5%-55% has been reported but an overall 60-70% of patients with SCD will develop gallstones at one stage of their lives particularly in children less than 5 years of age.22-25 Intracerebral hemorrhage was recognized in 1 case (2.5%) 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.11,12,16,17,26

**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. In Gujarat, south Gujarat shows presence of sickle gene range from 5 to 34 % in tribal population.9

<table>
<thead>
<tr>
<th>Systemic localization of infections causing death in SCD patients.</th>
<th>No. of cases (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract</td>
<td>7 (43.75 %)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>5 (31.25%)</td>
</tr>
<tr>
<td>Genitourinary tract</td>
<td>1 (6.25%)</td>
</tr>
<tr>
<td>Acute nonspecific carditis</td>
<td>1 (6.25%)</td>
</tr>
<tr>
<td>Septicemia</td>
<td>1 (6.25%)</td>
</tr>
<tr>
<td>Cholecystitis with cholelithias</td>
<td>1 (6.25%)</td>
</tr>
</tbody>
</table>

**Figure 6:** Photomicrograph showing pulmonary vessels congested with sickled RBCs (H&E, x40).

**Table 4:** Systemic localization of infections causing death in SCD patients.
The incidence of death from chronic organ failure related to SCD was very low in our study (2.5%), the primary cause being cirrhosis. 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.

Among the cases of SCD, 4 cases (10%) were non haemoglobinopathy related such as fall (accidental), organophosphorus poisoning, snake bite and intra operative complication. In the study by Manci EA et al, 8.4% of death was non haemoglobinopathy related.

There was a one case of 3 year male child admitted for hernia operation and he was collapsed during surgery. This intra operative complication is likely due to factors such as hypoxia, acidosis, or hypothermia promotes erythrocyte sickling and it causes acute tissue injury by vaso-occlusion. The prophylactic preoperative erythrocyte 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 Patel DK et al, the commonest cause of mortality was painful crisis (44%), followed by malaria (26%), renal failure (14%), stroke (6%) and other causes (10%). Median age at death was 25 year. Persisted splenic enlargement is common and related to high HbF and malaria. Endemic malaria and tuberculosis are important cause of high morbidity and mortality.

In study by Platt OS et al, 18% of death occurred due to overt organ failure predominantly renal failure and 33% were clinically free of organ failure and died during acute sickle cell crisis.

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%).

One striking gross morphological finding of our autopsy study is persistent splenomegaly in adult patient. In our study splenomegaly was found in 21 cases (52.5%). In the study by Manci EA et al, 25.4 % cases of splenomegaly were reported. In the study by Behrens RJ, progressive atrophy of spleen in adult has been documented and splenic sequestration is rare after age of 5 years. Splenic sequestration refers to an acute condition of intrasplenic pooling and trapping of large amounts of erythrocytes. In our study not a single case show atrophy and >50% cases of splenomegaly. As 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 it is associated with higher level of fetal hemoglobin level.

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 gamma-gandy body. These findings are similar to the study by Chopra R et al.

The spectrum of microscopic findings in lung ranges from pulmonary edema (25%), pneumonia (12.5%), tuberculosis (5%), well differentiated invasive squamous cell carcinoma (2.5%) to chronic venous congestion and fibrosis. The study by Manci EA et al reported pulmonary edema in 30.8% and pneumonia in 15.4% of cases which is comparable to our study. No bone marrow emboli or fat emboli or thrombus were detected in lung. As the lung vasculature transits from acute to sustained pressure-induced injury, lung capillaries are exposed to stress failure, i.e., loss of cellular integrity promoting edema within the interstitial and alveolar compartments.

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 (10%), acute tubular necrosis (7.5%), focal glomerulosclerosis (4%) and infiltration with lymphoid cells. In the study by Manci EA et al, papillary necrosis was found in 14.5% of cases. 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.

CONCLUSION

Sudden unexpected death may occur in susceptible persons when poor physical conditioning, dehydration, heat stresses or hypoxic states precipitate sickling of abnormal erythrocytes. Careful monitoring and aggressive treatment of acute events, especially within the first 24 hour of presentation, is warranted.

The main pathological findings include widespread intravascular sickling, but the exact cause of death is not always explained after a complete autopsy. Morphological findings are only indicative of the possible mechanism of death and do not prove it. The discovery of normal size and enlarged spleen in patient with SCA in post mortem prompted the need to re-evaluate the general belief that autopsplenectomy is the rule among them.
A complete autopsy with in-depth knowledge of clinical status of patient, circumstances of death, systematic histologic examination, hemoglobin electrophoresis, molecular studies and toxicological analysis should be evaluated in any unexplained sudden death in a young patient. Community awareness and proper counseling programs are helpful in preventing sickle cell disease and able to craft holistic care for the treatment and management of SCD crisis among individuals living with this disease.

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