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Original Research Article

Pattern of mortality in sickle cell disease: an autopsy study

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ABSTRACT

Background: Sickle haemoglobin is highly prevalent in western India. 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 –thalassaemias (Hbs b-thal). While doing autopsy in case of death with no apparent cause, the possibility of death may be due to vaso-occlusive crisis in sickle cell disease should be kept in mind. The findings at autopsy are variation of features which may or may not be directly connected to death. The goal is to draw awareness among physicians and relatives on need of autopsy as to minimize future unexpected death from complication or crisis and to enhance knowledge on both parties.
Methods: This was a study of autopsy specimens received between January 2015 to December 2015 at tertiary care hospital.
Results: Total of 679 autopsy cases were received, out of which sickled erythrocytes were detected in 25 cases. The mean age at death was 30 years, a male/female ratio of 1.5:1 and peak mortality was in the 2nd to 4th decades of life. The commonest presentation was sudden death. The cause of death in middle aged patients were vaso occlusive crisis, in paediatric patients were infection and in older patients were chronic organ damage.
Conclusions: Early diagnosis, prompt treatment and extended screening programme are necessary in prevalent tribal belt of western India to reduce morbidity and mortality. we should also introduce awareness programmes in tribal belt of western India.

Keywords: Autopsy, Sickle cell disease, Sudden death, Vaso occlusive crisis

INTRODUCTION

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 –thalassaemias (Hbsb-thal). Haemoglobinopathies are the commonest inherited disorders worldwide and SCD shows an important proportion of these. The clinical features are variable and relate to diverse factors, ranging from climate, socioeconomic condition, haemoglobin level, level of fetal haemoglobin and the type of abnormal haemoglobin that accompanies the Hbs in the heterozygous form.[1] In spite of much improvement in treatment, disease is still associated with high morbidity and mortality. This study is to evaluate the autopsy findings at our centre and compare them with that of other places as to create awareness among the physicians and relatives/public and to minimize future unexpected death from complications or crisis from SCD.

Sickle haemoglobin is highly prevalent among the tribal of central, southern and western India with variable frequency ranging from 10-23%.[2,3] Increased prevalence is also reported in the non-tribal communities of these areas. Death in clinically asymptomatic patients with sickle cell disease or sickle cell trait is not uncommon.

But, unfortunately less numbers of deaths were reported due to sickle cell anaemia because of unawareness or unavailability of history in prevalent tribal areas with high prevalence.

METHODS

During year January to December 2015, we have reported 679 autopsies. Out of which 25 autopsies showed presence of sickled red blood cell in histopathological examination of various organ. We analyzed clinical presentation, morphological (gross and microscopic) examination of heart, liver, lung, kidney, brain and spleen and cause of death.

This study is retrospective and all patients were not documented cases of sickle cell anemia except for one case, and data regarding Hb electrophoresis or HPLC was not available so homozygosity, heterozygosity or presence of other haemoglobinopathy could not be assessed. We have included cases which showed presence of sickled RBC in various organs on histopathological examination.

RESULTS

A total 679 autopsy cases were seen in one year period (January-December 2015) out of which 25 cases showed presence of sickled RBC on histopathological examination of various organs.

Peak age of mortality in our study was between 2nd to 4th decades of life and mean age was 30 year. In present study male: female ratio was 1.5:1 which reflects male predominance.

Comparison of male: female ratio in different age groups.

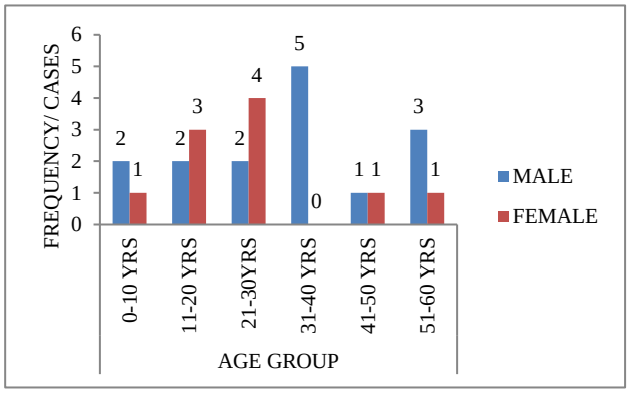

Figure 1: Age and sex distribution.

Clinical presentation (Table 1) was sudden and unexpected death in 12 cases (48%) followed by acute chest syndrome in 6 cases (24%) which includes combination of 1 or more symptoms like fever, chest pain, difficulty in breathing. Next common presentation is Fever in 3 (12%), gastrointestinal symptoms 3 (12%) like acute abdominal pain and acute gastroenteritis. One lady had history of pesticide ingestion.

Table 1: Various clinical presentations in death due to SCD.

Clinical presentation	Cases
Sudden death	12 (48%)
Acute chest syndrome	6 (24%)
Fever	3 (12%)
Gastrointestinal symptoms	3 (12%)
Ingestion of pesticide	1 (4%)

We have evaluated morphology (Table 2) of different organs which are summarised in a following table.

Table 2: Morphology of different organs in SCD cases.

Organ	Pathology	FREQ/ Number of sases
Spleen	Splenomegaly	10
	Gamna gandy bodies	6
Lung	Pulmonary edema	5
	Pneumonia	2
	Chronic venous Congestion	2
	Intra-alveolar hamorrhage	2
Liver	Chronic venous congestion	2
	Steatosis	2
	Cirrhosis	2
Heart	Coronary artery disease	5
	Hypertrophy	2
	Changes of ischemia	2
Kidney	Focal glomerulosclerosis	3
	Acute tubular necrosis	2
	Acute pyelonephritis	1
	Chronic pyelonephritis	2
	Chronic renal disease	1

Apart from these, marked congestion of internal organs were noted in all cases.12 cases had Splenomegaly, 6 cases had shrunken, fibrosed and calcified spleen. Among 5 cases of Coronary Artery Disease, 3 were of older age group (>45 years) but 2 cases (32 and 35 years old) showed thrombus in Left Anterior Descending artery.

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

Causes of death	
Vaso-occlusive crisis	18 (72%)
Infections	4 (16%)
Pneumonia	2 (8%)
Gastroenteritis	1 (4%)
Septicemia	1 (4%)
Chronic organ damage	3 (12%)

Most common cause of death (Table 3) is vaso-occlusive crisis in 18 cases (72%) followed by infection in 4 cases (16%). Other 3 (12%) cases showed changes of chronic organ damage.

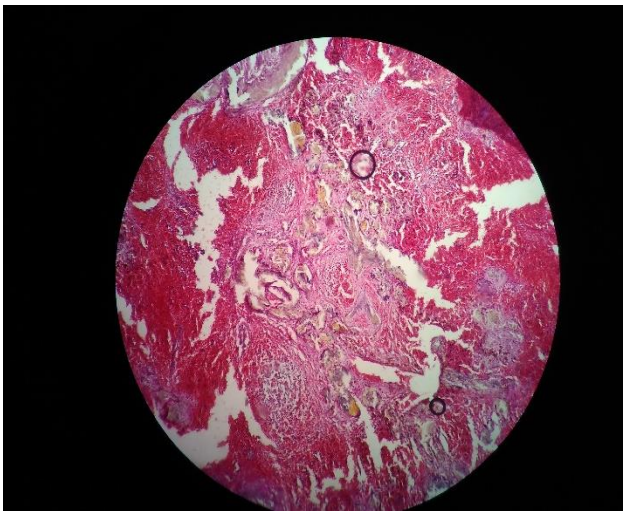

Figure 2: Sickled RBCs and Gamna gandy bodies in spleen.

DISCUSSION

Sickle cell disease, the classical prototype of hereditary hemoglobinopathy has an autosomal recessive inheritance. It manifests in two forms viz. heterozygous (sickle cell trait) or homozygous (sickle cell disease). It results from the point mutation in the genetic code where glutamate is replaced by valine at the sixth residue position of the beta globin chain.[4] 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.[5]

In present study, male: female ratio was 1.5:1 which reflects male predominance. According to Manci et al, no significant sex difference was noted in frequency of acute events. In present study, peak age group of deaths is between 15-40 Years and the mean age at death of 30 years is similar to the death reported between 32 to 45 years in other study series.[6-10] In present study 12 cases (48%) of SCD patients presented with sudden death which may reflect bias in case selection as these were all medico legal cases. Manci et al. also noted Increased frequency of sudden unexpected death (40.4%) and rapid course within 24 hours of presentation (27.7%).[10]

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.[7,11] Most common mode of death in our study was sudden unexpected death. Terminal event were fainting, convulsion, chest pain, gabharaman and sudden collapse without any prior symptoms or death after short illness. The exact pathogenesis leading to sudden death is multifactorial.

Another commonest presentation is acute chest syndrome (ACS) in 6 cases (24%), which is comparable to the studies of Thomas and Platt in which ACS is presenting feature in 22.3% and 13.9% respectively. ACS in Young children presents with fever and cough while adults are often afebrile and had complaint of chest pain, difficulty in breathing.[6,8] Most common cause of death in present study is vaso-occlusive crisis, seen in 18 cases (72%) out of all deaths. Out of which 9 cases were of sudden death and 9 cases were presented with acute symptoms. These results suggest that pain episode due to acute events or vaso occlusive crisis is the main presentation of death in adults with SCD.[5] It may be due to limited access to medical care in developing counties. Acute events in the sickle cell disease include painful vasooclusive crisis, infarctive stroke, acute chest syndrome, priapism, aplastic crises, splenic sequestration, haemolytic crises and infections. The trait patients are mostly asymptomatic and sickle cell crisis can occur in them only if the patient is exposed to extreme hypoxic conditions. Hypoxia due to exertion induces a chain of events in a person with sickle cell anemia that causes sickling, leading to vascular occlusion, potentiating hypoxia and culminating in sudden death. Similarly, infection, fever, anxiety, abrupt changes in the body temperature or hypertonic dyes are precipitating factor for sickle cell crisis. But, in many cases no cause is obvious.[24]

In present study, most common cause of death is infection in pediatric patients, 2 cases where of pneumonia and 1 case was of acute gastroenteritis, which is comparable to the study by Manci et al, in which the most common route of infection was respiratory tract, followed by gastrointestinal tract.[10,12] 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 may be the precipitating factors for vaso-occlusive crisis especially in the cases of gastroenteritis.

Present study shows 6 cases (24%) of renal failure, in which chronic renal damage is seen in 12% of cases and all of them were more than 50 years of age. Findings are consistent with Darbari et al, according to this study, 22.6% of patients had the finding of renal failure and there was an association with increasing age. Other chronic organ damage include cirhhosis in 8% cases in present study. This is comparable with Darbari et al, according to whom 11.3% of patients had the finding of cirrhosis.[7]

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 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%).[13] 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%).[14]

In present study, among SCD deaths 1 case (4%) are that of non-hemoglobinopathy related death. According to Manci et al. 8.4% of deaths were non-hemoglobinopathy related.[10] One striking gross morphological finding of our autopsy study is persistent splenomegaly in adult patient. In our study splenomegaly was found in 10 cases (40%). In the study by Manci EA et al, 25.4% cases of splenomegaly were reported.[10] 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.[14] Splenic sequestration refers to an acute condition of intrasplenic pooling and trapping of copious amounts of erythrocytes. In present study 6 (24%) case show atrophy. 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 non-functional small spleens due to repeated infarcts and it is associated with higher level of fetal hemoglobin level.[3,13,15-21]

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 (gamna-gandy body). These findings are like the study by Chopra R et al.[21]

The spectrum of microscopic findings in lung ranges from pulmonary edema (20%), pneumonia (8%), intra alveolar hemorrhage (8%) to chronic venous congestion. 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.[10] 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.[22,23] 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 dyspnoea.

CONCLUSION

SCD is the commonest hereditary disorder which is associated with increased mortality and morbidity. Unavailability of relevant clinical history is a major shortcoming in diagnosis of SCD in sudden death. So, autopsy surgeon should keep the possibility of SCD in death due to unknown cause in high prevalent trible areas. We have presented this study to emphasise pattern of mortality and common circumstances of death. Sudden death is common in middle age group which commonly presented with sickle cell crisis. Infection is the commonest cause of death in pediatric patients involving mainly respiratory and gastrointestinal tract. In older age group, chronic organ damage is seen in almost all patients. The goal is to create awareness among physician and relatives on need of autopsy. Autopsy will give knowledge and relevant data to minimize future unexpected death from sickle cell crisis or complications in cases of SCD. So, for knowledge of disease and to prevent complications, screening programme is essential.

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