

Research Article

Death due to sickle cell anaemia, an autopsy diagnosis: a study at a tertiary care hospital

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ABSTRACT

Background: Sickle cell disease (SCD) is the generic term for the group of inherited haemoglobinopathies caused by the occurrence of Haemoglobin S (HbS) in the homozygous or heterozygous form in combination of Hbs with another abnormal haemoglobin such as HbSC or beta-thalassaemias (HbS-thal). Sickle cell syndromes are remarkable for their clinical heterogeneity, including their presentations as sudden and unexpected deaths due to a sickle cell crisis. Less numbers of deaths are reported due to this cause because of ignorance of autopsy surgeon in considering this disease as a cause of death despite of its high prevalence. While doing autopsy in cases of deaths with no apparent cause and physical over activity medical officer must keep in mind the possibility of death due to vaso-occlusive crisis in sickle cell disease.

Methods: The study covers a period of one year (January 2013 - December 2013) and it is a study of cases of autopsy carried out in a tertiary care hospital of South Gujarat.

Results: A total of 607 cases examined, out of which sickled red blood cells were detected in 17 cases. The respective records were reviewed. Out of 17 cases, 13 cases were male and 4 cases were females. The youngest person was 15 years female and oldest was 70 years male.

Conclusion: Sickle cell crisis is one of the causes of sudden unexplained deaths. The present study highlights the role of autopsy in such cases. Community awareness and marriage counseling programs are also helpful in preventing sickle cell disease.

Keywords: Sickle cell crisis, Sudden and unexpected deaths, Autopsy study

INTRODUCTION

Sickle cell anemia was first described by Herrick in 1910. Pioneering studies by Pauling et al. established that Sickle Cell Disease (SCD) results from a defect in the hemoglobin molecule.¹ The sickle mutation was characterized several years later by Ingram et al. as a glutamine-to valine substitution at the sixth residue of the beta globin polypeptide. Homozygosity for the sickle mutation (i.e., HbSS) is responsible for the most common and most severe variant of SCD. Sickle cell disease is an

autosomal recessive, genetically transmitted haemoglobinopathy which is responsible for a considerable amount of morbidity and mortality.²

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 show remarkable heterogeneity, some have repeated episodes of admissions while others are totally asymptomatic. Severity depends on various factors like climate, socioeconomic, haemoglobin level, various haplotypes, % of HbF and concurrent alpha thalassemias.^{3,4}

Sickle cell haemoglobinopathy is prevalent in the tropical and subtropical regions of the world and which may affect any organ or system of the human body.⁵ It is an irreversible and an untreatable health problem which is predominantly seen among various tribes in the world. With its present rate of spread, in another 25 to 40 years, over 150 lakh children will suffer and die of sickle cell disease, and over 300 lakh people will inherit the abnormal haemoglobin trait.⁶ In India, the Haemoglobin S (HbS) was first detected in the Vedeloid tribes in the Nilgiri hills of Tamil Nadu and it was later discovered in other tribes also like the Veddian tribes of south, tribes of western India, labor tribes of Orissa and Assam, certain tribes of Marathi.^{7,8} Its incidence varies from 5 to 34 % and it is mainly restricted to the tribal population.⁹

In spite of much improvement in treatment, life survival is still associated with high morbidity and mortality. The findings at autopsy are variation of features which may or may not be directly connected to death. This is not only due to few autopsy studies but lack of interest of populace for autopsy to be carried out. The fact remains that the relatives will ignore any further studies having known the patient genotype. This study reviews the autopsy findings that are seen in incidentally detected sickle cell anemia cases in terms of showing major morphological changes; importance and frequency of those lesions that possibly lead to death. This is to evaluate the pathological autopsy findings in our Centre and to create awareness among the physicians and relatives/public and to minimize future unexpected death from complications/crisis from SCD.

Keeping this perspective in mind here we report our analysis in terms of pathological changes seen in various organs in 17 cases of sickle cell anemia in whom the diagnosis was not previously known.

METHODS

The study covers a period of one year (January 2013 - December 2013) and it is a study of cases of autopsy carried out in a tertiary care hospital of South Gujarat. A total of 607 cases examined, out of which sickled Red blood cells were detected in 17 cases. The respective records were reviewed.

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

RESULTS

We could detect presence of sickled red blood cells in histopathological examination of received organs of 17 cases out of total 607 cases of autopsy. Out of 17 cases, 13 cases were male and 4 cases were females. The youngest person was 15 years female and oldest was 70 years male.

In clinical history three cases having complained of abdominal pain out of which two cases are with peptic perforation and haemoperitoneum. Five cases with complain of fever, two cases with signs and symptoms of jaundice. Two cases with history of convulsion out of which one case was of pregnant female. Two cases with history of giddiness and collapse. One case with history of sudden death. One was suicidal case and one was snake bite history. On visceral examination finding eight cases show grossly splenomegaly and one case show changes of splenic atrophy along with chronic venous congestion changes and presence of Gamna Gandy body. One case show changes of pneumonia in lung and one case with presence of microfilaria. Three cases show changes of healed myocardial infarction.

On gross examination of, all the pieces of the viscera showed marked congestion. Light microscopical examination of each organ was carried out and all the organs showed markedly dilated and congested vessels with stuffed sickled red blood cells. The spleen showed partial architectural effacement by the sickle cells. The red pulp and the sinusoidal space within the pericapsular areas were packed with irreversibly Tactoid sickled cells. The rest of the organs showed the same microscopical picture and they were packed with sickle cells, especially the liver and the brain. The final histopathological diagnosis was given as sickle cell crisis which led to an acute sequestration crisis and a vaso-occlusive crisis.

DISCUSSION

The clinical course of sickle cell disease is punctuated by acute painful episodes traditionally referred to as 'crises' which are the hallmark of the disease. The clinical consequences of sickle cell 'crises' are diverse and have been the subject of numerous varied reports in medical literature. This disease first manifests in children or adolescents. Patients mostly present with hemolytic anemia, jaundice, repeated vaso-occlusive crises, hand foot syndrome, acute chest syndromes, and splenic sequestration crises etc.¹⁰ They can also get repeated infections like pneumonia, osteomyelitis, dactylitis etc.

Sickle cell disease is a chronic condition with acute episodes which are related to vaso-occlusion, leading to high mortality. Virtually every system of the body can be affected by the ischemia which results from the obstruction of the blood vessels by the clumps of the deformed erythrocytes. The strongest evidence implicates that intravascular sickling with tissue injury and even

death is by an extreme exercise (exertion), with dehydration and relative hypoxia (altitudes).¹¹

Sickle cell haemoglobin is a mutant form of normal adult haemoglobin. Under low oxygen concentrations, the mutant deoxyhaemoglobin polymerizes and eventually leads to a change in the red cell shape, giving a pointed tip to the RBCs that mean irreversible Tactoid sickled RBCs.¹² This phenomenon is called sickling and hence the mutant haemoglobin is called sickle cell hemoglobin (HbS).¹² The most common cause of death for all the sickle cell variants and for all the age groups was infection (33-44%).¹³ The terminal infection was heralded by upper respiratory tract syndromes in 72.6% and gastroenteritis in 13.7% of the infants. Other causes of death included stroke (9.8%), splenic sequestration (6.6%), pulmonary emboli (4.9%), renal failure (4.1%), hepatic failure (0.8%) and left ventricular failure (0.4%).¹³ The death was sudden and unexpected (40.8%) or it occurred within 24 hours after the presentation (28.4%) and was usually associated with acute events (40.8%) as per Mancini EA et al.¹³

DNA structure of Asian halotype has high levels of HbF and coincided with alpha thalassemia. Both these features inhibit sickling. So they have persistent splenomegaly, which minimizes pneumococcal septicemia, acute chest syndrome and malaria infection. This also prevents chronic organ damage, even though mortality is high with painful crisis in Asian halotype.^{4,14} In our study we found splenomegaly in eight cases (47%) and only one case show splenic atrophy. Only one case show changes of pneumonia.

The main pathophysiology in sickle cell disease is, oxygenated sickled Hb is soluble while deoxygenated sickled Hb leads to hydrophobic interaction between adjacent HbS leading to polymerization. This polymerization stiffens the sickled RBCs, which adhere to adjacent vascular endothelium and are prone to hemolysis leading to vascular clogging, tissue hypoxia and necrosis.¹⁵ Clinical manifestations are diverse and any system or organ may be affected, which are divided into vaso-occlusive crisis and splenic sequestration crisis.¹⁶ Vaso-occlusive crisis occurs when microcirculation is obstructed by sickled RBCs. Various factors precipitating vaso-occlusive crisis are cold weather, infection, dehydration, acidosis, alcohol intoxication, emotional stress, pregnancy etc. Vaso-occlusive crisis leads to life threatening major organ infarct. In all our cases we saw that all vessels were clogged with sickled RBCs.

There are various studies regarding the cause of death in SCD. Knowledge about the causes of mortality in SCD is vital to focus the future efforts for improvement in management and treatment of patients. In one study 33% death occurred in relatively healthy patients without chronic organ failure but died during classical sickle crisis and 78% died during acute painful episode or acute

chest syndrome.¹⁷ Platt et al. studied 3764 patients of SCD and studied 209 adult patients who died of SCD pattern and mortality varies with age. Peak incidence of death among children with sickle cell anemia occurred between 1-3 years of age and death among patients less than 20 years of age were due to pneumococcal sepsis. 18% of death in adult was due to chronic organ failure and 33% of death occurred in relatively healthy patient who died during a classical sickle crisis. 78% died either due to painful episode or acute chest syndrome.¹⁸

In most of the studies death in SCD is due to acute chest syndrome, sickle cell crisis, chronic organ damage, painful and splenic sequestration crisis, bone marrow embolism in decreasing order of frequency. Sickle cell crisis is the second most common cause of death. So in person coming from endemic area of SCD with any medical problem, intensive supportive care and good management keeping always in mind the suspicion of sickle cell disease will prevent catastrophic event.

In our study, the histopathology revealed a sickle cell crisis in all the organs, especially in the spleen, liver, and the brain. Sickle cell crisis is a broad term for several acute conditions with sickle cell disease, including acute sequestration crisis, vaso-occlusive crisis, and haemolytic crisis. Acute sequestration crisis is the most common disorder results from splenic enlargement due to a sudden accumulation of large quantities of blood. Further, it leads to severe anaemia, shock and death. This finding is seen in eight cases.

Vaso- occlusive crisis results due to an aggregation of deformed erythrocytes i.e. clumps of sickled RBCs which obstruct the blood vessels. This results in ischaemia and infarction of the adjacent organs like the lung, liver, kidney, spleen and the cerebrum. During the periods of crisis, the susceptibility to infections in young children is increased mainly due to *Pneumococcus* and *H.influenza*. They lead to rapidly fatal systemic infections and severe septicemia.^{13,19} In our study, three cases show changes of healed myocardial infarction and one case show pneumonia.

Failure of early intervention in patient with SCD contributed to sudden deaths of this group of patient. This is because the disease was not known until after autopsy. This is important that relatives of patients grant consent for autopsy to aid the physicians in effective management of future patients. Aggressive screening must be done at all possible levels for sickle cell disease. The education regarding the precipitating factors like dehydration, physical stress etc. is given to the individuals and Exposure to such factors is avoided in these cases. Prophylactic treatment is needed in diagnosed cases to improve the quality of life. Our ultimate motive should be to keep future generation free from mortality due to such preventable causes.

CONCLUSION

Sickle Cell Disease (SCD) is the commonest hereditary hematological disorder which is associated with increased mortality and morbidity. The goal is to create awareness among physicians and relatives on need of autopsy as to minimize future unexpected death from complication/crisis and enhance knowledge on both parties. We presented this study to emphasize that sickle cell crisis is one of the causes of sudden unexplained deaths and to highlight the role of autopsy in such cases. Community awareness and marriage counseling programs are also helpful in preventing sickle cell disease.

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