CAUSES OF DEATH IN SICKLE CELL DISEASE – AN AUTOPSY STUDY

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ABSTRACT

Taking our huge population size, more than 50 % of world sickle cell anemia cases are in India [(1)]. Clinical picture of sickle cell disease in our country is extremely variable, little information is available on the cause of death at different ages, but several symptoms have been reported in sickle cell diseases cases from different parts of India[(2)]. More precise analysis of causes of death is needed to focus research efforts and improve morbidity and mortality in sickle disease. Hence the purpose of the study was to analyze the autopsy findings at the time of death in sickle cell crisis.

Keyword: Vaso occlusive crisis, sickle cell disorder.

INTRODUCTION

Hemoglobinopathies are characterized by the production of structurally defective hemoglobin due to abnormalities in the formation of the globin moiety of the molecule. Abnormal hemoglobins are inherited as autosomal codominants.

The sickles Hemoglobinopathies are hereditary disorders in which the red cells contain Hb-S, They include the heterozygous (Sickle cell trait) and the homozygous (SS disease) states for the Hb-S. in deoxygenated state , the solubility of Hb-S is ten percent of that of Hb-A the conformational changes in Hb-S induced by deoxygenation causes the cells containing the abnormal hemoglobin to become rigid and deformed , assuming a sickle or crescent shape.

The sickling of red cells in circulating blood has two major pathological effects.

(a) The distorted and rigid cells block small blood vessels, impairing flow and causing ischemia and infarction.

(b) Repeated sickle- unsickles leads to premature destruction of RBC.

Hb-s differ from Hb-A in the substitution of valine for glutamic acid in the sixth position from the n-terminal end of β chain.

Red cells containing large amounts of Hb-S begin to sickle at an oxygen tension of 50 – 60 mm Hg. This tension is experienced by the cells in parts of the microcirculation and thus sickling occurs in viva.

The abnormal hemoglobin of sickle cells disease was first demonstrated in 1949.

Taking into our huge population size, more than the 50 % of the worlds sickle cell anemia cases are in India[(1)]. It is estimated that most of the cases are in the central and south India.

In Maharashtra sickle cell gene is widely spread in all districts of eastern Maharashtra (known as vidarbha region) and same parts of marathwada region[(1)]. The prevalence of sickle cell disease is very high among the Bhil and Pawara group from the Nandurbar district[(4)]. Nandurbar district is at a distance of 80 km from our hospital. Hence the need to review the mortality due to this disease.

MATERIAL & METHOD

- This is a retrospective analysis of 34 cases of autopsy death due to sickle cell crisis, since the year 2001 to 2010.
- A total of 2458 autopsies were done in this 10 year.
- We receive organs for histopathological examination from autopsies carried out in peripheral health center, rural hospital and civil hospitals, along with the brief clinical history and postmortem findings similarly autopsies are conducted in our college hospital.

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- The age, gender, ethnic groups, clinical presentations were gathered from the clinical records.
- All the histopathological slides along with the gross findings were reviewed.

RESULTS

- 34 cases died due to sickle cell crisis in the last 10 years out of a total 2458 autopsies.
- Out of 34 cases in 31 cases the post mortem was conducted in peripheral health centers and 3 cases the patients were referred from the periphery to our college hospital. They died within 6 Hrs. The Post Mortem of these 3 cases was carried out by our department.
- Table, Gender and age wise distribution of the patient are as follows.

Total	Male	Female	Total
Infant -4th Yr	1	0	1
Children (6 – 15 Yrs.)	7	7	14
Adult (16 – 65 Yrs.)	12	7	19
Total			34

- Season wise distribution of deaths.

20%	Rainy Season
10 %	Winter Season
04 %	Summer

- Patient belong to fallowing ethnic groups

Tribal population	19
Scheduled caste	14
Muslims	1

- Distribution of sickle cell trait among different tribal groups

Pawara	5
Bhil	4
Padvi	3
Tandvi	3
Gavit	2
Vasave	1
Total	19

- Year wise distribution of cases

01	1
02	3
03	1
04	4
05	2
06	3
07	8
08	3
09	7
10	2

- Disrict wise distribution of death

Dhule District	10
Jalgaon District	10
Nandubar District	14

- Clinical presentation of Patient

None of the cases were diagnosed as sickle cell Hemoglobinopathies in life.3 cases admitted in our hospital were from talukas from Dhule district. All the 3 cases were anemia, showed signs and symptoms of congestive cardiac failure, they had Jaundice. A single Patient showed evidence of renal failure considering the ethnic group sample was send for solubility test. The solubility test was Positive but by the time patient was dead.

Positive findings seen on gross and microscopic

Presentation	No. of Death
Sudden death with Preceding history of fever, Not feeling well, Bodyache	24
Pain in abdomen, jaundice, Sever Anaemia, CCF	03 Admitted in hospital of our institution but Died within 6 hrs of Admission.
Sudden death with history of loose motion and vomiting	02 Ashram School Children
Post Tubectomy	01
Maternal death (Post-Partum)	01
Fitness test for Police Selection	01
Cradle Death	01
Head Injury	01 Admitted in private hospital And died on 2nd day.

Examination were as follows -

I) Cardio thoracic

Heart - Cardiomegaly was seen in all except in Infants

- Adult had cardiomegaly with Biventricular hypertrophy.

Common causes such as

- 2 adult male patient aged 65 and 56 yrs showed foci of old and recent degeneration. There was no e/o atherosclerosis, grossly as well as an life

Lungs - Pulmonary edema in majority of cases confirmed on microscopy

- Thickening of pleura seen in adult patients.
- Bronchopneumonia seen in 2 patient-one adult and one children.
- Grade I Pulmonary hypertension was seen in few adults.

II) Abdomen

Hepato-biliary system

- Hepatomegaly in all cases except in cradle death, person undergoing fitness test, cradle death and head injury.
- Zonal necrosis around central vein in 2 cases who had jaundice.

Spleen - Spleen was fibrosed and reduced in size along with gamma Gandy bodies formation in 2 adult female patients.Rest showed Spleenomegaly except in 3 cases who did not show hepatomegaly.

Intestine - Grossly congested mucosa showed ulceration in 3 cases whose autopsies were done in our institution. In rest of the case Intestine was not received.

Kidney - Grossly kidney were normal in all cases except in patient showing clinically Renal failure, the kidneys were reduced in size and showed scars.

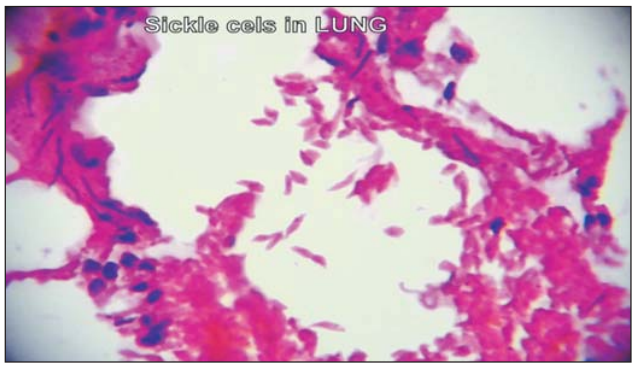
Central nervous system-Grossly Brain was normal.

On Histopathology -

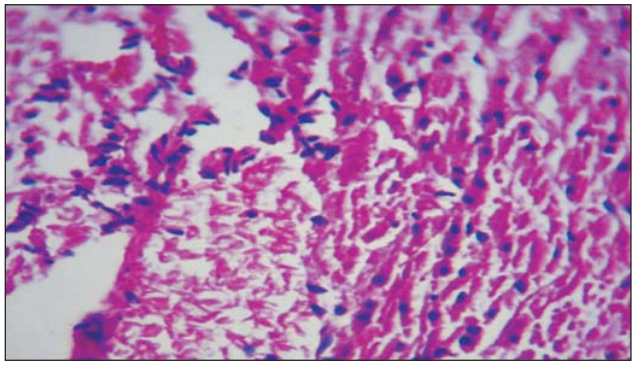
All the organ capillaries were clogged with sickled shaped RBC's. In liver sinusoids, kupffer cells were too clogged with RBCs spleen showed marked congestion in all cases. Sinusoids filled with sickled shaped RBCs. Intestine mucosal ulceration were confirmed on microscopy.The sub capillaries in mucosa and submucosa were clogged with sickled shaped RBCs.

Uterus received in maternal death and in tubectomy patient too showed capillaries clogged with sickle shaped RBCs.

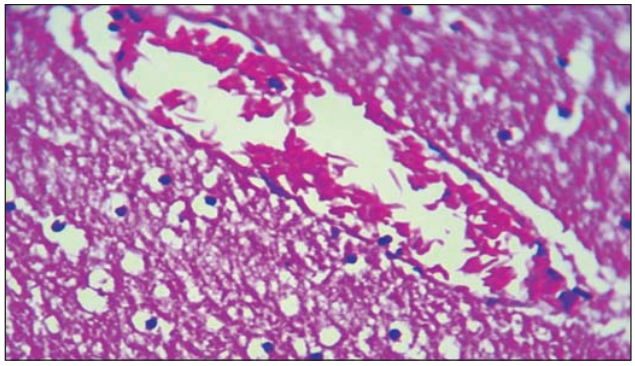
Impression– vaso occlusive crisis



Legend 1 : Photograph showing Lung studded with sickle shaped cells



Legend 2 : Photomicrograph showing Spleen studded with sickle shaped cells



Legend 3 : Photomicrograph showing Brain capillaries studded with sickle shaped cells.

DISCUSSION

Sickle gene was first discovered by Lehman and Cutsbush (1952) among the tribal's of nilgri hills[2] .Since then more than 300 tribal groups have been screened to look for the presence of sickle cell gene [5,6,7]. In certain states like Madhya Pradesh, Orissa, Chhattisgarh, Jharkhand, Gujarat and Maharashtra it forms a major public health problem.

Sickle cell disorder is mostly confined to socio-economically backward groups like scheduled tribes and nomadic tribes [4]. Prevalence of sickle cell disorder is very high amongst the tribal population groups form Nandurbar district 20 %.

Table showing distribution of sickle cell trait[4] in various tribes.

Tribal Groups	District	Sickle Cell Carrier%
Pawara	Dhule ,Jalgaon	25.18
Bhil	Nandurbar	20.6
Kokana	Dhule ,Nashik	3.50
Tandvi	Jalgaon	8.30

Thus our findings has been co-rrealted dwith the epidemiological data of (S L Kate et al, Ajit S Gorashkar) our cases belonged predominantly to tribal population followed by scheduled caste . It was seen more in Nandurbar district Pawara and Bhil tribal groups showed more mortality we had a single case who was Muslim Ajit s Gorashkar did find sickle cell cases in Muslim.

The mortality was more seen in rainy season followed by winter maximum cases were seen in the year 2007,2009 Because the Rainfall co related with Mohanty D et al. the reason behind it is vaso occlusive crises is precipitated by extremes of ambient temperature [7]. The mortality was seen more in adults due to high fetal hemoglobin level seen and maintenance of life at low hemoglobin level[7].

26 cases presented with sudden death sudden.Death was defined as an unexpected death occurring in relatively healthy patient who suddenly died either at home or in the hospital. However our patient of sudden death presented with preceding complains of fever,not feeling well, body ache (which may be joint pain).This preceding symptoms were not taken seriously .Extensive clinical studies by Kar BC et al too noted that attack of pain, fever and anemia were the predominant presenting features[9].

According to Kate SL et al anemia, intermittent Jaundice, severe Joint pain, recurrent infection where the common symptoms. Three Patients who where admitted in our hospital showed the same presenting symptoms. In rest

of the cases the detailed history was not available as the post mortem examination was not carried in our institute.

There was a single case of maternal death.Preagnancy per say is known to be a state of oxidative stress and may technically bring about severe hemolytic crisis episodes. Similarly infection stress on the body like post tubectomy, in our case head injury too precipitate vasocclusive crisis[10].

Two Ashram school children had sudden death with preceding events of loose motion and vomiting This indicating sickle cell disease patient are more prone to infection this causing gastroenteritis According to Elizabeth A Manci et al Gastroenteritis makes 13.6% of mortality in her study[11].

Case 1- A 4 months old infant had a sudden death in a cradle. On HPE capillaries of all the organs were clogged with sickle shaped RBCs . This can be explained by the warmth of the cradle and tradition of wrapping the baby in clothe could have created hypoxia favoring vaso-occlusive crisis.

Case 2. A young male collapsed at police selection camp. An important complication of sickle cell disorder is un expected exercise related death (ERD) .12 Such cases was reported among healthy men in 1981 in us armed force basic training by Kark J.A. The pathogenesis in ERD is during exercise PH decreases causing increase in temperature at tissue level to facilitate oxygen delivery, this causes highest concentration of deoxygenated hemoglobin leading to sickling[12].

Cardiomegaly was seen in 80 % of cases. The findings co related with Carlos T et al [13].Two adult patients showed foci of old and recent degeneration in absence of atherosclerosis. This finding co related with James T N et al[14]. They found abundant foci of old and recent degeneration in the sinus node, atrio-ventricular node, bundle of his and the coronary chemoreceptor . They suggested that these findings might indicated that some patients with SCD who die a sudden death without significant autopsy finding might have an lethal cardiac instability[14].The significance of these findings in uncertain but they do indicate the need for detailed cardiac examination at autopsy in sickle cell disease.

Lung - Pulmonary edema in all cases and finding of pulmonary hypertension in 3 adult male patient. Graham J K found pulmonary edema 47.6 % and pulmonary hypertension in 33.3 %[15].

Bronchopneumonia was seen in 3 cases thickening of pleura noted in 8 adult patient reflects organization of pleural exudation related to prior episode of pneumonia[13].

Hepatomegaly with sinusoids and Kupffer cells distended with sickled RBCs with areas of focal necrosis around central vein in patient presenting with jaundice co-related with Thomas et al who observed hepatomegaly in 91 % cases along with similar findings and liver cell necrosis in 31 % of cases[16].

Spleenomogaly was seen in 82 % of cases while 2 adult female patient showed evidence of fibrosis along with Gamma gandy bodies. On HPE examination it showed findings of spleenic sequestration. According to Kamble et al[17] spleenic sequestration was the commonest cause in his study.

While a single case showed clinically as well as on HPE evidence of renal failure. Deepika S Darbari et al reported 47.8% of renal failure patients over 40 yrs of age[8] .

The environment of renal medulla is characterized by hypoxia ,acidosis and hypertonicity that pramote hemoglobin S polymerization and red cell sickling which ultimately leads to glomeruli malfunction manifestated initially as protenuria and potentially progressing to chronic renal failure[18].

Mucosal ulceration in Intestine was also observed by van der Neut F W in homozygous sickle cells disease in female patient[19].

Has all the organs showed capillaries packed with sickle shaped RBCs the terminal event of death was put as vaso-occlusive crisis state. This finding co related with Patel MM, who observed vaso occlusion by sickle RBCs in 5 autopsy cases of sudden death [20].Similar finding was seen by Konotey Ahuti et el in Ghana [21].

DNA structure of asian halotype has high level of HbF and coincided with alpha thalassemia. Both these features inhibit sickling,so they have persistent spleenomegaly which minimize pneumoccocal septicemia, acute chest syndrome and malarial infection. This also prevents

chronic organ damage even though mortality is high with painful crisis in Aisan halotype[22,23].

There was not a single death of a case which was diagnosed as sickle cell disorder during life in our hospital. Thus it explains that early diagnosis can reduce the mortality of the disease by giving good medical counseling and medical care.

Hence it is a need to join hands together and reach the tribal population and to take part in sickle cell control Programme by providing diagnostic facilities, health education, genetic and marriage counseling ,medical care and reducing the mortality due to sickle cell disorder.

Study of autopsy death due to sickle cell disorder was not presented earlier hence the need to present the data.

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