Clinico-Epidemiological And Hematological Profile Of Sickle Cell Anemia With Special Reference To Penicillin Prophylaxis In A Rural Hospital Of Central India

K Swarnkar, A Kale, B Lakhkar

Abstract
Research questions: clinical, epidemiological and Hematological characteristics of a cohort of children with sickle cell anemia attending a specialist out-patient clinic in a rural hospital?Objectives:1. To study the pattern, type and frequency of crises/infections in sickle cell anemia children.2. To observe the effect of intervention (penicillin prophylaxis, folic acid, regular follow up) on the pattern of crisis and infections in disease. 3. To study the hematological values in sickle cell anemia children at recruitment.4. To correlate hemoglobin and hematocrit values to number of crisis/infections in disease.5. To study the effect of intervention on academic performance in disease.

INTRODUCTION
Nearly 20 million people suffer from sickle cell anemia in India. The sickle cell gene in India was first described among tribal groups in South India (1) but is now recognized to be widespread, especially in Central India, where the prevalence in different castes and communities varies between 9.4-22.2 % (2). Sickle cell disease is an inherited hemoglobinopathy arising from the substitution of glutamic amino acid by valine in the sixth position of the beta globin chain (3). Inheritance of the sickle cell trait follows a recessive autosomal pattern. Phenotypically, only persons with double recessive genes of sickle cell (ss homozygote) do manifest disease, whilst the heterozygotes (AS) are being referred to as carriers. Children with sickle cell anemia have been known to have an increased susceptibility to severe bacterial infections, particularly those due to Streptococcus pneumoniae. Meningitis, pneumonia, and septicemia caused by this organism have been recognized as the major causes of death among children with the disorder, with those under three years of age at highest risk. (4-8). The incidence of pneumococcal septicemia among children with sickle cell anemia under the age of five years appears to have remained remarkably constant, at 7 to 8 per 100 person-years of observation. (9-11) This illness is often Fulminant, progressing from the onset of fever to death in less than 12 hours; the case fatality rate may be as high as 35 percent (10, 12-13). Sickle cell disorder has remained a neglected field of research in this country and magnitude of problem has never been appreciated in spite of the fact that the sickled RBCs were detected in the blood of Indian patients as early as 1952. This was largely because most of the subsequent reports spread a misconception that the sickle gene in India was confined to the tribal population or some scheduled castes only. This paper describes the clinico-epidemilogical profile, hematological characteristics and efficacy of oral penicillin prophylaxis in children with sickle cell anemia attending a specialist out-patient clinic in a rural hospital of...
Material methods - The present study was conducted in Department of pediatrics, Jawahar lal Nehru medical college and Acharya Vinoba Bhave Rural Hospital, sawangi (wardha), during the period of 1st June 2009 to 31st July 2010. The study group consisted of 131 cases of proven sickle cell anemia, who presented to the Pediatric outpatient department, or admitted to the ward. Detailed history, general and physical examination was carried out and growth was assessed. The hemoglobin and hematocrit along with battery of investigations to detect crises and organ failure were carried out. The management was done as per IAP Pediatric Hematology Chapter Protocol 2007 Guidelines. Details were documented in a pre designed proforma. All the patients with proved sickle cell disease were started on penicillin prophylaxis. The patients with disease were followed up for a period of one year at one monthly interval. Patients with trait were followed without prophylaxis once in three months. Every visit growth was assessed and the parents were enquired about any illness from the preceding visit. The growth and illnesses were documented in the chronological order.

Throughout the study patients with SS pattern on electrophoresis were called as ‘disease’ and AS pattern were called ‘trait’. Sickling was done by using freshly prepared 2% sodium metabisulphite solution followed by sealing the assembly and observing for early sickling after 30 min and late after 24 hours. Hemoglobin electrophoresis was done on cellulose acetate test strip with Tris phosphate buffer at a pH of 8.4. Blood indices were estimated by cell counter and hematology counter ABX Micros 60, Horiba Diagnostics, Horiba. Serum investigations were done by fully automated biochemistry analyzer ECO Plus, manufactured by Logotec Pvt. Ltd. Rome (Italy). Patients with SS pattern were given penicillin V tablets in dose 125 mg in children below 3 years of age and 250 mg in children above 3 years of age in 12 hourly doses daily with tablet folic acid 5mg once daily. Kuppuswamy’s Socio-economic Status Scale- Update for 2007(14) was used for classification of patients. Height was taken on stadiometer and weight was taken on electronic weighing machine which was calibrated on daily basis. Height and weight were plotted on CDC Growth charts 2000. Academic performance was taken as percentage of marks in last term ending exam. It was graded as Poor if < 50%, Average 50-60%, Good >60-70%, Excellent >70-80% and Outstanding >80%. Poor follow up was defined as missing >15 days of the drug for two consecutive months or more than an average of 6 days of drug for three consecutive months. Steady state was defined as a crisis-free period of at least 2 months.

Data Handling - The collected data was entered in Microsoft Excel and Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) (version11.5). Means of normally distributed data were compared using the Student’s t-test. Categorical variables were compared using Pearson’s chi-square test as indicated. P values <0.05 were considered significant.

Ethical considerations - This study was approved by Ethical committee of Jawahar lal Nehru Medical College. Written informed consent was obtained from the parents or guardians of all subjects after explaining them in their own language.

RESULTS

Figure 1

Figure 1: Age and Sex Wise Distribution Of Patients With Sickle Cell Trait And Disease.

Total number of patients presenting with sickle cell anemia were 131. Out of which 58 were of disease and 73 were traits. Male: female ratio in disease was 1.07:1 while that in trait 1.08:1. Most patients, in both disease and trait, belonged to the age group of 4-8 years comprising 47.32% of total patients. There was no significant difference in sexes between the disease and trait group (t test: Male Vs Female in Disease p=0.57, Male Vs Female Trait p=0.58, Males in Disease Vs Trait p=0.97, Females in Disease Vs Trait p=0.99).
Most of the patients of SCD were belonging to Hindu religion (51.72%) followed by Buddhist (44.82%) in the disease, while in SCT only (45.20%) patients belonged to Hindu community preceded by Buddhist community (54.79%) in traits. There was no significant difference between proportion of Hindus and Buddhists either in disease or traits ($\chi^2 = 3.44, p=0.32$).

Patients of lower socio-economic status constitute the most common class in both in disease (67.24%) and trait patients (65.7%).

The mean hemoglobin and hematocrit levels were significantly low in disease as compared to the traits ($Z$-test for Equality of Means: $p<0.01, p<0.01$). The mean levels of MCV, total leukocyte count, polymorphonuclear leukocyte...
count, reticulocyte count, were significantly elevated in disease patients.

**Figure 6**

Figure V-Scholastic Performance Before and After Intervention in Both Disease and Trait Patients.

Of the school going population in disease patients, 68.16% patients belonged to Average and Poor performance group while in traits 14.28% patients belonged to Average and Poor performance group before the intervention. There was statistically significant improvement in scholastic performance of patients with disease after intervention as compared to the traits (p<0.01). This is shown by increase in number of children in Good and Excellent performance group. There was also significant difference in scholastic performance in disease and trait group (Independent T-test p=0.03) before intervention.

**Figure 7**

Table 3: Correlation of Hemoglobin Levels with the Average Number of Crisis and/or Infections Per Year With and Without Penicillin and Folate Prophylaxis in Disease Patients.

<table>
<thead>
<tr>
<th>Hemoglobin Level (gm/dl)</th>
<th>Total number of crisis/infections</th>
<th>Total number of patients suffering</th>
<th>Mean number of crisis and infections with prophylaxis</th>
<th>Mean number of crisis and infections without prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 gm% (n=15)</td>
<td>46</td>
<td>15</td>
<td>3.06</td>
<td>0.06</td>
</tr>
<tr>
<td>0-4 years</td>
<td>22</td>
<td>8</td>
<td>2.75</td>
<td>0.125</td>
</tr>
<tr>
<td>4-8 years</td>
<td>16</td>
<td>4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>&gt;8 years</td>
<td>8</td>
<td>3</td>
<td>2.66</td>
<td>0</td>
</tr>
<tr>
<td>5-8 gm% (n=31)</td>
<td>60</td>
<td>51</td>
<td>1.93</td>
<td>0</td>
</tr>
<tr>
<td>0-4 years</td>
<td>18</td>
<td>10</td>
<td>1.8</td>
<td>0</td>
</tr>
<tr>
<td>4-8 years</td>
<td>37</td>
<td>18</td>
<td>2.05</td>
<td>0</td>
</tr>
<tr>
<td>&gt;8 years</td>
<td>5</td>
<td>3</td>
<td>1.66</td>
<td>0</td>
</tr>
<tr>
<td>8 gm% (n=12)</td>
<td>17</td>
<td>12</td>
<td>1.41</td>
<td>0.68</td>
</tr>
<tr>
<td>0-4 years</td>
<td>4</td>
<td>3</td>
<td>1.33</td>
<td>0</td>
</tr>
<tr>
<td>4-8 years</td>
<td>8</td>
<td>5</td>
<td>1.6</td>
<td>0.2</td>
</tr>
<tr>
<td>&gt;8 years</td>
<td>5</td>
<td>4</td>
<td>1.25</td>
<td>0</td>
</tr>
</tbody>
</table>

There was a statistically significant difference in the number of crisis/infections a year prior intervention between hemoglobin <5 gm% and >5-8 gm% group and >8 gm% (p<0.01, p<0.01 one-way ANOVA). However there was no significant difference in the number of crisis/infections per year between >5-8 gm% and >8 gm% (p=0.119). When hemoglobin <5 gm% group was considered, there was a significant difference between >4-8 years group, and 0-4 years (p<0.015) and >8-14 years in number of crisis/infections (p=0.032). There was no significant difference in number of crisis/infections per year between different age groups within other hemoglobin or hematocrit categories. There was also significant reduction in the mean number of crisis/infection in the year after intervention (p<0.01, Student’s paired T-test).

**DISCUSSION**

The childhood diseases in rural area pose difficulty for diagnosis and management, as the signs and symptoms are modified by the haemoglobinopathies like sickle cell disorders. The manifestations of crisis also aggravate the course of the disease. Moreover, it is beyond the scope and competency by the peripheral health institutions to identify such genetic disorders. Only high index of suspicion and screening can guide the community physicians for better management of cases and prevent childhood morbidity and mortality. The present study measures and highlights the clinico-epidemiological and hematological profile of sickle cell disorders in the rural children. In the present study total number of patients presenting with sickle cell anaemia were 131. Out of which 58 were of disease and 73 were traits. Male: female ratio in SCD was 1.07:1 while that in SCT 1.08:1. No significant difference was observed in sex wise prevalence of sickle cell disorder. Similar observation were also made in other studies(15-18) but in some study male show high preponderance to SCD may be because males are more prone to crisis as they are more exposed to known precipitating factors (19). Most patients, in both disease and traits, belonged to the age group of 4-8 years comprising 47.32% of total patients(18-20). Most of the patients of SCD were belonging to Hindu religion (51.72%) followed by Buddhist (44.82%) in the disease, while in SCT only (45.20%) patients belonged to Hindu preceded by Buddhist religion (54.79%). In Buddhist religion mahar community was mostly affected constituting (100%)in both SCD and SCT group followed by kunbi (21.64%) in Hindu religion. Similar results were also shown in other studies(2, 16, 21) These observations show that sickle cell gene had
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predilection for certain communities mostly belonging to backward class and schedule caste may be because of consanguinity and, caste and area endogamy, some communities show a very high incidence, making the disease as a major public health problem in our country. Patients of lower socio-economic status constitute the most common class in both in disease (67.24%) and trait patients (65.75%)(22-23).

Recurrent fever (51.14%) was the most common symptom in both group followed by abdominal pain, joint pain and fatigue. Splenomegaly (44.27%) was the most common sign followed by Hepatomegaly, pallor, Icterus and Lymphadenopathy, similar pattern of clinical profile was also observed in other studies (19, 23-25). Patients with sickle cell disease presented most commonly with vaso-occlusive crisis (51.72%) of which hand-foot syndrome was most common (20.69%), followed by splenic sequestration (20.69%). Septicemia (15.51%) was the most common infection found in the patients with sickle cell disease (26-30). The clinical spectrum of homozygous sickle cell disease varies widely between patients. Factors contributing to this variability include alpha-thalassemia, persistence of high HbF levels, hematology, social circumstances, and geographical and climatic variation(31). The mean hemoglobin and hematocrit levels were significantly low in disease as compared to the traits. The mean levels of MCV, total leucocyte count, polymorphonuclear leucocyte count, reticulocyte count, were significantly elevated in disease patients. Similar findings were also observed in other studies (24-25, 32-33). We found that there was a significant decrease in MCV in disease patients at presentation and after one year of follow up. A double blind controlled trial of supplementation with folic acid showed that in the folic acid supplemented group, a significantly lower mean cell volume was found than the placebo group and experiencing less episodes of vaso-occlusive crisis(34). Thus folic acid deficiency is obviously present in our patients and supplementation is required. Of the school going population in SCD patients, 68.16% patients belonged to Average and Poor performance group while in traits 14.28% patients belonged to Average and Poor performance group before the intervention. There was statistically significant improvement in scholastic performance of patients with disease after intervention as compared to the traits. This is shown by increase in number of children in Good and Excellent performance group.(35-37). Hemoglobin less than 5gm% and age group 0-4yr is associated with highest number of crisis or infection but there is statistically significant decrease in episodes of crisis/infection following penicillin prophylaxis (38-40).

CONCLUSION

Sickle cell disorders in children are indistinguishable both clinically and haematologically. They run in families and seen in siblings. Therefore, the children with recurrent episodes of painful attacks in abdomen, musculoskeletal pain, ARI, fever, splenomegaly, anemia and epistaxis should be suspected of sickle cell disorders. They should be screened by simple sickling test to identify the genetic disorder. Parental counseling and preventive measures like penicillin prophylaxis, regular folate supplementation, early treatment of ARI with simple antibiotics and management of pain with simple analgesics will be helpful in decreasing morbidity and mortality in childhood with sickle cell disease, hence With a comprehensive medical care and management approach, the health status and life expectancy of these patients can be improved considerably.

Limitation of study- The main problem with small sample studies is interpretation of results, in particular confidence intervals and p-values. Another major limitation of small studies is that they can produce false-positive results, or they over-estimate the magnitude of an association. There are also limitations associated with the statistical analysis. When examining risk factors or other association, it is often necessary to allow for the effect of important prognostic factors (confounders). This is done using methods such as multivariate linear or logistic regression and Cox’s regression (for survival data). However, when the number of observations is small and researchers attempt to adjust for several factors, these methods can fail to produce sensible results or they produce unreliable results. But in spite of limitation there is nothing wrong with conducting well-designed small studies; they just need to be interpreted carefully and Instead, data from such studies should be used to design larger confirmatory studies.
Figure 8

Consent Form

Place of study: Department of Pediatrics Jawahar Lal Nehru Medical College & Acharn Brahma Viroha Rural Hospital
Patient name: ______________________
Registration No. ______________________

Title of Project: Clinico-epidemiological and hematological profile of sickle cell anemia with special reference to penicillin prophylaxis in a rural hospital of Central India

Name of Researcher: Dr. Keerti Shankar

1. I confirm that I have understood the information (In local language) for the above study.
2. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
4. I understand that relevant sections of any of my medical notes and data collected during the study may be made available by responsible individuals from HOSPITAL AND INSTITUTION, where it is relevant to any partaking in this research. I give permission for these individuals to have access to my record.
5. I agree to take part in the above research study.

Name of Patient: ______________________
Date: ______________________
Signature: ______________________

Date: ______________________

References

30. Stankovic Stojanovic K, Lionnet F, Girot R, Lescure FX,


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