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What Factors Influence the Age at Diagnosis of Sickle Cell Anemia in Enugu, Nigeria?

Chukwu BF*, Ezenwosu OU, Eke CB, Chinawa JM, Ikefuna AN and Emodi IJ

Department of Pediatrics, College of Medicine, University of Nigeria, Enugu Campus, Nigeria

Abstract

Objectives: This study aimed at determining the factors that influence the age at diagnosis of sickle cell anemia among children in Enugu, Nigeria.

Methods: One hundred and fifty seven children with sickle cell anemia were recruited consecutively using a researcher administered questionnaire. Information obtained from patient's mother included patient's bio-data, social history, family history, age at confirmation of diagnosis and clinical information.

Result: There was a wide variation of the age at diagnosis of sickle cell anemia ranging from 2 months to 14.7 years with a median age of 24 months. Only 10.4% were diagnosed before the age of six months and all were diagnosed after they have presented with symptoms and complications. The age of the mother and having an elder sibling with sickle cell anemia significantly affected the age at which the disease is diagnosed.

Conclusion: There is a delay in the diagnosis of sickle cell anemia in Enugu with mother's age and having an elder sibling with the disease influencing the age at diagnosis.

Keywords: Age; Diagnosis; Sickle cell anemia; Enugu objectives

Introduction

Sickle cell anemia (SCA) is a hereditary disease of blood characterized clinically by episodes of acute illness referred to as crisis and progressive end organ damage and dysfunction [1]. It is the commonest single gene disorder worldwide affecting about 1 in 400 black Americans [2]. It is estimated that about 85% of sickle cell disorders and about 70% of all affected births occur in Africa [3]. Nigeria has the highest population of patients with SCA with prevalence that ranges from 2% to 3% and contributes substantially to child morbidity and mortality [4,5]. About 25% of the population has the sickle cell trait while about 150,000 births are affected annually by sickle cell disorder [6]. It is estimated that about 30,000 school children has the disorder in Eastern Nigeria [7].

Sickle cell anemia is caused by a mutation in the ß-globin gene in which adenine replaces thymine in the 17th nucleotide resulting in glutamic acid being replaced by valine in the 6th position of the ß-globin chain. The resultant sickle hemoglobin (HbS) in deoxygenated state precipitates and forms crystals which grow and form polymers within the erythrocyte thereby distorting its wall architecture, shape and malleability. The rate and extent of polymerization is dependent on the concentration of HbS and the amount of fetal hemoglobin (HbF) in the erythrocyte as HbF does not participate in polymerization. This change in architecture makes the red blood cells vulnerable to destruction (hemolysis) and entrapment in the microcirculation (vaso-occlusion) with resultant anemia and infarction in various organs respectively. The two major pathophysiological processes, hemolysis and vaso-occlusion (mediated by adhesive interaction between erythrocytes, leucocytes and endothelial cells) are responsible for all the clinical manifestations of sickle cell anemia.

The clinical manifestation of sickle cell anemia is progressive and age dependent. HbS is present at birth but the disease does not manifest until about 6 months of age or less due to high level of HbF in the first 2-3 months of life [8].

Early diagnosis of the disease in utero or during the neonatal period has been shown to improve the quality of life and reduce the mortality rate among affected individuals [9]. In countries where there are neonatal screening programs the life expectancy of the patients has been prolonged [9] due to early intervention and prevention of complications. In areas where there are no universal screening programs like Nigeria, the age at diagnosis will depend on age at which clinical symptoms and signs of the disease manifest and this may affect the outcome of the disease.

Despite high burden of sickle cell disorder in Nigeria, there is no neonatal screening program and patients are diagnosed only when signs of the disease manifest thereby delaying early diagnosis and intervention programs such as counseling and prevention of complications. The main objectives of this study therefore are to determine the age at diagnosis and the factors affecting the age at diagnosis of SCA at the University of Nigeria Teaching Hospital (UNTH), Enugu, South-East, Nigeria. It is hoped that the outcome of this study will stimulate awareness to relevant health policy makers to institute prenatal and neonatal screening program for SCA in Nigeria so as to make early diagnosis and reduce the morbidity and mortality arising from the disease.

Subjects and Methods

The study was descriptive and cross-sectional and was conducted at the pediatric sickle cell clinic of UNTH, Ituku-Ozalla, Enugu over a six

***Corresponding author:** Chukwu BF, Department of Pediatrics, College of Medicine, University of Nigeria, Enugu Campus, Nigeria, Tel: +2348036757003; E-mail: barth.chukwu@unn.edu.ng

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month period. The pediatric sickle cell clinic holds weekly and attends to children with sickle cell anemia who are ≤18 years of age.

Ethical clearance was obtained from the University of Nigeria Teaching Hospital Health Research and Ethics committee. Also consent was obtained from parents or caregivers of patients before enrollment.

The subjects included all children with confirmed genotype SS (using Hb electrophoresis) attending the pediatric sickle cell clinic who presented during the study period. They were recruited consecutively over a period of 6 months (October 2013-March 2014). Patients who were brought to the clinic by persons other than the biological mother were excluded from the study.

Data collection was by use of a pre-tested structured questionnaire. Information obtained included patient's current age, gender, social class, age at diagnosis, events necessitating diagnosis, parents' age at diagnosis, parents' premarital knowledge of genotype, any counseling following premarital genotype. Social classification was done using the protocol proposed by Oyedeji et al. [10] which adopts parents' highest educational attainment and occupation.

Data analysis was by use of Statistical Package for Social Sciences, version 16 (Chicago II, USA) software. Data presentation was in form of tables and charts. Frequencies, proportions and percentages were calculated for categorical variables. Results of continuous variables were expressed as means (SD) and medians. Chi-square analysis was used to test for association between categorical variables while student t- test and Mann-Whitney U test was used to test significant relationship between parametric and non-parametric continuous variables respectively. Test of significance was set at $p<0.5$.

Results

Patients' characteristics

A total of 157 patients with sickle cell anemia were recruited over the study period. The subjects comprised 87 (55.4%) males and 70 (44.6%) females. The age of the subjects ranged from 11 months to 18 years with median and mean ages of 8 years and 7.9(4.6) years. Table 1 shows the gender and age distribution of the patients.

Age at diagnosis

The age at diagnosis of sickle cell disease among the subjects ranged from 2 months to 176 months (14.7 years) with a median age of 24 months. The modal age group at which sickle cell disease was confirmed was 13 to 36 months age category. Sixteen (10.4%) of the subjects were diagnosed before six months of age and 56 (35.7%) diagnosed within period of infancy (Table 2). It is interesting to note that about 21% were diagnosed after five years of age.

Determinants of age at diagnosis

The age at diagnosis of sickle cell disease was significantly higher among the females than the males (t=2.4, p=0.01) with mean and median age at diagnosis among the males of 33.3 (29.2) and 24.0 (2-144) months while that for females was 47.09 (42.74) and 36 (2-176) respectively.

Age group (years)	Male	Female	Total
< 1	1	0	1
1< 3	14	7	21
3< 5	16	12	28
5< 10	28	23	51
10< 15	19	20	39
15<18	9	8	17
Total	87	70	157

Table 1: Age and Gender distribution of subjects.

Age category at diagnosis (months)	No of subjects	Percent	Cumulative percent
0-6	16	10.2	10.2
7-12	40	25.5	35.7
13-36	41	26.1	61.8
37-60	27	17.2	79.0
61-120	30	19.1	98.1
121-180	3	1.9	100.0

Table 2: Distribution of subjects according to age category at diagnosis.

Also, the age at diagnosis was noted to increase with parents' age. This was consistent with increasing mothers' age with a positive correlation (Spearman's rho=0.4, p=0.00) but inconsistent with father's age (rho=0.02, p=0.81). Table 3 shows the age at diagnosis and mother's age.

Overall, there was a significant difference in the age at diagnosis with respect to mother's level of education (Kruskal Wallis, p=0.04). The lower the maternal level of education, the higher the age at diagnosis although this trend was not consistent.

Children who have elder siblings previously diagnosed of sickle cell disease were diagnosed earlier (31.1 months) than those who did not have elder sibling with the disease (42.2 months) although the difference in their mean age at diagnosis was not significant (t=1.5, p=0.12). Children whose parents knew they have AS genotype before marriage were diagnosed earlier (mean=25.6, median=18 months) than those whose parents did not know their genotype or wrongly diagnosed to be AA before marriage (mean=38.7, median=24 months). The difference in the age at diagnosis among these two later groups of children was significant (t=2.4, p=0.01) (Table 4).

It is important to note that all the children presented with suspicious clinical features to a health facility before a diagnosis of sickle cell disease could be confirmed. In other words, none was diagnosed as a result of routine screening even among those whose parents knew they have sickle cell trait.

Discussion

In the current study the age at diagnosis of sickle cell disease ranged from 2 months to 176 months (14.67 years). This wide variation was also documented by Akudu et al. [10] in South West Nigeria. Many factors could have contributed to such wide variation including health seeking behavior of parents and caregivers, social issues as well as poverty and inadequacies in the health care delivery. Most children were diagnosed between second half of infancy and three years of age. The reason for this is because fetal hemoglobin reduces to about 30% after 6 months and continues to wane progressively to adult level at about one year with increasing level of sickle hemoglobin concentration. Therefore, it is from this second half of infancy that symptoms of the disease start to manifest in most patients. For those who were diagnosed earlier, it is possible that they had a faster decline in the level of their fetal hemoglobin concentration.

The mean age at diagnosis was significantly higher among the females than the males. This gender difference was also documented by Akudu et al. [11] in Lagos, Nigeria. Plausible reason for this difference could be because males are more exposed to precipitating factors of crises such as strenuous exercise [12] or because in our environment

Mother's age group (years)	Age at diagnosis (months)	
	Mean (SD)	Median (range)
17-25	15.05 (11.86)	12.0 (3.0-48.0)
26-30	32.93 (31.97)	21.0 (2.0-120)
31-35	40.41 (36.13)	24.0 (5.0-144)
36-40	55.12 (44.66)	48.0 (9.0-120)
41-44	68.38 (40.45)	77.0 (9.0-120)

Table 3: Mother's age at diagnosis of sickle cell disease in subjects.

Maternal education	Frequency*	Median (Range) age at diagnosis in months	Mean (SD) age at diagnosis in month0073
No formal education	4	90 (84-96)	90.0 (6.9)
Primary education	29	36 (3-144)	50.8 (44.4)
Secondary education	69	18 (3-176)	33.7 (33.6)
First degree	48	24 (2-144)	38.5 (35.9)
Second degree	3	60 (12-72)	48.0 (31.7)

*Educational level of four mothers could not be ascertained

Table 4: Age at diagnosis with respect to mother's educational level.

[13] and some Asian countries [14] parents have preference for male children and therefore pay more attention to their health needs.

Maternal age had influence on the age at diagnosis of sickle cell anemia in the present study as children of younger mothers were diagnosed earlier than those with older mothers. It is possible that younger mothers may be more informed on sickle cell disease through social media or have seen their friends suffer the illness and therefore know the need for early diagnosis and institution of preventive measures. The reason may also be that younger mothers still have small family size and may have more resources that are channeled to the health needs of the family while older mothers with larger family size and more economic responsibilities may delay seeking health care for the family. Small family size as a factor for early diagnosis of sickle cell anemia was also documented by Akudu et al. [11] in Lagos, South West Nigeria.

Even among parents who have premarital knowledge of their genotype; their children were not diagnosed until they fell ill. The reason for this could be due to poor health seeking behavior or poverty on the part of such parents or inadequate information and knowledge about sickle cell disease, lack of health facilities or poor service delivery on the part of the health sector. A study by Olarewaju et al. [15] in Jos, North Central Nigeria showed that about 25% of his study group had false belief that sickle cell disease is caused by evil spirit and about three quarters of those interviewed had stigmatization attitude towards individuals with the disease. These false believes negatively affect their health seeking behavior.

Children whose elder siblings had sickle cell disease were diagnosed earlier than those who had no elder sibling with the disease. This finding has not been collaborated by other studies and therefore will need to be authenticated by other studies. However, the reason for the present finding may be due to previous health and social challenges the parents had experienced from the elder children with sickle cell disease. With such challenges it is expected that they would seek medical attention earlier for the younger children so as to avert or ameliorate the challenges.

The educational level of the mother also had significant influence on the age at diagnosis. Mothers with higher level of education had their children diagnosed earlier than those with lower or no formal education. The reason for this could be due to better awareness and heath seeking behavior among the more educated mothers. It has been documented [16] that well educated mothers seek and utilize the health facilities for their children more than the uneducated mothers. As noted by Akudu et al. [11] and Brown et al. [17] children from the upper economic strata were diagnosed earlier than those from the lower strata. It has been documented by Oyedeji et al. [10] that a socioeconomic stratum of a family was dependent on maternal education among other things.

As it was noted in the study, none of the children presented for routine screening rather diagnosis was made after symptoms and complications have developed. Early diagnosis of sickle cell disease is very crucial as complications can be prevented through early intervention and treatment of these complications. Studies [18,19] have shown that sepsis which is one of the causes of death among children with sickle cell disease in the first two years of life can be prevented by penicillin prophylaxis starting early in life and vaccination against streptococcus and invasive hemophylius influenza bacteria. Early diagnosis through prenatal and newborn screening will also pave way for early education and counseling of mothers and caregivers to recognize complications that require immediate care.

In conclusion, the study has shown that there is substantial delay in the diagnosis of sickle cell anemia in our center. It therefore becomes imperative that early screening program for sickle cell disease be established in Enugu and other regions of the country. This screening can be during the prenatal, neonatal or at most in infancy, during welfare clinics using DNA analysis or Agar gel electrophoresis.

Limitations of the Study

The exclusion of patients whose biological mothers were not present to give information limited the number of patients that could have been recruited and therefore the outcome of the study may not have shown a true representation problem.

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