PREVALENCE OF SICKLE CELL GENE AMONG APPARENTLY HEALTHY UNDER-TWO SOUTH-EAST NIGERIAN CHILDREN: WHAT IS THE ROLE OF PARENTAL PREMARITAL COUNSELLING AND SOCIO-DEMOGRAPHIC CHARACTERISTICS? A PILOT STUDY.

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ABSTRACT

OBJECTIVE:
This cross-sectional descriptive study examined the role of parental premarital counselling and socio-demographic characteristics on the prevalence of sickle cell gene among 82 apparently healthy under-two children.

METHODS:
Subjects were recruited from under-two children attending child welfare clinic at Nnamdi Azikiwe University Teaching Hospital, Nnewi, South-East, Nigeria.

RESULTS:
More than half of their mothers were aware of their hemoglobin phenotype (64.6%) and that of their husbands (53.6%). In about half of the families (52.4%), the parents had a premarital counselling intervention against sickle cell disease (SCD). Among the 44 families where parents were aware of their phenotype before marriage, only one couple (2.3%) was at risk of having an offspring with SCD. None of the subjects had SCD and the prevalence of sickle cell trait (SCT) among them was 22%. Premarital counselling intervention in families seemed to increase the prevalence of SCT when compared to those not counselled but this was not statistically significant (p = 0.30). The lower prevalence of SCT among children of more educated women suggests that educational status may affect the distribution of the sickle cell gene in the population.

CONCLUSION/RECOMMENDATION:
Premarital counselling and screening may be effective in reducing the prevalence of SCD but the higher prevalence of SCT among the population where this intervention occurred portends an ominous sign for the future. Integration of malaria eradication and competent genetic counselling, with avoidance of discrimination against people with SCT or SCD, into screening programmes are essential for reducing the burden and impact of SCD.

KEYWORDS: Sickle cell gene, sickle cell disease, prevalence, premarital screening, counselling

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INTRODUCTION

Sickle cell disease (SCD) is a major public health concern in Nigeria and other Sub-Sahara African countries. Sickle cell disease is a genetic disorder caused by an autosomal recessive single gene defect in the B-globin chain of adult red blood cell hemoglobin (HbA) which produces a mutant form of the hemoglobin known as sickle hemoglobin (HbS). Sickle cell anaemia results from inheritance of HbS from both parents. Inheritance of HbS from one parent and another abnormal hemoglobin variant (HbC or B-thalassemia) from the other parent results in heterozygous form of sickle cell disease (HbSC or HbSβthal). Inheritance of abnormal HbS gene from only one parent gives rise to the carrier state or sickle cell trait (SCT) (HbAS).

The Sickle cell gene is highly prevalent in Sub-Saharan Africans and their descendants worldwide. The disease is also common among people whose ancestors came from India, Saudi Arabia and Mediterranean countries.[1],[2] The high prevalence in Nigeria and other malaria endemic African countries has been attributed to a survival advantage which sickle cell trait confers against malaria.[3] Currently, Nigeria has the highest

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burden of sickle cell globally and more than 150,000 children are born annually with sickle cell anaemia in the country.[2]

Sickle cell disease has serious health, and socioeconomic implications on the affected child and family. These result from the adverse consequences of recurrent sickle cell crises and other associated morbidities on the child's quality of life, education, physical and psychosocial development.[3] Unlike developed countries where individuals affected by sickle cell disease survive into adulthood, most affected children in Nigeria and other developing countries die before their 10th birthday due to inadequate health care services and social welfare system.[4] Care givers of affected children are also faced with enormous financial, psychological and inter-personal problems.[5] Therefore, prevention of the disease is very important in Nigeria considering its high burden and adverse consequences.

To reduce the burden and impact of sickle cell disease, the World Health Organization (WHO) recommended several control measures[3]. These include: genetic counselling for intending carriers couples to enable them make informed decision on whether to call off or go ahead with their marriage, prenatal diagnosis, newborn screening for early detection and timely interventions that can prevent avoidable sufferings and deaths among affected children. Prenatal diagnosis and newborn screening are often difficult to access in developing countries like Nigeria. Therefore, premarital screening and counselling remain the easiest means of preventing the disease in the country.

In Nigeria, the churches have taken up the challenge of preventing sickle cell disease by creating awareness on the disease and demanding for hemoglobin phenotype test results from couples intending to wed, thereby encouraging premarital Hb phenotype screening. As a follow-up, churches counsel intending carrier couples on the avoidance of marriage. They are counselled to marry individuals who are Hb AA to forestall having sickle cell affected children. However, there are limited reports on the effectiveness of this counselling intervention on the reduction of the prevalence of sickle cell disease or trait. Indeed our hypothesis is that this kind of intervention can increase the prevalence of SCT (HbAS), as malaria tends to preserve them in the population, eventually leading to an unmanageable situation in which there's increasing prevalence of SCT (HbAS) in the population.

This study was carried out to determine the prevalence of sickle cell trait among apparently healthy under-two children attending child welfare clinic in Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi and its relationship with parents' premarital counselling intervention and some socio-demographic characteristics; hence testing our hypothesis. The study also served as an effort towards early detection of sickle-cell disease or trait for prompt referral and relevant interventions. Results will assist stakeholders in strengthening sickle cell disease preventive strategies.

Materials and methods

This was a cross-sectional study comprising a total of 82 mothers and their babies. The mothers were interviewed, using a questionnaire, in the child welfare clinic of NAUTH, Nnewi. Demographic data included parent's marriage type, haemoglobin phenotype of parents and whether the parents received premarital counselling concerning sickle cell disease (SCD).

Two milliliters of blood was collected from the children and the blood samples were dispensed into tubes containing Ethylene diamine tetra acetic acid (EDTA) for haemoglobin electrophoresis and full blood count (FBC) of the babies. Haemoglobin electrophoresis and FBC were done manually according to standard procedures.[6], [7]

Statistical analysis of data obtained was done with statistical package for social sciences software package version 20 (SPSS lnc., IL, Chicago, USA). Values obtained were tabulated by age, haemoglobin phenotype, parents' highest educational attainment and occupation, and expressed in percentages. Chi square tests were used to compare frequencies and generate p values. P values less than 0.05 were considered significant

Results

Some socio-demographic characteristics of the children are presented in table 1. About half of the children were infants between the ages of 6 to 12 months. Majority of their mothers (80.4%) and fathers (62.2%) completed secondary school education. Their fathers were all income earners and predominantly traders (65.9%) while 19.5% of their mothers were non-income earners. Majority of their parents (74.6%) wedded in the church.

As shown in Table 2, none of the children had sickle cell disease but the prevalence of sickle cell trait among them was 22%. More than half of the mothers were aware of their hemoglobin phenotype (64.6%) and that of their husbands (53.6%). The predominant phenotype of the parents was AA (mothers=52.4%, fathers=39.0%). In about half of the families (52.4%), the parents had pre-marital counselling intervention against SCD. Only one (2.3%) "at risk" couple was

identified among the 44 mothers that premaritally knew their phenotype as well as that of their husbands. This couple were premaritally counselled against sickle cell disease and wedded in the church. Only mother's educational status was significantly associated with the presence of sickle cell trait as shown in Table 3.

The mean PCV of children with AA genotype was 0.29 + 0.03 while that of children with AS genotype was 0.27 + 0.03 (t-test=2.50, p=0.015). The mean WBC of children with AA genotype was 8.39 + 2.95 while that of their AS counterparts was 8.39 + 2.63 (t-test=-0.368, p=0.714).

Discussion

It is interesting to note that in this study, mothers' education was significantly correlated with the prevalence of sickle cell trait (SCT) in the study population; and that premarital counselling intervention against SCD by the churches increased the prevalence of SCT in families, compared to those where there was no intervention. However, this relationship didn't reach statistical significance (p=0.3).

The prevalence rate of sickle cell anaemia (HbSS) in this study is at variance while that of sickle cell trait (HbAS) agrees with previous Nigerian reports.[8],[9],[10] About 2% of all babies born to Nigerian parents have been reported to have sickle cell anaemia at birth.[2],[8],[10] After the neonatal period, the prevalence of sickle cell anaemia was reported to progressively decrease and at the age of 1-4 years, which is inclusive of the age of the subjects involved in this study, HbSS prevalence decreases to 0.4%.[8],[9] Therefore, the zero prevalence of HbSS in this study was surprising and may be attributed to improved awareness of the disease, premarital counselling, environmental factors and small sample size. Zero prevalence of HbSS was previously reported by a Nigerian study[11] but that study was conducted among students older than 17 years and the finding may be attributed to the high childhood mortality associated with sickle cell disease in developing countries like Nigeria. On the contrary, a high HbSS rate of 17% was reported among children less than 5 years in Kano, Northern Nigeria[9] and this was attributed to high rate of consanguineous marriage and polygamy which are uncommon in South-east Nigeria.

More than half of the parents of subjects in the index study had premarital counselling intervention against sickle cell disease and this might have reduced their risk of giving birth to an offspring with HbSS. Hence only 2.3% of the couples that admitted knowing their genotype before marriage were actually at risk of having an offspring with HbSS. This finding was supported by the report from a previous study conducted in the same center, which showed that only 2.8% of intending couples seeking routine premarital services in the center are at risk of having an infant with sickle cell anaemia, and majority of them would voluntarily call off their marriage if there was a risk of their offspring inheriting sickle cell anaemia.[12] Larger community based studies are needed to determine the true magnitude of sickle cell anaemia among children in similar age group.

The premarital awareness of haemoglobin genotype by more than half of the parents in this study agrees with previous reports.[13],[14] Mandatory screening and awareness of haemoglobin genotype as well as counselling intervention against sickle cell disease has been reported as a premarital condition for a similar proportion of south-eastern Nigerian couples[13] Premarital screening has been demonstrated to significantly reduce the burden of sickle cell disease by increasing the frequency of voluntary cancellation of marriage proposals among "at risk" couples thereby reducing the prevalence of "at risk" couples and sickle cell disease.[15] Experience in Saudi Arabia revealed that within 5 years of the implementation of mandatory premarital screening, the frequency of voluntary cancellation of marriage proposals among "at risk" couples increased by five-fold while the prevalence of "at risk" couples decreased by 60%. However, the effect of this intervention on SCT has not been well documented. Theoretically, though there is reduction of SCD, SCT would continue to increase, if individuals who are HbAA are forcibly matched with those who are HbAS in order to reduce "at risk" couples. Although Mendel's law suggests that SCT individuals will make up about 50% of the population in the above situation (Fig. 1), the prevalence is likely to be more, considering that these (SCT) individuals have a survival advantage in our clime where malaria is endemic.[3] This study provides evidence to support this hypothesis. As seen in table 3, the sub-population of our data set which had counselling intervention against SCD had an increased prevalence of SCT when compared to the sub-population that did not. It therefore becomes imperative to confirm or refute this observation by using a study population with higher statistical power. An affirmation of this observation will radically change strategies geared towards reducing SCD burden; as it will be unwise to, in the long run, increase the prevalence of SCT to very high levels in any population. The sickle cell gene has been documented to thrive in Sub-Saharan Africa due to malaria endemicity in the region.[3] Therefore, the significant relationship between higher maternal education and lower prevalence of sickle cell gene implies that a reduction in the prevalence of the sickle cell gene could be achieved with improved education - especially of the girl child- in addition to malaria

control/eradication in Sub-Saharan Africa.

The significant relationship between mother's educational status and having sickle cell trait suggests that education plays a major role in accessing and utilizing health care.[16] This can lead to several beneficial effects which can reduce the burden of SCD. These include: adequate contraception, and utilization of prenatal diagnostic services in the case of " at risk couples". The improvement in awareness and socioeconomic conditions that education brings also leads to the avoidance of consanguineous marriages. Nigerian reports show that some individuals falsify their haemoglobin phenotype results in reaction to threats by some priests not to wed intending couples that are both carriers of sickle cell trait.[17] Thus, efforts at improving premarital HbS screening uptake should be accompanied by improved efforts at ensuring adequate public education on the disease and carrier status, accurate laboratory screening, competent genetic counseling for individuals with the trait or disease as well as improved health care package for individuals affected by the disease.[17] Therefore, adequate counselling on the implications of possible test results as well as options for individuals with the trait or disease should be integrated into every screening programme. This will enable individuals make informed decisions which should be respected.

The slight but significantly lower haematocrit of children with HbAS compared to HbAA is at variance with previous reports which are, however, limited.[18],[19] Findings from previous studies suggest a higher rather than lower haematocrit in children with HbAS compared to HbAA and this was attributed to lower oxygen delivery capacity of HbAA compared to HbAS.[18] More studies are needed to understand the relationship between sickle cell trait and haematcrit. Although sickle cell trait is generally regarded as a benign condition with normal life expectancy, it has been increasingly linked with adverse outcomes like higher risk of chronic kidney disease, exertional rhabdomyolysis, sudden death, venous thromboembolism, haematuria and hyposthenuria.[20] Reports indicate that under extreme conditions such as high altitude, severe dehydration and low oxygen tension, a person with sickle cell trait can experience some of the same problems as a person with sickle cell disease.

[Figure 1: Mendelian cross between individuals with normal haemoglobin (AA) and SCT (AS)]

Conclusion

The zero prevalence of sickle cell disease in this study implies that premarital counselling and screening may be effective in reducing the prevalence of the disease. However, the higher prevalence of SCT among the population where this intervention has occurred portends an ominous sign for the future. The prevalence of sickle cell trait is significantly lower among children of more educated women and this suggests that improved education- especially of the girl child, may lead to better socioeconomic conditions, greater awareness and utilization of health services in such a way as to positively affect the distribution of the sickle cell gene in the population.

Recommendations

Premarital intervention against SCD, the way it is currently practiced in our clime, may have the potential of increasing the prevalence of the sickle gene in our population in the long run, even though it transiently reduces the prevalence of HbSS individuals. The authors therefore propose improved education, especially of the girl child, with control/eradication of malaria and competent genetic counselling, including prevention of discrimination against people with sickle cell trait or disease; integrated into screening programmes and the School Health Programme as the way forward.

Limitation of study: this is a pilot study and its conclusions need to be affirmed by a study with a larger sample size.

Table 1: Distribution of the children according to some socio-demographic characteristics

Characteristic	Frequency	%
Age (months)		
6-12	45	54.9
13-24	33	40.2
DNR	4	4.9
Mother's HEL		
Primary	10	12.2
Secondary	43	52.4
Tertiary	23	28.0
DNR	6	7.3
Father's HEL	‘	
Primary	21	25.6
Secondary	47	57.3
Tertiary	4	4.9
DNR	10	12.2
Mother's occupation		
Unemployed/students	16	19.5
Artisans	5	6.1
Public servants	23	28.0
Traders	30	36.6
Professionals	1	1.2
DNR	7	8.5
Father's occupation		
Artisans	13	15.8
Public servants	5	6.1
Traders	54	65.9
Professionals	5	6.1
DNR	5	6.1
Parent's marriage type		
Church	61	74.4
Non-church	21	25.6
Total	**82**	**100.0**

Table 2: Distribution of the families according to their phenotype and pre-marital counseling intervention

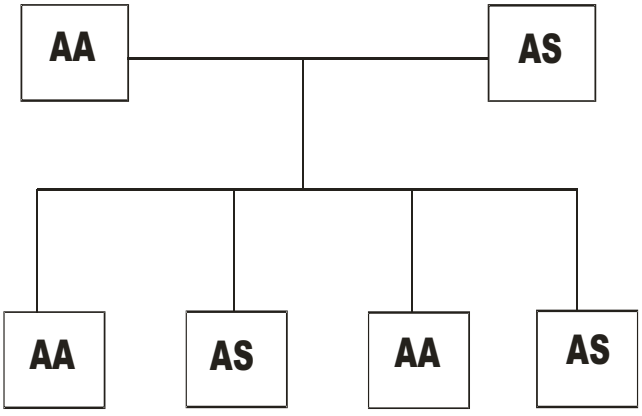
Characteristic	Total	%
Child's phenotype		
AA	64	78.0
AS	18	22.0
Mothers' phenotype		
AA	43	52.4
AS	10	12.2
Unknown	29	35.4
Father's phenotype.		
AA	32	39.0
AS	12	14.6
Unknown	38	46.3
Pre-marital counseling intervention for parents		
Yes	43	52.4
No	35	42.7
DNR	4	4.9
Total	**82**	**100.0**

Table 3: Factors associated with presence of sickle cell trait

	AA N(%)	AS N(%)	Total (%)	X^2	P-value
Mother's HEL					
Primary	4 (40.0)	6 (60.0)	10 (12.2)		
Secondary	36 (83.7)	7 (16.3)	43 (52.4)	8.65	0.01*
Tertiary	18 (78.3)	5 (21.7)	23(28.0)		
DNR	6 (100.0)	0 (0.0)	6(17.3)		
Father's HEL					
Primary	17 (81.0)	4 (19.0)	21(25.6)	0.09	0.96
Secondary	37 (78.7)	10(21.3)	47(57.3)		
Tertiary	3 (75.0)	1 (25.0)	4((4.9)		
DNR	7(70.0)	3 (30.0)	10 (12.2)		
Mother's occupation					
Unemployed/students	13 (81.3)	3 ((18.7)	16 (19.5)		
Artisans	3 (60.0)	2 (40.0	5(6.1)	7.19	0.21
Public servants	18(7.8)	5(21.7)	23 (28.0)		
Traders	25 (83.3)	5(16.7)	30(36.6)		
Professionals	0 (0.0)	1 (100.0)	1(1.2)		
DNR	5(71.4)	2(28.66)	7((8.5)		
Father's occupation					
Artisans	7 (53.8)	6(46.2)	13(15.8)		
Public servants	4(80.0)	1(20.0)	5(6.1)	5.32	0.15
Traders	45 (83.3)	9(16.7)	54 (65.9)		
Professionals	4 (80.0)	1(20.0)	5 (6.1)		
DNR	4 (80.0))	1(20.0)	5 (6.1)		
Parent's marriage type					
Church	47(77.0)	14(23.0)	61(74.4)	0.14	0.71
Non-church	17(81.0)	4 (19.0)	21(25.6)		
Pre-marital counseling intervention for parents	32 (74.4)	11(25.6)	43(52.4)		
Yes	29(82.9)	6(17.1)	35(42.7)	0.42	0.30
No	3(75.0)	1(25.0)	4(4.9)		
DNR					
Total	**64**	**18**	**82**		

*Statistically significant

Figure. 1 Mendelian cross between individuals with normal haemoglobin (AA) and SCT (AS)



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