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Original Research Article

Prevalence of subclinical Rickets in Sickle cell anemic children at the Jos University Teaching Hospital, North-Central Nigeria

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Abstract

Introduction: Bone diseases are a common co-morbidity in sickle cell anemic (SCA) children. In our environment skeletal abnormalities are well documented but there is limited documentation on metabolic bone disorders, such as rickets, despite the heighten risk in these children. Furthermore, differentiation between the clinical features of rickets and that of SCA is challenging because of an overlap of clinical features.
Aim: To determine the prevalence of subclinical rickets (SR) in the study population.
Methods: This was a cross-sectional study amongst SCA children aged 2-18 years. All 113 subjects randomly sampled had their clinical and demographic data taken. Blood sample were also taken for calcium, phosphate and alkaline phosphatase assay. Data was computed using EPI info version 7.0 statistical software. SR was compared with socio-economic variables using the chi square test or fisher exact score at 95% confidence interval.
Results: Subclinical rickets was present in 21.2% of the studied population and was significantly association with age (P = 0.01). However SR was not association gender, social economic status, religion and place of residence.
Conclusion: SR is a medical burden among children presenting with sickle cell anemia in JUTH. In order to maximize health potentials, children with SCA should be screened for SR in our environment.
Keywords: Subclinical Rickets, Sickle cell Anemia.

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1. Introduction

Sickle Cell Anemia (SCA), an autosomal recessive haemoglobinopathy that affects 2-3 % of Nigerians [1, 2,] results in chronic hemolytic anemia and reversible micro vascular-occlusion leading to chronic hypoxia, infarction and eventual multi organ pathologic changes [2]. The bone, is commonly affected, with either a structural bone disease [3,4] or the minimally reported covert metabolic bone disease.

Deficiencies of Vitamin D, osteo-malacia and decreased bone mass density have been reported in SCA children [4-7]. Furthermore, Nutritional deficiency of micro-elements including calcium and phosphorous needed for effective mineralization of the growing bone have also been reported in SCA children [8, 9]. Deficiencies of these elements (Vitamin D, calcium and phosphorous), underlie the aetio-pathogenesis in nutritional rickets [10, 11].

Clinical rickets and SCA may present with bone pain, frontal bossing, impaired mobility, failure to thrive, delay in growth and motor development and pathologic fractures [12]. Because these features overlap, diagnosing clinical rickets in sickle cell anemic children may be challenging, resulting in delayed or missed diagnosis. But subclinical rickets can be diagnosed in the presences of elevated alkaline phosphatase (AP), which is a measure of osteoblastic activity. [10, 13-16].

The use of alkaline phosphatase assay is a cheaper alternative to VD in screening for rickets especially in resource limited settings. The screening of SCA children for Subclinical rickets is needful. This information will help

set an agenda for developing secondary prevention which is recommended for high risk groups [17].

This study will determine the prevalence of subclinical rickets among SCA children and relate the findings to specific socio-demographic characteristic.

2. Methods

2.1 Study site and population

The study was carried out in JUTH; Jos. Jos Metropolis is the capital of Plateau state in Nigeria. It is situated at latitude 9^0 56' N and longitude $8^0$53' E within the tropics with a climatic condition that is tropical savannah. It is at 1217 Meters above sea levels with temperature ranges between 11^0C and 25^0C [18]. The rainfalls are usually between the months of March/April to October/November [18]. Jos is multicultural and multi-religious with some of the Muslim women and girl dressing in Hijabs/Prudah.

2.2 Sample population

This study was conducted at the Pediatric hematology clinic of Jos University Teaching Hospital (JUTH). The clinic attends to almost all the sickle cell anemic patient less than 18 years of age living in and around Jos.

2.3 Inclusion Criteria

All SCA children aged 2- 18 years receiving care at pediatric hematology clinic in Jos University Teaching Hospital.

2.3 Exclusion Criteria

Children with **c**linical evidence of chronic kidney disease, evidence of chronic liver disease and evidence of extensive dermatologic disease.

2.4 Study design: Cross-sectional prospective study

2.5 Sample size determination

Using the formula for estimation of sample size in a prevalence study

$$S = \frac{Z^2_{1-\alpha} P(1-P)}{d^2}$$

the minimum number of subjects needed to be studied can be calculated thus [19]:

Abbreviations:

S = sample size for infinite population

P = Prevalence (unknown) = 0.5

= level of significance, 5% (p = 0.05)

= Standard normal deviates for 95% confidence interval = 1.96

d = margin of error tolerable, 5% (d= 0.05)

S = = 384.16

Minimum sample size **S** was 385.

Adjusting with the finite population correction factor as the population to be sampled was finite.

The sample size will be adjusted using the formula for finite population.

$$N = S/ (1+S/n)$$

N = sample size calculated.

S = sample size calculated from the formula above which was 385.

n = finite population sampled from the average of 160 SCA children attending the Peadiatric SCA clinic in JUTH.

The adjusted sample size will be:

N= 385/ (1+ 385/160)

N= 113

Minimum sample size after adjustment will be 113 children.

2.6 Sampling Technique:

Stratified sampling technique was used to sample the study subjects. The weekly booking register was used as a sampling frame. Children booked for a clinical review were stratified by age into those aged between 2-9 years and10-18 years. A sampling interval of two (2) was gotten by dividing the average number of children attending clinic (160) by the minimum sample size (113) and it was rounded up to two (2). From each stratum therefore, every other child was selected. This procedure was repeated every week until 113 SCA patients were enrolled.

2.7 Training of Research Assistants:

Research assistants, which included 3 pediatric resident doctors and a nurse, a phlebotomist and a medical laboratory scientist, were given one day training by the researcher, where the schedule of the research was explained.

2.8 Ethical Issues:

Ethical clearance was obtained from the Jos University Teaching Hospital (JUTH) ethical Committee before the study commenced. Written informed consent was also sought for and obtained from the parents/caregivers of each child.

2.9 Data Collection:

An interviewer questionnaire was used to obtain information on socio-demographic variables Weight and height were measured using a beam balance weighing scale and standio-meter. Weight was measured in the nearest 0.1kg.

2.10 Bone biochemistry:

Five milliliters of blood was sampled from each child for analysis of calcium, phosphate and AP. Each sample was centrifuged and the serum for bone biochemistry was stored between 0 to -4^0C. Bone biochemistry was done at the Jos University teaching Hospital Pediatric department research laboratory using a Mispa excel Chemistry analyzer model 1.3e manufactured in 2009. All analysis were performed using the same Randox reagent (Switzerland) for AP, calcium and phosphorous.

2.11 Outcome parameters:

Subclinical rickets was defined as elevated AP, normal phosphate and hypocalcemia; elevated AP, normal calcium and hypo-phophatemia; elevated AP, hypocalcaemia and hypo-phosphatemia; elevated AP, hypocalcaemia and hyperphosphatemia [12, 20].

Hyperphosphatasia was defined as serum AP above 368 IU/L (four times the upper limit of normal (92IU/L), hypocalcaemia as serum calcium less than

2.2mmol/l and hypo-phosphatemia as serum phosphate less than 1.25mmol/l [12].

2.12 Data Management:

All data were entered and analyzed using EPI INFO VERSION 7 statistical soft ware by Center for Disease Control (CDC). Total calcium (g/dl), alkaline phosphatase (IU/L) and phosphate (mg/dl) were presented as proportion, mean and standard deviation. The test of association between the outcome measure subclinical rickets and dependent variables was carried out using the Chi square test (categorical parameters) and Students T test (continuous variable). This was applied for paired and unpaired observation. For all test a confidence interval of 95% was used.

3. Results

3.1 Socio-demographic characteristics of subjects:

One hundred and thirteen subjects participated in the study. Out of the 113 subjects analyzed 58(51.3%) were males while 53 (48.7%) were females, giving a male/ female ratio of 1:0.9. The mean age of the studied population was 8.7± 4.2 years with an age range of 2-17 years. Female subjects had a higher mean age of 8.9 ± 4.5 years compared to 8.5 ± 3.9 years for males. However, this difference was not statistically significant (p=0.65). There were 35 (31.0%) children who were aged 2-5years, 33 (29.2%) aged 12-17 years and 45 (39.8%) aged 6-11years. Sixty five (57.2%) of the one hundred and thirteen children were from Christian families, while (99[87.6%]) were resident in urban area while 14 (12.3%) were resident in rural area. The total monthly income was below the national minimum wages in 26 families (23.0%) and above in 87 families (77.0%). Based on the Odusanya's socio economic strata (SES) 8 (7.1%) families were categorized as SES I, 12 (10.6%) families belong to SES II, 62 subject (54.9%). (Table 2)

3.2 Calcium, phosphate and alkaline phosphatase:

The mean total serum calcium in the study population 8.9± 1.56 mg/dl with a median and modal value of 8.77 mg/dl and 8.89mg/dl respectively. Hypocalcaemia (serum calcium <8 mg/dl) was present in 30 (26.5%) of the subjects. The mean phosphate was 5.4± 0.95 mg/dl. The range was 3.1-7.6 mg/dl, with a median and modal value of 5.43mg/dl and 4.40mg/dl. Hypo-phosphatemia was present in 1.8 % (2) of subject, hyper-phosphatemia in 38.9 %(44) subjects. The serum alkaline phosphatase ranged between 145-575 IU/L with a mean of 370 ± 91.0 and a median, modal value of 364.37 IU and 345.0 respectively.

3.3 Outcome measure:

Subclinical rickets was documented in 21.2% of the study subjects (Table 3). Subclinical rickets was prevalent in 30.5% of 59 children below the age of 10 years compared to 11.1% of 54 children above the age of 10 years, this difference was statistically significant (p <0.05). No statistical association was observed between gender, socio-economic class, place of residences, and housing and sub-clinical rickets in the study population. p> 0.05.(Table 2)

Table 1: Prevalence of subclinical rickets among Children with SCA

Criteria N (%)	Frequency
Elevated AP + normal phospahate + hypocalcemia	19 (16.81)
Elevated AP + normal calcium + hypophophatemia	1 (0.88)
Elevated AP + hypocalcemia + hypophosphatemia.	2 (1.77)
Elevated AP + normocalcemia + hyperphosphatemia	2 (1.77)
Total	24 (21.23)

Table 2: Relationship between Socio-demographic and Subclinical rickets

	Total	Subclinical rickets		χ^2	p value
		Yes	No		
	113	24	89		
Age group					
< 10 years	59	18	41		
≥10 years	54	6	48	6.34	0.01
Gender					
Male	55	12	43		
Female	58	12	46	0.02	0.88
Housing					
Bungalow	104	21	83		
Storey building	9	3	6	0.86	0.12
Residence					
Rural	14	2	12		
Urban	99	22	77	0.46	0.50
Religion					
Christianity	65	10	55		
Islam	48	14	34	3.13	0.08
Minimum wage					
Above	87	20	67		
Below	26	4	22	0.70	0.41
Social class					
Upper (I & II)	20	6	14		
Lower (III, IV, V)	93	18	65	1.12	0.25

4. Discussion

This study determined the prevalence of subclinical rickets among children with sickle cell anemia and found that one fifth of these children had subclinical rickets. SR rickets was defined using markers of increase bone turnover, an elevated alkaline phosphatase. Like our study, the study by Azinge *et al* [21] in Nigerian sickle cell patients and Mohammed *et al* [22] found an increase bone turnover in sickle cell subjects compared to non-sickle cell controls. Bone turnover in these studies were demonstrated by a significant rise in serum alkaline phosphatase and urinary hydroxyl-proline. Similar studies on subclinical rickets used biomarkers of increased bone turnover such as serum Vitamin D, Parathyroid Hormone and Alkaline phosphatase, even though amongst non-sickle cell anemic adolescent. Shah *et al*[14, 15] in Pakistan and Alduryan *et al*[16] further demonstrated a correlation between higher mean alkaline phosphatase and low mean serum vitamin. Although Vitamin D assay still remains the gold standard, alkaline phosphatase which is readily available and affordable is still very useful in assessing bone turnover in resource limited setting like ours.

Although studies that define subclinical rickets as in this current study were not sighted, studies that defined subclinical rickets on the basis of Vitamin D assay among children with sickle cell anemia exist. These studies reported a high prevalence of subclinical rickets from thirty percent and above in sickle cell children receiving care in Jos, USA, India, and Spain have been reported to have subclinical rickets when their Vitamin D status, a proxy marker for SR was assayed [5-7,23-26]. This high burden of SR is comparable to the findings reported in this study were about twenty percent of the children living in sunny tropical country at about 9 degree south of the equator were identified with subclinical rickets.

It is our thought that majority of our SCA may have a similar biology, and may modify their environmental factors such as dressing and play behavior to prevent acute vaso-occlusive crises. These behavioral changes will decrease sun exposure with resultant decrease in the skin's ability to synthesis vitamin D and subsequent development of subclinical rickets

In this current study, subclinical rickets was significantly commoner in children whose ages where below ten years compared to older ones. However, it difficult to compare this finding with other local studies because most local studies focus on clinical rickets among under five. [11, 12] However, studies in adolescent girls have been documented by Shah *et al* and Juryan *et al* [14,16], has clearly demonstrated that subclinical rickets is a burden amongst adolescent girls. This current study demonstrated that over ten percent of adolescent [10 years and above] had subclinical rickets. This is an important observation because adolescent with or without SCA may not present with classic features of rickets as observed in early childhood and may still go ahead to developed bony deformity, such as rachitic pelvic which may impact negatively on maternal outcome during delivery because the pelvic bone becomes flat and contracted.

This current study did not find any association between the presences of subclinical rickets and the gender of subjects. These may suggest a similarity in behavioral pattern and lifestyle amongst sickle cell patients living in Jos irrespective of gender. This study did not show any relationship between subclinical rickets and parental socio-economic status and income. It was observed that about three quarter of these patients belong to the lower and middle socio-economic class. This skewed distribution across Socio economic class may be responsible for the lack of difference observed.

The association of rickets with religion may differ from locality to locality; in this study children with Islamic background had higher proportion of children with subclinical rickets this contrast to the report of Akpede *et al*[12] where children with Islamic background had less rickets when compared with other religion.

However, our study design which is a cross sectional design could not make any inferences on factors that factors that influence subclinical rickets, rather suggest the need to institute routine screening of sickle cell patients for subclinical rickets and further studies that assess the bone density of sickle patients in our environment.

5. Summary

Subclinical rickets is prevalent in SCA children who are in steady state andattend clinicin Jos, Plateau state Nigeria. There is a need for early bone assessment through routine screening for subclinical rickets. Further studies are needed to understand the risk factor associated with subclinical rickets and be able to identify steps towards primary and secondary prevention.

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Authors contributions:

All Authors contributed at all stages of the research. Dr Katja Konrad was the supervisor for this research project.

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