Gout is more frequent in sickle cell disease than in haemoglobin AA among sub-Saharan Africans

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Abstract

Background: Sickle Cell Disease (SCD) is a common autosomal recessive disorder worldwide that mostly affects Africans. Hyperuricemia, a common biochemical finding, occurs in up to 41% of SCD patients. Although hyperuricaemia is the most important risk factor for gout, the latter is uncommonly reported in SCD.
Objective: To determine the frequency and factors associated with hyperuricaemia and gout among patients with Sickle Cell Disease (SCD).
Design: This was a cross sectional study.
Methods: The study involved 104 SCD patients and 104 haemoglobin AA (HbAA) controls. The diagnosis of gout was based on the demonstration of monosodium urate crystals in the synovial fluid of symptomatic individuals. Hyperuricaemia was found in 28 (26.9%) and 2 (1.9%) of SCD and control participants respectively ($p<0.001$). The median (range) Serum Uric Acid (SUA) was higher among patients (330 µmol/L [146 to 702 µmol/]) than in controls (232 µmol/L [143 to 440 µmol/L]), ($p<0.01$). Six (5.8%) cases of gout were found among the patients and none among the controls ($p=0.029$). The pattern of articular involvement was monoarticular in 2 (33.3%), oligoarticular in 3 (50%) and polyarticular in 1 (16.7%). One (16.7%) patient had subcutaneous tophi. Factors associated with gout in SCD were age, hyperuricaemia, more than two SCD crises in the past year and more than two hospital admissions in the past year.
Conclusion: Gout as is hyperuricaemia, is more frequent in persons with SCD than in the general population. It is mostly oligoarticular and older patients with multiple attacks of painful joint swelling as well as frequent hospital admissions may be at higher risk of gout.

Key words: Sickle cell disease, Hyperuricaemia, Gout, Africans

Introduction

Sickle Cell Disease (SCD) is one of the most common severe autosomal recessive disorders in the world and the majority of the patients live in Africa[1]. The co-existence of haemoglobin S with another defective haemoglobin such as haemoglobin S, haemoglobin C or beta-thalasaemia characterizes SCD. Hyperuricemia, a common biochemical finding in haemoglobinopathies due to a shortened red blood cell life span, is found in up to 41% of SCD patients[2]. Hyperuricaemia is also the most important risk factor for gout, though gout is uncommonly reported in SCD. The fundamental risk factor for hyperuricemia in humans is a mutation of the gene for uricase, the enzyme that breaks down urate in lower animals into the more soluble allantoin[3].

Absence of the uricase enzyme predisposes humans to hyperuricaemia whenever they are exposed to conditions of overproduction or under-elimination of urate. These conditions include renal under-excretion of urate, excessive cell and purine turnover, high purine dietary intake and genetic factors that result in primary urate overproduction[4,5]. Aside from the increased production of urate in SCD, sufferers are also prone to various degrees of impairment in renal function from years of recurrent vaso-occlusive episodes and other mechanisms. The various osteoarticular manifestations of sickle cell disease include bone pain crises, osteonecrosis, osteomyelitis and arthritis[6]. Several forms of arthritides, both inflammatory and non-inflammatory, have been described in association with SCD. These include gout, septic arthritis, and bone infarcts which may progress to bone erosion and articular damage[7]. Crystal arthropathies are the most common causes of inflammatory arthritis with gout associated with cardiovascular

and renal disease[8]. The risk of developing gout increases with increasing hyperuricaemia, but there is no point at which gout becomes inevitable[9].

Since SCD patients commonly develop self-limiting attacks of arthralgia which are common in gout, the frequency of gout may be under-estimated in these individuals. Additionally, clinical awareness for gout and other inflammatory arthritides is generally low in sub-Saharan Africa which in part is due to the scarcity of rheumatologists in the region. We aim to describe the frequencies and clinical attributes of hyperuricaemia and gout in adult patients with SCD at the University of Ilorin Teaching Hospital (UITH) - Nigeria.

Materials and methods

A study of adult patients with SCD was conducted at the adult SCD clinic, General Out-patient Department (GOPD) and the Medical Emergency Unit of UITH. All consenting patients aged 18 years or older with haemoglobin SS or SC were serially recruited if they met the inclusion criteria. One hundred and four patients with SCD were studied and 104 individuals with haemoglobin AA genotype were also recruited as control participants. The control individuals were drawn from consenting, apparently healthy patients' relatives and they were age and sex matched with the patients. The exclusion criteria for both patients and control participants included individuals with other diseases which could affect Serum Uric Acid (SUA) levels e.g. cancers, established renal failure, psoriasis and systemic hypertension as well as the use of drugs such as antihypertensives, low dose aspirin, pyrazinamide, ethambutol and cytototoxics.

A semi-structured, interviewer-administered questionnaire was used to collect demographic and relevant clinical information. All painful or swollen joints were documented. Each participant was examined for tender and/or swollen peripheral joints. Subcutaneous deposits that were suspicious of tophi were also documented. A 10ml sample of venous blood was obtained from each participant for SUA, serum creatinine and haemoglobin genotyping by electrophoresis. Genotyping was done for all control participants and for patients where a documentation of their haemoglobin genotype was not available. Analysis of SUA was by enzymatic method using uric acid reagent kit (R1, 10 x 84ml, by ABBOTT Laboratories, Abbott Park, IL 60064, USA). Hyperuricaemia was defined as a SUA concentration higher than 420µmol/l in the males and postmenopausal women and 360µmol/l in premenopausal females[5]. Estimated Glomerular Filtration Rate (eGFR) was determined using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) method. All patients with articular symptoms in the form of pain and/or swelling were considered for joint aspiration. Within an hour of aspiration, Synovial Fluid (SF) was examined for monosodium urate crystals under a polarized microscope (AmScope PZ200TA polarizing trinocular microscope, Irvine, California). Ethical approval was granted by the research and ethics committee of UITH.

Data analysis: All data obtained were analyzed using SPSS version 21.0 for windows (IBM USA, Armonk, NY 10504). Associations between each of hyperuricaemia and gout within both participant groups as well as the determinants of gout in SCD were evaluated using the Chi-Square test for categorical variables and independent sample T-test or Mann-Whitney U test for continuous variables. Associations between SUA and serum creatinine was analyzed using Spearman's rho correlation. Statistical significance was set at P-value < 0.05.

Results

Characteristics of the study population

There were 56 (53.8%) males and 48 (46.2%) females in each of the patient and control groups (Table I). The mean ages of the patients and controls were 27.4±8.3 and 27.7±8.0 years respectively (p=0.727). The mean age of the male patients was 26.6±7.7 years and the female patients, 28.2±8.9 years (p=0.327). Eight of the patients had genotype SC while the remaining 96 had SS. The pattern of consumption of purine-rich diet was comparable between both groups while values of height, weight, body mass index, systolic blood pressure and diastolic blood pressure were significantly higher among the control subjects. No patient was on routine hydroxyurea treatment.

Table 1: Characteristics of the study population

	Patients n=104 (%)	Controls n=104 (%)	P-value*
Age groups (years)			
18-27	59 (56.7)	58 (55.8)	0.952
28-37	35 (33.7)	35 (33.7)	
38-47	9 (8.7)	9 (8.7)	
48-57	1 (1.0)	2 (1.9)	
Male	56 (53.8)	56 (53.8)	1.000
Level of education			
None	5 (4.8)	1 (1.0)	0.117
Primary	26 (25.0)	15 (14.4)	
Secondary	53 (51.0)	61 (58.7)	
Tertiary	17 (16.3)	24 (23.1)	
Postgraduate	3 (2.9)	3 (2.9)	
Marital status			
Single	85 (81.7)	62 (59.6)	**0.001**
Married	16 (15.4)	41 (39.4)	
Separated	3 (2.9)	1 (1.0)	
Divorced	0 (0.0)	0 (0.0)	
Occupation			
Student	53 (51.0)	59 (56.7)	**0.001**
Trading	26 (25.0)	0 (0.0)	
Artisan	14 (13.5)	0 (0.0)	
Civil servant	7 (6.7)	34 (32.7)	
Professional	1 (1.0)	11 (10.6)	
Others	3 (2.9)	0 (0.0)	
Tribe			
Yoruba	99 (95.2)	96 (92.3)	0.470
Igbo	3 (2.9)	2 (1.9)	
Hausa	0 (0.0)	1 (1.0)	
Others	2 (1.9)	5 (4.8)	
Dietary habits			
Seafood	98 (94.2)	97 (93.3)	0.775
Animal organs	97 (93.3)	101 (97.1)	0.195
Sweetened beverages	93 (89.4)	100 (96.2)	0.061
Alcohol consumption	3 (2.9)	8 (7.7)	0.121
Smoking	2 (1.9)	3 (2.9)	0.651
Height (mean SD)	1.660.06	1.690.05	**0.001**[t]
Weight (mean SD)	54.57.3	64.09.6	**0.001**[t]
BMI (mean SD)	19.81.9	22.22.6	**0.001**[t]
SBP (mean SD)	109.813.4	119.612.8	**0.001**[t]
DBP (mean SD)	68.910.3	74.18.8	**0.001**[t]

*= P-value determined by Chi-square test except where otherwise indicated, SD=standard deviation, BMI=Body Mass Index, SBP=systolic blood pressure, DBP=diastolic blood pressure, t=P-value determined by T-test.
Bold fonts represent statistically significant P-values

Serum uric acid among the study participants

The median (range) SUA among patients and controls were 330 µmol/L (146 to 702 µmol/L) and 232 µmol/L (143 to 440 µmol/L) respectively. These values showed statistically significant difference with a p-value < 0.01.

Relationship between serum uric acid and SCD

Twenty eight patients (26.9%) and 2 (1.9%) control participants had hyperuricaemia (p<0.001). The proportions of patients with hyperuricaemia in each age group showed a rising trend with increasing age. Twelve (42.9%) of these hyperuricaemic patients with SCD were males and 16 (57.1%) were females. Twenty-five (89.3%) were of genotype HbSS while 3 (10.7%) had HbSC. The mean age of SCD patients with and without hyperuricaemia were 31.7 ± 9.9 years and 25.7 ± 7.0 years respectively (p=0.001). The median SUA (range) among SCD patients with hyperuricaemia was 440µmol/L (366 - 702 µmol/L).

Correlation between uric acid and renal function in SCD patients

A Spearman's rho correlation coefficient was computed to assess the relationship between the SUA and serum creatinine levels in patients with SCD. There was a positive correlation between the two variables (r=0.480, p<0.001).

Gout and SCD

Arthralgia was found in 31 patients out of which 14 had demonstrable effusion. Six cases of gout were found by the identification of monosodium urate crystals in the SF. All cases of gout were found among patients with SCD (5.8% of SCD cases). Five of them had genotype HbSS while only one was HbSC. There was a statistically significant difference in the frequencies of gout between SCD and control participants (p=0.029) but not between HbSS and HbSC cases (p=0.389). None of the individuals had ever been diagnosed with gout before. The mean age of patients with gout was 41.7 ± 6.0 years while the mean BMI was 20.6 ± 2.6 kg/m^2.

All six patients had SUA in the hyperuricaemic range. The median SUA was 504.5 µmol/L (range 435.0-702.0). Four (66.7%) of these individuals were male, giving a male-female ratio of 2:1. No subject with gout was overweight or obese. The affected joint count was monoarticular in 2 (33.3%) patients, oligoarticular in 3 (50%) and polyarticular in 1 (16.7%). The involved joints are shown in Table 2. Five individuals reported having had painful and swollen joints on more than two occasions in the past while only one reported a single previous episode. Only one gout patient had subcutaneous tophi.

Table 2: Characteristics of the patients with gout

	Age (years)	Sex	Genotype	SUA (µmol/L)	BMI (Kg/m^2)	Joints involved	Presence of tophi
1	52	F	SS	435	23.31	Ankles	Yes
2	41	M	SS	480	17.51	Lt. knee, Rt. MTP1	No
3	37	M	SS	702	19.84	Rt. Ankle	No
4	41	M	SS	510	20.20	Knees, Rt elbow, ankles	No
5	44	F	SS	460	18.87	Rt. Ankle, Lt. knee, Lt. MTP1	No
6	35	M	SC	440	24.06	Lt. Knee	No

SUA = Serum Uric Acid; BMI=Body Mass Index; Lt .= Left; Rt.=Right; MTP1=1st metatarsophalangeal joints

Factors associated with gout in patients with SCD

Table 3 shows the comparison of clinical and laboratory characteristics between patients with and without gout. There was a statistically significant association between age and the diagnosis of gout in patients with SCD (p= 0.001). The mean ages of the patients with and without gout were 41.7±6.0 and 26.47.6 years respectively. Other factors found to have significant association with gout included: hyperuricaemia, history of more than two SCD crises in the past year and more than two hospital admissions in the past year (p < 0.01 in each case). Habits like seafood consumption, animal innards consumption, consumption of sweetened beverages, alcohol use and smoking were not found to be associated with gout in SCD.

Table 3: Factors associated with gout among patients with SCD

	Patients with gout (n=6) No. (%)	Patients without gout (n=98) No. (%)	P - value
Genotype			
SS	5 (83.3)	91 (92.8)	0.389
SC	1 (16.7)	7 (7.1)	
Age, years (meanSD)	41.7±6.0	26.47.6	**0.001**
Sex			
Male	4 (66.7)	52 (53.1)	0.684
BMI			
Underweight	1 (16.7)	28 (28.6)	0.753
Normal weight	5 (83.3)	68 (69.4)	
Overweight	0 (0.0)	2 (2.0)	
Hyperuricaemia	6 (100.0)	22 (22.5)	**0.001**
Frequency of SCD Crises			
More than 2	5 (83.3)	18 (18.7)	**0.002**
Two or fewer	1 (16.7)	80 (81.6)	
Frequency of admissions			
More than 2	5 (83.3)	18 (18.7)	**0.002**
Two or fewer	1 (16.7)	80 (81.6)	
Seafood consumption	6 (6.1)	92 (93.9)	0.532
Animal innards consumption	6 (6.2)	91 (93.8)	0.498
Sweetened beverage consumption	4 (4.3)	89 (95.7)	0.121
Alcohol consumption	0 (0.0)	5 (100.0)	0.738
Smoking	0 (0.0)	2 (100.0)	0.724

SCD= Sickle Cell Disease; BMI= Body Mass Index, n=number
Bold fonts represent statistically significant P-values

Discussion

This is the first study of gout in African patients with SCD and the evaluation of a control group without SCD enabled us to compare the frequencies and attributes of hyperuricaemia and gout in both groups. Early mortality associated with SCD is likely to be worse in sub-Saharan Africa where quality healthcare is lacking compared to the Western world. For this reason, diseases associated with advanced age may be less frequent among patients on the African continent. Less than half of the patients found in this study were older than 27 years of age. This pattern reflects the early mortality in SCD with the age distribution similar to findings from other studies[10,11]. Ogun *et al*[12] reported the mean age at death among Nigerians with SCD as 21.3 years. Chijioke *et al*[13] noted that the mean age of Nigerian patients with SCA was 23 years compared to 40 years in HbAA controls.

The association between SCD and hyperuricaemia found in our study is consistent with previous knowledge while the prevalence of 26.9% is in tandem with frequencies of 22-34% found in other studies[14-18]. The high prevalence of hyperuricaemia in SCD has been attributed to the rapid red cell turnover among other things. In SCD, average erythrocyte lifespan is as low as 12 days[19]. This is much shorter than the average lifespan of 120 days in normal red cells. The median SUA in adult SCD patients of 330 μmol/L found in this study is comparable to the

values of 336 μmol/L reported by George-Opuda *et al*[20] from Port Harcourt, Nigeria and 327 μmol/L reported by Moreira *et al*[15] from Fortaleza, Brazil. It is however higher than the finding of 264 μmol/L by Cerqueira *et al*[21] from Salvador, Brazil.

This difference is likely due to the fact that the mean age of the patients studied by Cerqueira *et al*[21] was 20.5 years in contrast to the higher mean age of 27.4 years from the present study. Furthermore, all patients from the study by Cerqueira *et al*[21] were in stable state without blood transfusion, hospitalization, or any infections. Age-related progressive decline in uric acid excretion with deteriorating renal function is another important cause which explains why the prevalence of hyperuricaemia increases with increasing age[22]. The decline in renal function and fractional excretion of urate reflected by rising serum creatinine and decreasing glomerular filtration rates is responsible for the association of hyperuricaemia and renal parameters[2].

The prevalence of gout of 5.8% found in this study is lower compared with a prevalence of 14.4% found by Gupta *et al*[23] in a 2015 study of 90 patients with SCD. The difference is likely due to the higher mean age of SCD patients of 42.7±13.1 years in their study. Also, the exclusion of hypertensive and renal failure patients from the present study may have contributed to the lower number of gout cases found. Hypertension and renal dysfunction are two of the most important co-morbidities associated with gout[24]. In the general population, it is reported that only about 10% of people with hyperuricaemia will develop gout[25,26]. This proportion may even be lower in people with SCD for various reasons.

It has been found that aging within the joint creates the platform for urate crystallization and subsequent ingestion by inflammatory cells but sadly many SCD patients do not live long enough for some of these changes to be established[27]. Additionally, years of recurrent thromboses and vaso-occlusive crises involving the small synovial vessels in SCD may result in circulatory impairment preventing the migration of inflammatory cells into the joint thus limiting the provocation of crystal arthritis attacks[28]. However, these factors may not be enough to prevent a higher likelihood of gout in SCD as survival of these patients has improved over the years due to improved care and the widespread use of anti-sickling therapies.

The mean age of gout cases seen was 41.7±6.0 years lower than the 48±14.4 years as found by Gupta *et al*[23]. This is due to the overall age distribution of the patients included in each study. Mean ages are however higher in gout cases than in the overall SCD subjects in both studies (41.7±6.0 vs 27.4±8.3 and 48.0±14.4 vs 42.7±13.1 years). Similarly, the mean age of gout cases noted in this study is much lower than the 53.4 years reported by Adelowo *et al*[29] among gout patients in the Nigerian general population. The relatively early onset of hyperuricaemia in SCD, coupled with the risks of degenerative changes within the joints of the patients occasioned by multiple episodes of vaso-occlusion and infarction, may have set the stage for earlier onset of crystal arthritis.

Unlike the protection women in the general population enjoy from gout, females with SCD may not be as less prone to gout. The male-to-female ratio of the gout cases found in this study was 2:1. This is much narrower than the 4-10:1 which has been reported among different general populations[30,31]. In the same light, the study by Gupta *et al*[23] reported a near-equal male-to-female distribution of 1.2:1 of gout among people with SCD. The uricosuric effect of estrogens, and by extension, protection from the risk of developing gout appears blunted in SCD.

Most patients with gout in our study had involvement of more than one joint. This contrasts with a 62% monoarticular pattern in the earlier Nigerian study by Gupta *et al*[23]. The tendency for delayed diagnosis in our setting is a possible explanation for this disparity. Typically, when a Nigerian patient with SCD presents with joint or bone pain, vaso-occlusive crisis is the first suspect and since a gout attack will naturally subside within a few days, repeated misdiagnosis of a crystal arthropathy may persist during which additive involvement of more joints may occur. The knee was the most frequently affected joint in our study in contrast to Gupta *et al*[23] where the first metatarsophalangeal (MTP) joint was most frequently affected. This disparity may be reflecting the disparities observed between the presentation of gout in Africans and Westerners[29].

A patient with SCD in the thirties or older, having multiple episodes of joint pain and swelling, with 2 or more admissions for painful crises per annum as well as hyperuricaemia appears to be a candidate for possible gout. The scarcity of rheumatologists in sub-Saharan Africa and the low level of awareness of rheumatic diseases have resulted in a poor index of suspicion for inflammatory arthritides. Unfortunately, long standing undiagnosed or poorly managed gout is associated with excess cardiovascular and all-cause mortality[32]. Sub-Saharan Africa is a rich source of in-depth research on SCD arthropathies, not just because of the largest patient population, but also because otherwise easy-to-manage but under-recognized musculoskeletal disorders may have had huge contributions to the morbidities and mortalities in these patients. This study is limited by its cross-sectional design as some patients with gout may have been seen when they were not having a flare and thus misclassified as free of gout.

Conclusion

The challenges confronting the wellbeing and survival of a patient with SCD in sub-Saharan Africa are numerous. With improving life expectancy come other ailments that are more prevalent after attaining adulthood. However, low emphasis on these non-communicable diseases has led to perennial under-diagnosis of gout and the inevitable adverse impact on the health and longevity of SCD sufferers. Gout is the most prevalent inflammatory arthritis worldwide and being a metabolic disorder resulting from hyperuricaemia, SCD patients

are constitutionally at risk. This study has shown that hyperuricaemia and gout are more frequent in SCD patients than in the general population with the knee joint mostly affected in Africans compared to the 1st MTP joint in Caucasians. Older patients with multiple attacks of painful joint swelling as well as frequent hospital admissions may be at higher risk of gout.

Disclosure of interest: The authors report no conflict of interest.

Acknowledgements

Dr Richard Akintayo was involved in the study design, data collection and analysis, and drafting of manuscript. Prof Olufemi Adelowo was involved in the study design and reviewing the manuscript. Prof Adindu Chijioke was involved in the study design and reviewing the manuscript. Dr Timothy Olanrewaju was involved in the study design, data analysis and review of the manuscript. Dr A. Yerima was involved in the drafting and reviewing of the manuscript. Dr A. Akpabio was involved in the drafting of manuscript and submission process. Dr Kehinde Olufemi-Aworinde was involved in the acquisition of data and drafting of the manuscript. Dr Foluke Akintayo was involved in the acquisition of data and drafting of the manuscript. All authors approved the final draft of the manuscript.

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