ORIGINAL ARTICLE

Prevalence and associations of symptomatic renal papillary necrosis in sickle cell anemia patients in South-Eastern Nigeria

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Abstract

Aim: To assess the prevalence and associations of symptomatic renal papillary necrosis (RPN) in sickle cell anemia patients.
Patients and Methods: The case notes of homozygous hemoglobin (Hb) S patients diagnosed with RPN were retrospectively assessed. Diagnosis was based on microscopic hematuria and positive ultrasound findings. Their steady state diastolic blood pressure, Hb, leukocyte count, platelet count, serum direct bilirubin, and aspartate transaminase, were obtained by automated analyzers. These were evaluated for any relationship with the occurrence of RPN.
Results: Two hundred and twenty patients were assessed aged 6–55 years with a median age of 24 years. The prevalence of symptomatic RPN was found to be 2.3%. RPN was positively associated with the female gender (Chi-square *P* value 0.001), but not with any other clinical or laboratory variable. However, other predictors of disease severity were positively associated with RPN such as age, diastolic blood pressure 0.180 (*P* = 0.016), serum aspartate transaminase, serum bilirubin 0.145 (0.027), Hb, and leukocyte count − 0.155 (*P* = 0.003).
Conclusion: The prevalence of symptomatic RPN is low in this group of homozygous S patients and occurs more commonly in females. Improvement in care for these patients will reduce these chronic complications.

Key words: Female gender, microscopic hematuria, renal papillary necrosis, sickle cell anemia

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Introduction

Improving health care and availability of facilities for faster diagnosis and intervention have ensured that sickle cell patients live longer. This has also led to the development of an increasing number of the chronic complications of the disease. The incidence of renal complications in sickle cell has been estimated to be 68% out of which 30–40%[1] have renal papillary necrosis (RPN).

RPN was first observed by Johann Wagner in Ludwig von Beethoven's autopsy report written in 1827 and translated into German by von Seyfreid in 1832.[2] This was hypothesized to be due to chronic alcohol and analgesic abuse. However, until recently the most widely accepted first account was documented by Friedrich in 1877,[3] in a patient with urinary

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obstruction secondary to prostatic enlargement. Gunther and Edmonson later made the association between RPN and diabetes mellitus,[4-6] whereas Spuhler was the first to describe analgesic nephropathy. The first observation of RPN in sickle cell was made by Sydenstricker *et al.,* in 1923.[6,7]

Other causes of RPN aside from sickle cell disease include; pyelonephritis, obstructive uropathy, tuberculosis, hepatic cirrhosis, analgesic abuse, renal transplant rejection/irradiation, diabetes mellitus, and systemic vasculitis.[7] Most of these conditions are associated with ischemia or hypoperfusion of the renal medulla with subsequent necrosis. Two forms of RPN have been widely observed; the medullary form and papillary form, based on the degree of renal parenchymal destruction. In the medullary form, there are discrete grain-sized necrotic areas, with intact fornices, while in the papillary form the entire calyceal systems and papillary surfaces are destroyed and easily outlined.[8] In most patients with RPN, the cause is multi-factorial and more than one of these factors are present. The systemic nature of the causative factors explains the bilateral renal involvement observed in most cases.

There is a wide variability in the clinical features of RPN, which ranges from an asymptomatic microscopic hematuria to acute gross hematuria with fever and flank pain which may lead to acute renal failure. RPN, being vaso-occlusive in etiology has also been known to occur, though with a lesser frequency in heterozygous sickle cell disease patients.[9] It may also be associated with episodes of severe urinary tract infection or prolonged use of analgesics, especially the non-steroidal anti-inflammatory drugs (NSAIDs), used in treating bone pain crisis.[10] Symptomatic and asymptomatic RPN has been recorded to occur with similar frequency in sickle cell disease, 65% and 62%, respectively.[10] Other studies have also estimated the incidence to be 30–40%,[11] though the most detailed study done in 334 patients showed a 39% incidence.[9] Apart from a few severe cases, RPN in sickle cell anemia (SCA) patients infrequently leads to a fatality, in most patients hematuria ceases after bed rest and rehydration with or without blood transfusion.

Investigations for RPN will include; urography, renal ultrasonography, and computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the kidneys. The pathogenetic mechanism is similar to that of other complications in sickle cell disease and involves vaso-occlusion of the vasa recta leading to ischemic necrosis of the renal pyramids (papillae). NSAID's also inhibit cyclooxygenases-1 and 2, which are involved in the synthesis of prostaglandins which have vasodilatory and renoprotective effects.[12] Renal hypoperfusion with tubular and glomerular ischemia ensues, further worsened by red cell sickling and vessel occlusion. The necrosed part subsequently sloughs off with attendant hemorrhage. Imaging techniques therefore show filling defects of loss of echogenicity in the case of renal sonography. More sensitive techniques include helical CT scan, which is expensive and may not be easily afforded by most patients.

The frequency of some chronic complications of sickle cell has been reported to vary widely between different patient populations. In resource-poor settings, in-depth investigation to diagnose RPN may be hampered by affordability of the cost of these investigatory modalities. This research is aimed at ascertaining the frequency of symptomatic RPN in a Nigerian subset of homozygous hemoglobin (Hb) S patients. It will also attempt to define the clinical and laboratory parameters that are associated with the occurrence of RPN.

Patients and Methods

This is a retrospective study of 220 homozygous S patients, seen in the adult sickle cell clinic over a 9 years period (from June 2005 to April 2014). Patients' steady state data were obtained from the case notes, and those who had been diagnosed with papillary necrosis were noted. The diagnosis of symptomatic papillary necrosis was regarded for those patients who had microscopic hematuria and positive ultrasound findings with the exclusion of other causes of hematuria. None of the patients had CT or MRI scan. Ethical approval was obtained from the University of Nigeria Health Research and Ethics Committee.

Data on age, sex, frequency of vaso-occlusive crisis per annum, diastolic blood pressure and steady-state platelet count, white cell count, Hb concentration, serum aspartate transaminase, and direct bilirubin were collected and analyzed. The relationship of these parameters with the occurrence of papillary necrosis was also determined and expressed in figures and tables.

Statistics

This was done using Statistical Package for Social Sciences (SPSS) 17.0, (Illinois, Chicago), USA. The Chi-square test was done to evaluate the relationship for ordinal and nominal variables, while the Kendall's tau-b correlation coefficient (two-tailed) was done for all numerical variables, without assuming equal variance. The *P* values were assumed to be significant for all values <0.05.

Results

The case notes of 220 homozygous S patients were reviewed; this included 63.5% (139) males and 36.5% (80) females. Their ages ranged from 6 to 55 years with a median age of 24 years, and a mean age of 24.1 ± 7.3 years. The prevalence of symptomatic RPN in SCA was determined to be 2.3% (5). Of the 5 patients who had symptomatic RPN, there were 4 females and 1 male, and there was a significant

Table 1: Clinical and laboratory parameter in sickle cell patients with and without renal papillary necrosis

Parameters	Mean±SE	Median	Correlation	*P*
Age (years)				
RPN (*n*=5)	28±6	24	0.002	0.971
No RPN (*n*=209)	25±0.5	24		
Diastolic blood pressure (mmHg)				
RPN (*n*=4)	73±6	70	−0.061	0.362
No RPN (*n*=181)	66±1	70		
Frequency of crisis per annum				
RPN (*n*=3)	7±3	8	−0.123	0.105
No RPN (*n*=131)	4±0.4	2		
Hemoglobin concentration (g/dL)				
RPN (*n*=4)	6.9±0.8	7.4	0.057	0.358
No RPN (*n*=172)	7.7±0.2	7.8		
Leukocyte count ($\times 10^9$/L)				
RPN (*n*=4)	27.7±14.6	14.1	−0.101	0.080
No RPN (*n*=200)	12.3±0.4	10.9		
Platelet count ($\times 10^9$/L)				
RPN (*n*=4)	324±63	341	0.006	0.918
No RPN (*n*=182)	351±13	330		
Direct bilirubin (μmol/L)				
RPN (*n*=3)	16.8±9.3	11.1	0.031	0.683
No RPN (*n*=118)	23.9±2.8	12.8		
Aspartate transaminase				
RPN (*n*=3)	52±21.5	33.0	−0.033	0.676
No RPN (*n*=113)	76.3±5.4	60.0		

RPN=Renal papillary necrosis present; No RPN=Renal papillary necrosis absent; SE=Standard error

association between the female gender and occurrence of RPN (Chi-square *P* value of 0.001).

The mean and median age, Hb concentration, diastolic blood pressure, white cell count, the frequency of crisis per annum, platelet count, aspartate transaminase, and serum direct bilirubin values found in those with and without symptomatic RPN are shown in Table 1. Table 1 also contains the *P* value as well as the correlation coefficient-Kendall tau-b for all numerical variables. There was no association between the occurrence of RPN and the age, frequency of crisis per annum and the diastolic blood pressure in this group of patients [Table 1]. One hundred and seventeen of the patients in this study had a history of blood transfusion in the past, and this was not significantly associated with the occurrence of papillary necrosis ($P = 0.99$). The frequency of vaso-occlusive crisis also showed no relationship with the occurrence of symptomatic RPN, Kendall tau-b −0.061 ($P = 0.438$).

However, significant relationships were found to exist between the age of the patients and the leukocyte count −0.159 ($P = 0.001$) and platelet count −0.115 ($P = 0.025$), respectively. In addition, significant association was also noted between the female sex and Hb concentration

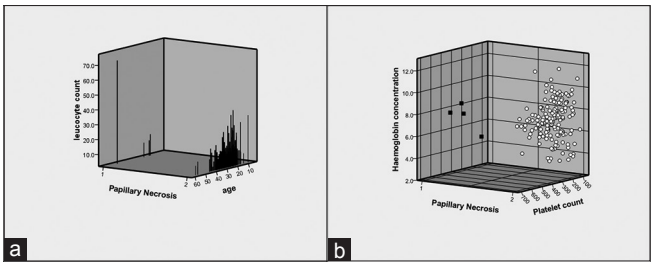

Figure 1: (a) Age and leukocyte count of sickle cell anemia patients with and without renal papillary necrosis. 1=Papillary necrosis present; 2=Papillary necrosis absent. (b) Hemoglobin concentration and platelet count in sickle cell patients with and without renal papillary necrosis. 1=Papillary necrosis present; 2=Papillary necrosis absent

0.124 ($P = 0.048$). Furthermore, a significant inverse relationship was observed between the Hb concentration and the leukocyte count − 0.155 ($P = 0.003$). The diastolic blood pressure was also observed to be positively associated with patients age 0.180 ($P = 0.016$). The serum aspartate transaminase was also found to positively correlate with the serum direct bilirubin 0.145 ($P = 0.027$).

Exploratory plots of these variables were done and are shown in Figure 1a and b. Figure 1a is a line plot of the distribution of the patients' age and leukocyte count in patients with and without RPN. The plot indicates that no observable difference exists in for these variables in the patient groups. Figure 1b, on the other hand, shows the dot blot of the distribution of the Hb concentration and platelet count in the two groups. This shows some apparent relationship between higher Hb levels and platelet counts in patients with RPN.

Discussion

There was a low prevalence of symptomatic RPN among our population of SCA patients. This agrees with previous studies involving 74 SCA patients aged 10–52 years in Zaria, North-West Nigeria.[13] RPN is generally painless and therefore unless clinically obvious hematuria is observed, patients may not complain. Furthermore, availability and affordability of diagnostic modalities which include CT, MRI, and urography may also be responsible for this observed apparent low prevalence. In most centers, routine investigation of patients with homozygous Hb S does not include these investigatory modalities. This complication, therefore, is most likely under-diagnosed, and this may explain the low prevalence of symptomatic RPN. However, the occurrence of a lower prevalence of some of the chronic complications of SCA, like sickle leg ulcer[14] and priapism[15] has been recorded in some studies done in Nigerian patients by Madu *et al.*, and this may be a continuation of this observed trend. Also worthy of note is that low prevalence of RPN in homozygous S patients was also recorded in two separate studies by Akinkugbe[16] and

Ibinaiye *et al.*,[13] in South-West and North-Eastern parts of Nigeria, respectively.

Diagnosis of RPN in this study was based on microscopic hematuria with suggestive ultrasonography findings; none of the patients in this study were screened using more sensitive imaging techniques – CT, MRI or urography. This may be further proof that radiological changes indicative of RPN may be seen in most SCA patients even without the occurrence of observable urinary symptoms, as had been hypothesized by Pandya *et al.*[10]

The patients involved in this study included both adults and children aged 6–55 years with homozygous S, and this may also explain the lower frequencies of RPN observed. The prevalence of symptomatic RPN was found to be 2.3%, this is much less than previous studies done by Odita *et al.*,[1] who diagnosed their patients using urography and also examined an older patient population (13–51 years). The onset of chronic complications of SCA has been generally observed to be more frequent with increasing age. Analgesic abuse also plays an important etiologic role and is usually seen in patients old enough to self-medicate. The presence of the sickle hemoglobinopathy in those patients with history of prolonged use of NSAIDs further increases the propensity to develop RPN.

The occurrence of symptomatic RPN in homozygous Hb S patients was determined to be significantly associated with the female gender. This has also been observed in diabetics with RPN in the study done by Mandel.[17] However, other clinical and laboratory features of severe sickle cell disease did not show any association with the occurrence of RPN. This may be a further indication that the occurrence of chronic complications in homozygous Hb S patients may be influenced to a large extent by the presence of other environmental and genetic factors. The pathogenesis of RPN is generally thought to be similar to the process involving vaso-occlusion and ischemic necrosis known to occur in SCA. This is further worsens by the low renal medullary oxygen tension. This may require further investigation as this assumption will infer that patients with frequent crisis and severe forms of the disease would most likely have RPN. This observation is contrary to our findings.

Conclusion

RPN can lead to obstructive uropathy renal failure, further adding to the causes of chronic kidney disease in SCA patients. The prevalence of RPN in homozygous S patients has been determined to be 2.3%, and this is lower than the prevalence noted in other geographical locations where SCA is rife. This complication is positively associated with the female gender, but not with other indicators of disease severity. Recent findings support the lower prevalence of complications in some sickle cell patient populations, and this may be due to environmental effects or better patient care.

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Conflicts of interest
There are no conflicts of interest.

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