Priapism: A Review of Children with Sickle Cell Disease in Port Harcourt, Nigeria

I. O. George[1,*], I. Gbobo[2] and C. N. Aiyedun[1]

[1]*Departments of Paediatrics, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria*

[2]*Departments of Surgery, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria*

Abstract: *Background:* Priapism is a complication of sickle cell disease (SCD) that if left untreated results in irreversible fibrosis and impotency. The aim of this study was to determine the prevalence, pattern, steady state laboratory parameters of children with priapism and their treatment.

Methods: A retrospective study of children with sickle cell disease who were diagnosed with priapism at the Sickle Cell Clinic and the Emergency Ward of the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria, from 1st August 2010 to 31st July 2015. Demographic as well as steady-state clinical data were extracted from the patients' medical records. Laboratory parameters were aged matched with children (HbSS) without priapism in steady state. Data analysed included age, sex, steady-state packed cell volume, leucocyte and platelet count; and treatment.

Results: A total of 345 folders of children with SCD (342, HbSS; 3HbSC) were retrieved during the period under review. Five children were found with diagnosis of priapism. The mean age was 8.0±4.6 (range 3-15years). The mean packed cell volume (PCV), white blood cell count (WBC) and platelet counts were 22±2.7; 8±2.9 and 179.4±25.7 respectively. The mean PCV of children with priapism was significantly ($P<0.05$) higher than the control. Fever 4(80%), dehydration 2(40%), rigorous physical exercise 1(20%) and emotional disturbances 1(20%) were associated risks factors. Stuttering pattern was the commonest 3(60%). Most 4(80%) of them were managed conservatively with irrigation of saline and adrenaline. None of them had exchange blood transfusion. Two(40%) of them had shunt after intumescence of 5 and10 days respectively. Only 1(20%) had recurrence. None had impotency.

Conclusion: The prevalence of priapism among patients with SCD is low (1.5%) in Port Harcourt. High steady state haematocrit values were significantly associated with priapism. Fever and dehydrated were the commonest pre-morbid conditions associated with priapism. The treatment options for all types of priapism were initially conservative but surgical therapy must be available when applicable to circumvent erectile dysfunction.

Keywords: Sickle cell diseases, priapism, treatment.

1. INTRODUCTION

Sickle cell disease (SCD) is a haematological disease that affects multiple organs, thus causing episodes of chronic pain, acute anaemia and infection, due to a single nucleotide mutation in the *β*-globin gene, which results in the substitution of a glutamic acid residue in place of valine on the *β*-globin chain of the resultant haemoglobinprotein molecule, the sickle haemoglobin (HbS) [1]. SCD is a major cause of morbidity and mortality characterized by episodes of vaso-occlusive crises, pain syndromes and end organ dysfunctions. It is a major genetic disease in most countries in Sub-Saharan Africa. Nigeria has the highest number of SCD patients with about 100,000 births each year [2, 3].

The pathophysiologic feature of sickle cell disease is periodic occurrence of vasoocclusive events that results in acute painful episodes [23]. Due to the deformed shape, HbS induces red blood cell(RBC) membrane damage leading to calcium influx into the cell. Calcium influx leads to crosslinking of the membrane proteins and activating channels that allow for the efflux of potassium and water from the cell. This results in RBC dehydration exacerbating the sickling. Vaso-occlusive crisis results from the sickle red cells obstructing and reducing blood flow to the vital organs leading to ischemia, necrosis and pain.

Pain crises constitute the most distinguishing clinical feature of sickle cell disease. It begins suddenly and may last several hours to several days and terminates as abruptly as it began. The pain can affect any body part (abdomen, bones, joints, and soft tissue).Anaemia is commonly present. It is chronic and hemolytic in nature and usually very well tolerated. Children exhibit few manifestations of anaemia because they readily adjust by increasing heart rate and stroke volume; however, they have decreased energies, which may be observed on the playground or when participating in physical education class.

Priapism is a sustained, painful, and unwanted erection of the penis that pathophysiologically is the result of either increased arterial inflow (i.e., high flow) or, more commonly, the failure of venous outflow (i.e., low flow), resulting in blood trapping within the erectile

*Address correspondence to this author at the Departments of Paediatrics, University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria;
Tel: +2348033309766; E-mail: geonosdemed@yahoo.com

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bodies. Although rare in the general population, [1] priapism was documented as a serious problem of SCD as early as 1934 [4]. Since then, many investigators have projected its incidence and prevalence in various populations and the choices for its treatment [4-9]. Prompt recognition and appropriate treatment of a priapism episode in males with sickle cell disease (SCD) is critical, as the outcome of prolonged and/or repeated episodes of priapism can be ischemia and fibrosis in the corpus cavernosa of the penis, potentially leading to impaired sexual function and impotence.

Themajor cause of priapism in the developed nations has been use of intracavernosal therapy for erectile dysfunction (ED), majority of the causes in nations where sickle cell disease (SCD) are endemic result from venous occlusion from sickling and sloughing of the sickle red cells leading to low flow priapism.

Numerous therapeutic options have been attempted, including diethylstilbestrol, gonadotropin-releasing hormone analogues, various adrenergic agonists, and hydroxyurea. Few agents have actually been examined in a controlled clinical trial, making it difficult for practitioners to treat this complication. It is recommendation that treatment should be conservative initially, with the patient being encouraged to urinate, exercise, increase his fluid intake, and take oral analgesics [10]. If the episode of priapism persists beyond 2 hours, the patient should report to the emergency department for intravenous hydration and analgesics. If the episode persists beyond 4 hours, intracavernosal aspiration and instillation of an alpha-agonist should be performed and repeated as needed. If the priapism remains for longer than 12 hours, surgery should be considered for shunt placement. The aim of this study was to determine the prevalence, pattern, steady state haematological laboratory parameters and treatment of children with this condition. The outcome of this study will enrich existing knowledge of priapism and bring to light the need for an increased awareness of the problems associated with priapism among patients, families and medical professionals.

2. METHODS

This is a retrospective study of children with sickle cell disease who were diagnosed with priapism at the Sickle Cell Clinic and the Emergency Ward of the University of Port Harcourt Teaching Hospital (UPTH), Port Harcourt, Nigeria, from 1st August2010 to 31stJuly 2015. Approval was obtained from Ethics Committee of UPTH. Demographic as well as steady-state clinical data were extracted from the patients' medical records. Patients who were not HbSS on Hb electrophoresis were excluded from this study. Data analysed included age, sex, steady-state packed cell volume and leucocyte and platelet counts; and treatment. Steady-state values were recorded as values obtained during the absence of a crisis or clinically obvious infection in the patient. Laboratory parameters were aged matched with children with HbSS in steady state without priapism. This was randomly selected.

Data were analyzed using SPSS version 16.0 (Statistical Package for Social Sciences, Inc., Chicago, IL, USA). The descriptive data was given as mean ± standard deviation (SD). Student t- test was used to test for association. A value was considered to be statistically significant when <0.05.

3. RESULTS

A total of 345 folders of children with SCD (342, HbSS; 3HbSC) were retrieved during the period under review. Five children were found with diagnosis of priapism. The mean age was 8.0±4.6 [range 3-15years, Table **1**]. Patient's steady state laboratory parameters are shown in Table **1**. The mean packed cell volume

Table 1: Patients Steady State Data and Treatment for Priapism

No	Genotype	Age(years)	PCV(%)	WBC(10^9 / l)	Platelet(10^9 / l)	Priapism Pattern	EBT	I/A	Shunt	D(days)
1	SS	5	25	6.0	165	ST	No	Yes	C-G	10
2	SS	8	21	12.0	155	ST	No	Yes	No	3
3	SS	9	22	10.8	222	ST	No	No	No	1
4	SS	15	18	7.0	180	AS	No	Yes	No	4
5	SS	2	24	5.0	175	AS	No	Yes	IC	5

EBT = exchange transfusion; I/A = irrigation with saline and adrenaline; C-G = cavernosus-glandular shunt; IC = intercavenosalshunt; ST = stuttering priapism; AS = acute and severe priapism; D = detumescence.

Table2: Haematological Parameters of SCD Children with and without Priapism

Parameters	Patients with Priapism n=5	Patients without Priapism n=5	Statistical Significance
PCV (%)	22 ± 2.7	16 ± 1.8	P<0.05
WBC (10^9/l)	8.0 ± 2.9	9.2 ± 3.2	p>0.05
Platelet (10^9/l)	179.4 ± 25.7	183.6 ± 23.6	P>0.05

(PCV), white blood cell count (WBC) and platelet counts are 22±2.7; 8±2.9 and 179.4±25.7 respectively. Fetal haemoglobin test results were not available for them. Table **2** shows that the mean PCV of children with priapism was significantly (P<0.05) higher than the control. Fever 4(80%), dehydration 2(40%), rigorous physical exercise 1(20%) and emotional disturbances1 (20%) are associated risks factors prior to onset of priapism (Table **3**). Stuttering pattern was the commonest 3(60%) and none of them had chronic progressive pattern (Table **1**). Most 4(80%) of them were managed conservatively with irrigation with saline and adrenaline and none of them had exchange blood transfusion (Table **1**). None of the children with priapism were chronically treated with hydoxyuria before onset of illness. Other modes of treatment included intravenous fluid, analgesics and hyper-transfusion. Two (40%) patient had shunt after intumescence of 5 and10 days respectively (Table **1**). Detumescence was achieved within 2 hours of the shunt procedure in both cases. One of them had poor morning erection. Only 1(20%) had recurrence.

Table 3: Precipitating Factors

Factors	Number (n=5)	Percentage (%)
Fever	4	80
Dehydration	2	40
Sexual arousal	0	0
Drugs	0	0
Physical exercise	1	20
Emotional disturbance	1	20

4. DISCUSSION

Priapism in sickle cell disease occurs due to infarction of the venous outflow tract which results in increased blood volume in the paired lateral corpora cavernosaand single corpus spongiosum causing erection [11]. The basis for this is stasis, hypoxia and acidosis of venous blood during normal erection resulting in sickling of erythrocytes within the venous sinusoids of corpora cavernosa thus causing obstruction of venous outflow. Priapism can be prolonged or stuttering and ischaemic or non-ischaemic. If it persists for longer duration it may lead to fibrosis and impotence [12]. Stuttering was the commonest pattern in our study accounting for 60% of all cases.

The 1.5% prevalence rate of priapism obtained in this study is similar to the rate of 1.6% reported by Otaigbe and Yaguo-Ide in the same institution [13]. However; Fowler *et al,* reported 2-6% [14]. A United kingdom (UK) group reported a rate of 37% [15]. In Brasil, Furtado *et al,* reported a prevalence of 5.6% among children with sickle cell anaemia [16]. Environmental differences may have accounted for the observed higher values in the UK and Brazilian studies.

Previous studies have implicated several precipitating factors including fever, asplenia, sexual arousal and dehydration in the occurrence of priapism [11, 13]. We found fever (80%), dehydration (40%), physical exercise (20%) and emotional disturbance (20%) as the main factors associated with the onset of priapism.

The leucocyte count was lower than the control which is dissimilar to the observations of Nolan *et al,* [17]. The findings of this study also clarify why hydroxycarbamide, which causes leucodepletion, has not been successful in the treatment or prophylaxis of priapism.

The steady state packed cell volume of our patients with priapism was significantly higher than aged/sex matched children with SCD without priapism. This agrees with study by Ahmed *et al,* [18], but at variance with that of Nolan *et al,* [17], who reported a positive relationship between priapism and low haemoglobin concentration. Our result could explain why high steady state haematocrit levels could be an important causative factor of priapism. High PCV could lead to higher blood viscosity, which increases the risk of sickling, thrombosis and vascular occlusion within the channels of the corpora cavernosa, leading to the development of priapism.

Acute treatment for ischemic priapism should be instituted within hours given the increasing likelihood of cavernosal fibrosis and permanent erectile dysfunction. Literature is chock-full with different approaches of treating priapism all with varying degrees of success. The commonly mentioned treatment for ischaemic priapism is corporal aspiration. This was the main (80%) definitive treatment used in our series. Lawani *et al.* in their series also found carvenostomies to be effective in treating ischaemic priapism [19]. Standard treatment involves penile blood gas studies, corporeal aspiration, and phenylephrine injection to induce smooth muscle contraction and detumescence. SCD patients may benefit from early high-dose intracavernosal phenylephrine given that the acidic pH of the ischemic cavernosa may decrease the affinity of adrenergic receptors for their ligands [3]. They may also benefit from hydration, blood transfusions, exchange transfusions, or hyperbaric oxygen. Most (80%) of our patients were managed conservatively with intravenous fluid, intracavernosal saline/adrenalin irrigation, analgesics and hyper transfusion. If conservative measures fail, penile shunt surgery should be performed. This may involve anastamosing corpus spongiosum and corpora cavernosa to create an internal fistula. This was done for our patients following failed conservative approach and detumescence was noticed within 2 hours of the shunt procedure.

Some authors [20-23] have documented use of hydroxyuria, gabapentin, terbutaline and methylene blue in management of priapism among patients with sickle cell disease. For instance, Saad *et al*. studied the use of hydroxyurea in patients with sickle cell disease presenting with priapism [20]. Five patients were studied using 10mg/kg of hydroxyuria, and they developed stuttering priapism soon after the initial treatment. The dose of hydroxyuria was increased, this lead to decrease in the duration of priapism episodes. It was concluded that hydroxyurea might prevent priapism episodes in sickle cell disease at higher doses than usually prescribed for painful crisis prevention [20]. Permenis *et al,* in their study reported the use of oral gabapentin in patients with recurrent, refractory, idiopathic priapism [21]. All the three patients studied responded to gabapentin within 48 hours and showed continued efficacy in preventing recurrences up to 24 months when receiving a lower dose of the drug. Lowe and colleagues determined the use of oral terbutaline in the treatment of priapism and found a 36% efficacy as against 12% for placebo [22]. Their finding was at variance with that of Govier *et al,* that found no significant differences between terbutaline and placebo [23]. Methylene blue, a guanylate cyclase inhibitor, is a potential inhibitor of endothelial mediated cavernous relaxation and has been used for the treatment of priapism. Its efficacy for priapism secondary to intracavernous drugs, was initially reported by Martinez *et al*, [24]. They reported 100% efficacy of this compound in 22 patients, with injection of 5ml intracavernosally that was left in situ for five minutes. However, intracavernosal methylene blue therapy has not been successful in treating every case of priapism and should be reserved for cases not responding to conventional methods of treatment only. Oral baclofen, a γ-aminobutyric acid agonist traditionally used to treat spasticity, at a dose of 40mg/day has also been used with success in recurrent idiopathic nocturnal priapism not responding to other means of therapy [25].

CONCLUSION

The prevalence of priapism among patients with SCD is low (1.5%) in Port Harcourt. High steady state haematocrit values were significantly associated with priapism. Fever and dehydrated were the commonest pre-morbid conditions associated with priapism. The treatment options for all types of priapism were initially conservative but surgical therapy must be available when applicable to circumvent erectile dysfunction.

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