Original Research

Clinical and laboratory parameters, risk factors predisposing to the development of priapism in sickle cell patients

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Impact statement

Sickle cell disease is prevalent throughout the world with a 5.8% incidence of sickle cell trait among the Omani population, yet priapism was a relatively rare complication. Penile erection and detumescence are complex physiological processes, which require a delicate neurohormonal and cardiovascular response. In this cohort, young SCD patients developed priapism with a low incidence of complications. These patients had high WBCs, platelets, bilirubin, LDH, and reticulocytes with low hemoglobin as compared to controls, suggesting an increased hemolytic process. Favorable outcome was dependent on early intervention, with almost half of these patients needing surgical intervention.

Abstract

Although sickle cell disease is very common in Oman, priapism is a relatively rare complication of this disease. This study was aimed to identify the clinical and laboratory risk factors that predispose sickle cell disease patients to priapism. In a retrospective, case-control study, data on 21 male sickle cell disease patients, with priapism, were compared to 20 age and sex-matched sickle cell disease patients without priapism from the hospital medical records. Specifically, the demographical, hematological, biochemical, and clinical parameters including complications attributable to priapism were studied. Means for continuous measures and independent t-test were used to evaluate the association between the parameter studied and the occurrence of priapism. Priapism occurrence was associated with low basal hemoglobin (Hb), along with an increase in other parameters such as white blood cell count (WBC) ($P = 0.010$), platelet count ($P = 0.001$), reticulocyte count ($P < 0.001$), mean corpuscular volume (MCV) ($P < 0.001$), and mean corpuscular hemoglobin (MCH) ($P < 0.001$). Biochemical laboratory parameters revealed an association with an increased total bilirubin ($P < 0.001$). Patients with priapism were more likely to have acute chest syndrome, stroke, pulmonary hypertension, asplenia ($P = 0.006$), gallbladder stones, and consequently cholecystectomy. Blood exchange and Penile aspiration were the most frequent medical therapies ($P = 0.010$ and $P < 0.001$ respectively). Patients with sickle cell disease who presented with priapism were young adults with low Hb, high WBC's, platelets, reticulocytes, MCV, MCH, bilirubin, and LDH. These findings suggest an association of priapism with increased hemolysis.

Keywords: Sickle cell disease, priapism, risk factors, erectile dysfunction

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Introduction

Sickle cell disease (SCD) is a genetic disorder caused by a point mutation in the β-globin gene, in which glutamic acid was replaced by valine, at the sixth position of the beta gene chain.[1] This abnormality leads to the formation of abnormal less deformable sickled erythrocytes. The disease is prevalent throughout the world and among 5.8% of the Omani population.[2,3]

The disease is characterized by repetitive vaso-occlusive (VOC) process, predisposition to infections and chronic hemolytic process. Increased red cell destruction liberates free hemoglobin leading to the depletion of nitric oxide (NO), as well as the release of arginase redirecting the metabolism of arginine to ornithine rather than NO, and contributes to some of the manifestations of SCD such as stroke, pulmonary hypertension, and priapism. These hemolytic complications are also associated with high platelet and leukocyte counts and reduced NO levels.[4,5]

Priapism is a prolonged, persistent, and painful penile erection without sexual stimulation. Priapism could be caused by conditions like leukemia, myeloproliferative disorders, and injury and is also seen as a side effect of specific

antipsychotic medications; however, the majority of the cases occur in SCD.[6]

Priapism is usually described as either, ischemic and non-ischemic.[7,8] Ischemic priapism is a result of venous outflow obstruction so that the blood could not drain from the vessels, adequately, as in SCD. However, non-ischemic priapism is most often related to unregulated blood pooling into the sinusoidal spaces of the corpora cavernosa (as seen mostly in trauma).

Priapism is reported amongst 35% of SCD patients, three-quarters of whom, had their first experience before the age of 20, and the mean age of the first occurrence was 15 years.[9,10] Recent data suggest that the lowest priapism prevalence was 0.67%, whereas the highest was 48.0% with age ranging from 7 to 30 years old.[11] SCD is thought to be an etiological factor in approximately 23% of adult and 63% of pediatric cases of priapism.[12]

Priapism is closely related to sickle cell-related factors such as high leukocytes, platelets, LDH, aspartate transaminase (AST), bilirubin, and low Hb.[4,13,14] Patients with high pulmonary artery pressure and leg ulcers are at an increased risk of priapism, whereas α-thalassemia carriers are protected.[4,15–17]

Among the pathophysiological mechanisms suggested for priapism occurrence in SCD are recurrent inflammation, leucocyte adhesion, vasculopathy, increase RBC arginase, free Hb, and reduced NO bioavailability.[18,19]

Polymorphisms in the genes involved in the vascular tone regulation, as well as NO metabolism, coagulation, cell adhesion (integrin), and cell hydration have also been incriminated as causative factors for priapism in SCD; in particular, polymorphism involving *KLOTHO* gene.[16,20] Interestingly, recurrent priapism was also previously reported even in cases with sickle cell trait.[21]

In Oman, the knowledge about the clinical and laboratory features of priapism in SCD is limited. Thus, in this retrospective case-control study, patients with SCD, manifesting with priapism were compared to age and sex-matched SCD controls (without priapism), aiming to provide a better understanding of the clinical and laboratory parameters, as well as the risk factors that predispose SCD patients to priapism in this population.

Material and methods

Data on consecutive SCD patients with priapism were obtained from the electronic medical records of the hospital. Medical records of SCD patients with a history of priapism between July 2009 and June 2017 were recovered for analysis in this single-institution cohort. The study was approved by the local institutional medical research and ethics committee.

Twenty-one SCD patients were identified through the discharge summaries, who had priapism episodes, with 20 age and gender matched SCD patients without priapism who were randomly selected as controls during the same time frame. All patients were Omani Arabs with SCD (HbSS and HbSβ^o). Patients with other SCD genotypes were excluded.

Clinical features evaluated included history and the frequency of VOC, acute chest syndrome, pulmonary hypertension, splenectomy, cholecystectomy, and stroke. Asplenia was defined as radiologically proven small or absent spleen (including one case of surgical splenectomy). Laboratory data included Hb and WBC at presentation, platelet count, reticulocyte count, HbS, fetal hemoglobin (HbF), adult hemoglobin (HbA), Hemoglobin A2 (HbA2), MCV, MCH, total bilirubin, AST, alanine transaminase (ALT), and LDH. Additionally, the medical therapy like hydroxyurea (HU) treatment, blood cavernosal aspiration, shunting surgical intervention, and transfusion/exchange were all also obtained. Furthermore, clinical complications such as impotence and infertility were also considered in the data collection.

Statistical analysis

Clinical and laboratory parameters of both cases and controls were compared using the means for continuous measures and tested for association by independent t-test. All data recording, statistical analysis, and results extraction were achieved using the program of Statistical Package for the Social Sciences (IBM SPSS, USA, version 23).

Results

Twenty-one SCD patients who had at least one episode of priapism were enrolled as cases (mean (SD) age 24.2 (7.9) years), whereas 20 SCD patients who did not have priapism served as age and sex-matched controls (mean (SD) age 27.4 (7.2) years); 1, 4, 14, and 2 patients presented with priapism episode in the first, second, third, and fourth decade, respectively.

Laboratory data of hematological parameters are shown in Table 1. Patients with priapism showed a low baseline Hb, a significant increase in WBCs, platelet counts, MCV, MCH with a P-value < 0.05, (Student's t-test). Also, hemolytic markers were significantly higher in priapism cases, with an increase in reticulocyte counts and serum bilirubin showing statistical significance. A higher LDH, AST, and ALT were seen, although not reaching statistical significance. Although VOC was seen in both groups with equal frequency, priapism cases were more likely to have had ACS, stroke, pulmonary hypertension, asplenia ($P = 0.006$, Chi-squared test), gallbladder stones, and cholecystectomy (Table 2).

Discussion

Priapism prevalence is very variable, as reported in the literature, and there are only a few studies aimed at understanding the pathophysiology, clinical presentation, and management of this rather rare complication in SCD. We analyzed the clinical and laboratory parameters as well as risk factors that predispose SCD patients to priapism episodes, based on previously published studies. Accurate and consistent data on the incidence and prevalence of priapism in SCD are lacking, since this syndrome is relatively rare, associated with under-reporting, and not all patients

Table 1. Laboratory characteristics of cases with priapism and controls in a population of SCD patients age-adjusted means standard deviation.

	Cases $N = 21$	Controls $N = 20$	P
Age at presentation, yrs	24.2 ± 7.87	27.4 ± 7.21	0.189
Hb baseline, g/dL	9.4 ± 1.43	10.00 ± 1.25	0.115
WBC baseline, $\times 10^9$/L	12.9 ± 4.48	9.8 ± 3.87	0.019*
Platelets, $\times 10^9$/L	478 ± 154.58	320.1 ± 185.07	0.005*
Reticulocytes,%	11.9 ± 6.24	5.1 ± 2.74	0.00007*
HbS,%	83 ± 13.17	80 ± 12.48	0.455
HbF,%	6.5 ± 4.36	8.2 ± 4.23	0.210
HbA,%	1.36 ± 1.3	0.8 ± 1.7	0.155
HbA2,%	4.5 ± 0.83	4.9 ± 0.95	0.088
MCV, fl	79.8 ± 7.41	69.1 ± 5.97	0.00001*
MCV, pg	27.60 ± 3.35	22.9 ± 2.34	0.00001*
Tot. bilirubin, μmol/mg	83.52 ± 13.2	36.65 ± 9.34	0.022*
AST, U/L	59.1 ± 12.1	41.95 ± 10.2	0.937
ALT, U/L	45.57 ± 8.5	36.2 ± 4.5	0.787
LDH, U/L	503 ± 179.8	403.2 ± 206.3	0.139

*Student's *t* test, *P* value significant at $P<0.05$.

Table 2. Medical therapy and complications in cases with priapism and controls in a population of SCD patients, presented as frequency (%).

	Cases $N = 21$	Controls $N = 20$	P
SCD complications			
VOC	21 (100)	20 (100)	
ACS	16 (76)	14 (70)	0.664
Stroke	5 (24)	3 (15)	0.489
Pulmonary hypertension	1 (5)	0 (0)	0.329
Asplenia	13 (62)	4 (20)	0.006*
Gallstones/cholecystectomy	6 (29)	4 (20)	0.535
Medical therapy			
Exchange transfusions	21 (100)	14 (70)	0.01*
Simple transfusions	21 (100)	17 (85)	0.083
Hydroxyurea therapy	15 (71)	15 (75)	0.803
Penile aspiration	10 (48)	0 (0)	<0.001*
Shunting	3 (14)	0 (0)	0.08
Complications			
Impotence	2 (10)	0 (0)	0.162
Infertility	2 (10)	0 (0)	0.162

*Chi square test, *P* value significant at $P < 0.05$.

with priapism came to seek medical attention, except in persistent protracted cases.

In our cohort, our youngest patient presented at the age of 4, whereas, the oldest was 44 years old, with a mean age at the first presentation being 24.2 years. This mean age was noticeably higher than 15.0 years, as reported from the UK and Nigerian multicenter study,[9] but lower than 33.7 years, as reported by the US study.[22] However, it was similar to other studies reported from Nigeria[23] and US[4] (23.7 and 26.2 years, respectively). This variability reflects the difficulty of consistent data in this rare complication, confounded further by the delay in reporting these symptoms. Priapism episodes in this study seem to peak in the second decade and were rarely reported among children and adolescents. However, in a previous study, about a quarter of patients with SCD who developed priapism experienced their first episode before reaching the age of 10 years.[24] The physiology of priapism in children is still unclear and it continues to challenge clinicians concerned with its management.[25]

Our patients showed a significant increase in baseline WBC counts, platelet counts, MCV, and MCH ($P < 0.05$, Students' test). Polymerization of HbS, cellular adhesion, and vascular dysfunction are critical steps in the pathophysiology of SCD. It is known that sickled red blood cells are stiffer than normal cells and the capillary diameter is smaller than the red blood cells.[5,26] Therefore, the loss of flexibility, which is characteristic of sickled red cells, would result in a decreased capillary blood flow, leading to vessel occlusion. In addition, RBCs, WBCs and platelets in SCD patients are found to be more adhesive to the vascular endothelium than those found in normal people.[27,28] This consequently could worsen the process of occlusion caused by these sickled RBC's.

Interestingly, the MCV was higher in the study group as compared to the control, while HbA2 was slightly higher in the control group than the cases, but these differences did not reach statistical significance. This is consistent with a previously reported data that patients with coinheritance of thalassemia (alpha or beta) are less likely to have hemolytic complications, leading to protection against the occurrence of priapism episodes.[4,17]

In our study patients, hemolytic markers were significantly higher with a low baseline Hb, increase in reticulocyte counts, high serum bilirubin, and higher LDH as compared to controls. These results support the hypothesis that priapism occurrence in SCD is seen in association with NO depletion due to increased hemolyzed Hb, high reactive oxygen species, and NO synthase inhibitors that are found to be profoundly raised in SCD patients.[29,30] Furthermore, SCD patients have diminished vascular response to NO leading to endothelial activation. This subsequently results in the activation of coagulation factors and platelets, causing vascular dysfunction.[31–35] Our results with elevated hemolytic parameters are in keeping with previously noted observations[4,5,10,26]

Level of Hb seems to impact on the onset of priapism, and although priapism was shown in association with high Hb concentration,[23] patients with priapism in SCD are characterized by low hemoglobin baseline (steady-state) and increased rates of intravascular hemolysis. In keeping with this, the Hb baseline was lower in the priapism group than in the controls, although it did not reach statistical significance. Previous reports on the subject showed conflicting data, probably reflecting the relatively low prevalence of this condition, and lack of studies looking at environmental and genetic factors associated with it.[4,10,26]

White blood cell counts, platelet counts, and reticulocyte counts were increased in the cases as compared to controls. This caused an acceleration of cellular adhesion to the vascular endothelium accompanied by the release of cytokines via multiple mechanisms,[27,28] worsening occlusion and leading to sickle vasculopathy. Further, active hematopoiesis as a result of excessive hemolysis might be the reason behind the elevation of these parameters. Thrombocytosis and leukocytosis are common in SCD patients with priapism, as well as asplenia. These observations were not far

from what was seen in malignancy with priapism like in chronic myeloid leukemia.[36]

Expectedly, LDH as a hemolytic biomarker was higher in priapism cases, as described in multiple publications. Priapism was reported in association with pulmonary hypertension (PTH) and leg ulcer.[13] Similarly, increased total bilirubin was associated with priapism in this study as described in several publications.[4,10] This elevation of LDH and bilirubin was corroborated with a significantly high MCV and MCH strengthening the previously reported protective effect of thalassemia,[5,17] or because of reticulocyte level interfering with cell volume. Although α-thalassemia was known to lower the risk of priapism, we could not ascertain the role of sickle β thal in our priapism cases, although HbA2 was higher in the control, but it did not reach a statistical discriminatory level.[37] Furthermore, our sample size is also small to evaluate this suggestion.

HbF plays an ameliorating role in SCD manifestations by decreasing the intracellular polymerization and decreased endothelial adhesion. Our results showed a lower HbF in the priapism group, but it did not reach a statistical significance. HbF was found to be protective against some SCD clinical sub-phenotypes such as acute painful episode[38] and ACS[12]; however, it was not associated with priapism, PTH, and stroke.[14,17] These findings suggest that HbF plays a minor role in relation to the hemolytic manifestations, in comparison to the inflammatory complications of SCD patients, where the higher HbF levels are hypothesized to ameliorate these clinical manifestations.

VOC was found in all subjects, unlike ACS, which found slightly higher in priapism cases, but both did not reach statistical significance.[26] Priapism was observed to be more prevalent among SCD males, with PHT, and stroke than controls; however, again it did not reach statistical significance.[15] Asplenia has been implicated as a precipitating factor for the priapism occurrence.[23,26,39,40] This reflects a loss of the role that spleen plays as part of the reticuloendothelial system.

In our cohort, only one patient had surgical removal of the spleen, whereas, additionally, 12 patients had radiologically proven absent/or small spleens consistent with asplenia. Also, there was a significant correlation with asplenia ($P < 0.006$, Table 2). This is also in concordance with a previous study by Wali *et al.*,[41] in our Omani sickle cell children, showing that 28% of these children had a normal splenic function. Further, more than 60% overall, had preserved splenic function. Importantly, spleen size was one of the main factors significantly associated with splenic function in this study. Furthermore, raised platelet count, WBC count, which are seen more in asplenia and described earlier in this study, may also explain priapism episodes in patients who undergo surgical splenectomy or have auto-splenectomy (asplenia).

Management of priapism is still not clear and there are no evidence-based guidelines established; only some case reports and circumstantial practices. Primary non-surgical management of priapism cases includes aspiration, and injection of sympathomimetic agents, i.e. pseudoephedrine. Surgically, penile shunting should only be performed in the case of primary management failure due to a high risk of developing corporal fibrosis, impotence, and the loss of penile length. Impotence results from the inflammatory reaction that follows the occlusion and stasis of distorted erythrocytes in the corpora cavernosa. Transfusion/exchange was done in all cases, although there are no published guidelines to support this practice as prophylactic or therapeutic intervention.[26,42]

HU therapy plays a role in SCD management by raising HbF concentration and it is an effective NO donor. HU use was similar in both study groups, giving us a hint that this drug might not be very effective in relieving this syndrome. This is similar to a previously reported study examining HU use in priapism.[4] However, a case report published recently claimed that HU therapy restored complete erectile loss of SCD patients following priapism.[43] The efficacy of HU in this report suggests that HU treatment in priapism cases may implicate a NO-dependent pathway involved in the priapism of SCD; however, further studies are needed. HU is nevertheless still prescribed to reduce the other SCD complications and improve the life expectancy.

In conclusion, this study looked at the clinical and laboratory behaviors as well as the risk factors that predispose SCD patients to priapism. We found that priapism occurred more in patients with lower Hb, higher WBC and platelet counts, and high hemolytic markers such as reticulocyte count, LDH, and bilirubin. Co-association of thalassemia was more likely to be protective from these episodes, and HU did not seem to play a role in protection from these events.

Authors' contributions: SAK, SSA, and AP were fully involved in the conception, design of the study, acquisition, analysis and interpretation of data and were instrumental in drafting the article and critical appraisal before submission.

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