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Priapism in Sickle Cell Disease: A Hematologist's Perspective

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Abstract

Introduction—Priapism is a familiar problem to hematologists, well known for its association with sickle cell disease. It also occurs in a variety of other hematological illnesses, nearly all forms of congenital hemolytic anemia, including other hemoglobinopathies and red blood cell membranopathies and enzymopathies.

Aim—Provide urologists with a comprehensive review of priapism in sickle cell disease, with an emphasis on the perspective of a practicing hematologist.

Methods—Medline searches through July 2010 were conducted using the terms priapism, erectile dysfunction, and sickle cell.

Main Outcome Measure—Expert opinion was based on review of the medical literature related to this subject matter.

Results—In men with sickle cell disease, large epidemiological studies have linked the risk of priapism to clinical markers of the severity of intravascular hemolysis. Extracellular hemoglobin and arginase released during hemolysis has been implicated in reducing nitric oxide bioavailability, although the relevance of hemolysis to vascular dysfunction has been challenged by some scientists. Consistent with the role of impairment of the nitric oxide axis, mice genetically deficient in nitric oxide production have also been shown to develop priapic activity. Provocative new data indicates that hemolysis-linked dysregulation of adenosine signaling in the penis contributes to priapism in sickle cell mice. Serious questions have arisen regarding the efficacy of mainstays of textbook dogma for treatment of acute severe priapism, including intravenous fluids, alkalinization and exchange transfusion, and there is increasing acceptance for early aspiration and irrigation of the corpus cavernosum.

Conclusions—For sickle cell patients with recurrent priapism, there is very limited evidence for a medical prophylaxis role for hydroxyurea, etilefrine, pseudoephedrine, leuprolide, sildenafil, and other agents. Recent publications have highlighted nitric oxide and adenosine signal transduction pathways as worthy of additional research. Research and clinical management of sickle cell priapism is strengthened by multidisciplinary collaboration between hematologists and urologists.

Keywords

Priapism; Ischemic Priapism; Stuttering Priapism; Erectile Dysfunction; Sickle cell; Hematology and Priapism

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Introduction

The year 2010 marks the centenary of the first English language publication on sickle cell disease (SCD). In this case report, published in the Archives of Internal Medicine, photomicrographs of elongated red blood cells were presented by Dr. James B. Herrick, who coined the term “sickle-shaped red blood corpuscles” in the title of the manuscript.¹ The first report of priapism in patients with SCD is attributed to Dawson in 1939.² The next 23 years of progress were summarized in a 1962 publication of two new cases, survey of 24 cases from 13 large hospitals, and literature review of 33 cases by renowned sickle cell disease clinician Dr. Roland B. Scott and his colleagues, who observed that “treatment is symptomatic and generally unsatisfactory; however, needle aspirations of the corpora cavernosa appear to yield the most satisfactory results.”³

Although priapism has achieved the highest level of notoriety in SCD, it also has been reported in many other hematological disorders. Priapism also has been reported in patients with leukemia, multiple myeloma, thalassemia and other hemolytic anemias that will be discussed in more detail below.⁴ This observation may help to understand potential pathways perturbed in priapism. Priapism also is occasionally seen in patients without any known hematological dyscrasia.⁵

Pathophysiology of Sickle Cell Disease

Polymerization of hemoglobin S

SCD is fundamentally a disorder of polymerization of hemoglobin S (HbS), a mutant version of adult hemoglobin that involves a single amino acid change in the beta chain. SCD is known as the “first molecular disease” due to the finding by Nobel laureate Linus Pauling that the hemoglobin from patients with SCD migrates anomalously on gel electrophoresis.⁶ The nucleotide mutation in the beta-globin messenger RNA that gives rise to that change also among the first base-pair alterations reported in human disease.⁷ Polymerization of HbS causes stiffness of red cells, which is particularly important to the flow of blood, because red cells are larger than the capillaries through which they must flow. This impairment of red cell rheology occurs even at levels of HbS polymerization insufficient to cause the characteristic shape distortion that give SCD its name.

Cellular adhesion

Other investigators have also published evidence that red cells, white blood cells, and platelets are more adhesive to vascular endothelium in SCD. They have promoted the additional concept that these adhesive events, especially in the post-capillary venules, add to the vascular occlusion imposed by noncompliant red cells.^{8,9} Expression of cell surface adhesion molecules is driven by immature blood cells and inflammatory cytokines. These pathways have been worked out in very elegant detail in mouse models of sickle cell disease, but more confirmatory studies are needed in human patients with SCD. These ideas have led to clinical trials of anti-adhesive therapy in patients with SCD.

Vascular dysfunction

Both of the components of the blood vessel wall, the vascular endothelium and vascular smooth muscle, develop pathology in SCD that may contribute to vasculopathy or coagulopathy. Patients with SCD have blunted vasodilatory responses to nitric oxide (NO), the critical mediator of vascular homeostasis.¹⁰⁻¹² Similarly blunted responses to NO are seen in the SCD mouse.^{13, 14} Patients with SCD express high levels of endothelial activation markers,¹⁵⁻¹⁸ and hemostatic activation of platelets and coagulation factors.¹⁹ Many

elements of this vascular dysfunction overlap with the pathophysiology seen in atherosclerosis or diabetic vasculopathy.^{20, 21}

Clinical Complications of Sickle Cell Disease

Complications unique to SCD

There are a number of classical complications of SCD that are not seen in any other disease state. These include the *vaso-occlusive pain crisis*, also called the *acute pain episode*. These painful episodes usually are caused by ischemia or infarction of the bone marrow due to vaso-occlusion. They are often treated in the hospital with intravenous hydration and opioids, although this treatment is essentially palliative until self resolution occurs in several days. The incidence of severe painful episodes is often reduced by prophylactic chronic administration of hydroxyurea, provided it is prescribed at adequate dosages and properly supervised. A second unique complication is the *acute chest syndrome*, a common final pathway of acute lung injury in SCD that resembles acute respiratory distress syndrome. It may be triggered by pneumonia, pulmonary vaso-occlusion, or most commonly by embolization to the lung of infarcted bone marrow, overlapping in several ways the fat embolization syndrome seen in femur fracture patients without SCD. Acute chest syndrome causing hypoxia resolves most quickly with simple or exchange blood transfusion and attentive supportive care. Occasionally seen SCD complications include splenic or hepatic sequestration crisis. SCD patients can suffer acute infarctions of virtually any organ in the body.

Complications Not Unique to SCD

There are several commonly occurring complications of SCD that are also seen in other disorders, including priapism, leg ulcers, pulmonary hypertension, stroke and avascular necrosis of the femoral head. All of these complications are seen at unusually high rates in SCD, clearly implicating SCD as a major risk factor. However, these complications are most often reported in the absence of SCD, suggesting both that sickling is not required for their development, but conversely that sickling likely may contribute to these complications.

Priapism is not unique to SCD

Priapism has been reported in patients with a wide variety of hemolytic anemias beside SCD (Table 1), including thalassemia,²²⁻²⁸ hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria, unstable hemoglobin disorders,²⁹⁻³¹ glucose-6 phosphate dehydrogenase deficiency,^{32, 33} glucose-6 phosphate isomerase deficiency,³⁴ and congenital dyserythropoietic anemia.³⁵ In many of these cases, the onset of priapism followed splenectomy, leading to the suggestion that asplenia might be a risk factor for priapism.^{36, 37} Asplenia, a common feature of SCD, promotes thrombocytosis and leukocytosis. In patients with hemolytic anemia, asplenia is also associated with decreased extravascular hemolysis, partially offset by increased intravascular hemolysis, resulting in higher levels of extracellular plasma hemoglobin which might scavenge NO, higher levels of plasma microparticles, known to be pro-thrombotic, and higher levels of phosphatidylserine-externalized red cells, which are more adhesive.³⁸ The prevalence of leg ulcers and pulmonary hypertension in SCD correlate with markers of hemolytic severity, potentially implicating decreased NO bioavailability, asplenia and hemostatic activation in their etiology.³⁹ Similar to the case of priapism, leg ulcers and pulmonary hypertension have been reported in association with a wide variety of hemolytic anemias other than SCD.⁴⁰

Role of hemolysis in priapism, leg ulcers and pulmonary hypertension

An important consequence of HbS polymerization is premature breakdown of the red cell, which in SCD commonly survive in the circulation only about one-sixth the normal 120-day

red cell lifespan. Many publications present data implicating scavenging of NO by hemoglobin released from intravascular lysis of red blood cells in SCD,^{41, 42} compounded by depletion of arginine, the obligate substrate for NO synthase, by arginase-1 also released from red cells during hemolysis.⁴³ NO may also be scavenged by reactive oxygen species that are abundantly produced in SCD,⁴⁴ contributing to robust oxidative stress, further exacerbated by the oxidant properties of free heme and iron-catalyzed Fenton reactions.^{45, 46} Levels of endogenous inhibitors of NO synthase are also found in the plasma from SCD patients at triple the level of healthy control subjects.^{22, 47} Most of these markers also correlate with leg ulceration,⁴⁸ and with echocardiographic estimates of high pulmonary artery pressure, implying a role for hemolysis-linked NO deficiency in pulmonary hypertension, a life-limiting complication of SCD.^{49, 50}

The existence of hemolysis-induced impairment of NO deficiency in SCD has been challenged.⁵¹ Bunn and colleagues have suggested that the degree of intravascular hemolysis in SCD is insufficient to produce clinically significant NO deficiency. They concede that the degree of intravascular hemolysis in at least one hemolytic anemia, paroxysmal nocturnal hemoglobinuria (PNH), likely promotes NO scavenging and deficiency. They report no known link of PNH to priapism, although such a report has been published.⁵² They note that any role of NO scavenging in priapism in hemolytic anemias must be complex. Consistent with their caveat, erectile dysfunction is far more common than priapism in PNH,⁵³ and priapism appears to be more common in SCD than erectile dysfunction.^{54, 55}

Epidemiology of Priapism in SCD

Clinical epidemiology

In Pohl's 1986 literature review of 230 cases of priapism, SCD accounted for 11% of cases,⁵⁶ and as high as 67% of the cases in Winter's 1988 series of 105 patients with priapism.⁵⁷ Mantadakis and colleagues found that 29% of male children and adolescents with SCD reported priapism, and projected that up to 89% of SCD males would experience priapism by age 20 years.⁵⁸ Priapism is reported to be markedly less frequent in Saudi SCD males, attributed to genetically determined high levels of fetal hemoglobin, which generally attenuates SCD complications.⁵⁹ Greeks with SCD also have low rates of priapism, unrelated to α -thalassemia trait or elevated fetal hemoglobin levels.⁶⁰ In the Cooperative Study of Sickle Cell Disease, 273 males with a history of priapism had significantly lower levels of hemoglobin than 979 SCD males without priapism.⁶¹ They also had higher levels of serum lactate dehydrogenase, bilirubin, and aspartate aminotransferase; and higher reticulocyte counts, all markers of more severe hemolysis in SCD males with priapism, compared to those without priapism (Table 2). White blood cell and platelet counts were also higher in those with a history of priapism. Fetal hemoglobin levels were not different. In a separate study of 78 adult SCD males at the National Institutes of Health, priapism was most prevalent in those with steady state levels of LDH above 511 IU/L.⁶² Although these results from the United States supports a relationship of priapism to hemolytic severity, but not fetal hemoglobin level, these results are contrasted by a report of 23 SCD males in Nigeria with priapism who manifested higher hematocrit levels and lower fetal hemoglobin levels than those without priapism.⁶³ Coinheritance of α -thalassemia trait, which reduces hemolysis, is protective against priapism in the U.S. population.⁶¹ Priapism is associated with certain other clinical manifestations of SCD, such as ischemic stroke, avascular necrosis, acute chest syndrome, acute painful episodes, leg ulcers, chronic renal failure and chronic lung disease.^{61, 64, 65} Priapism is more prevalent in adult males with SCD who have high tricuspid regurgitant velocity, an echocardiographic marker of high pulmonary artery pressure.⁴⁹ These studies indicate that SCD males with priapism have a high risk of more severe additional complications of SCD.

Genetic epidemiology

Priapism in males with SCD has been associated with several genetic markers in two studies (Table 3). Klotho, a membrane protein that regulates nitric oxide synthase, was associated with priapism in SCD.⁶⁶ This result was not replicated in another smaller study, but several other significant associations were found. These included the transforming growth factor β receptor-3, the cell membrane water channel aquaporin-1, the blood clot stabilizing enzyme Factor XIII, and the integrin α_V .⁶⁷ This integrin is a subunit of the $\alpha_V\text{-}\beta_3$ endothelial adhesion molecule that is believed to bind to sickle erythrocytes to endothelium via intermediary proteins thrombospondin, von Willebrand factor and ICAM-4.^{9, 68} These interesting genetic associations remain to be validated in a replication cohort.

Additional evidence linking NO deficiency to priapism

Transgenic and knockout mice have provided additional support that a disordered NO pathway can be at least one cause of priapism (Table 4). Mice that are genetically deficient in endothelial NO synthase develop spontaneous priapic activity.⁶⁹ The frequency of priapic activity is even greater in the mouse doubly deficient in both endothelial and neuronal NO synthase.⁷⁰ This is an apparent paradox, since NO deficiency might be predicted to result in erectile dysfunction, which is seen in the mouse deficient in protein kinase G, an important mediator of NO activity exerted via the cyclic guanosine monophosphate (cGMP) signal transduction.⁷¹ The mechanism for NO deficiency-induced priapism is a chronic down-regulation of phosphodiesterase-5 (PDE5), the critical regulator of penile vascular homeostasis.⁷⁰ The same down-regulation of PE5 is observed in penile tissue from the SCD mouse, supporting the physiological effect of NO deficiency in SCD.^{70, 72, 73} This inhibition of PDE5 expression functionally mimics the effect of the erection-facilitating PDE5 inhibitors, such as sildenafil. NO pathways in priapism and erectile dysfunction remain complex and incompletely understood, with more investigation remaining to be done. These and other mechanistic pathways will be reviewed in more detail in an accompanying manuscript by Dr. Trinity Bivalacqua.

Adenosine pathways in sickle cell priapism

Recent data in animal models has implicated adenosine pathways in priapism (Table 4). Adenosine deaminase (ADA) deficient mice and SCD mice develop high levels of adenosine in the penis, associated with priapic activity, which is reversed by systemic administration of or ex vivo incubation with ADA enzyme.^{74, 75} Evidence suggests that the effect is mediated via the adenosine A_{2B} receptor. High penile concentration of adenosine is also associated with penile fibrosis, a serious end stage of priapism.⁷⁶ The applicability of this pathway to human priapism must be viewed with caution until human investigations are performed, because priapism has never been reported in humans with ADA deficiency, although the efficacy of enzyme replacement therapy (or frequent early lethality without ADA enzyme replacement) might account for this.

Medical Management of Sickle Cell Priapism

Management of mild priapism

SCD patients often report that light exercise is effective in terminating mild episodes of priapism. Other self-treatment approaches reported by patients have included voiding, opioid and nonsteroidal analgesics, ejaculation, or a warm bath or shower.^{58, 77, 78} These are all relatively safe approaches to consider in mild episodes of less than four hours duration.

Severe acute priapism episodes: longstanding unsupported dogma

Hematology and urology textbooks continue without reservation to prescribe for severe priapism episodes intravenous hydration, sodium bicarbonate to alkalize the urine, and exchange transfusion (Table 5). These recommendations have been printed and reprinted for half a century without objective published evidence of efficacy. More recently, published opinion has begun to question this textbook dogma, including the directive of exchange transfusion.⁷⁹ Not only is the efficacy of emergency exchange transfusion for priapism in question, but there have been reports of acute neurological complications in this setting.^{80, 81} In my own opinion based on literature reviews and 25 years of experience, treatment has advanced little since the 1962 observation of Dr. Scott cited in the first paragraph of this review. In severe acute priapism, the rite of administration of these usually futile treatments often serves simply to delay definitive aspiration of the penis, which in my experience is usually dramatically effective. This has been best documented by Mantadakis and colleagues from Children's Medical Center Dallas.^{78, 82} An accompanying review article in this issue by Dr. Gregory Broderick discusses urological management of acute sickle cell priapism in more detail.

Medical prevention strategies

There are no clear evidence-based guidelines in this area, only anecdotal experiences, some of which are published, and these have been reviewed in detail.⁷⁸ There is some limited experience with the use of hydroxyurea for priapism prevention.^{83, 84} A strong advantage of a therapeutic trial of hydroxyurea in a SCD patient is that the drug has been demonstrated to reduce pain complications and prolong lifespan in adults with symptomatic SCD,^{85, 86} so that there may be substantial likelihood of additional collateral benefit to the patient. Hydroxyurea is the only drug approved by the FDA specifically for SCD, and its effectiveness is only well characterized when titrated to maximum tolerated dose. As an alternative or additional strategy, some experienced clinicians, including this author, have advocated a therapeutic trial of oral pseudoephedrine 30 – 60 mg at bedtime.⁷⁸

Paradoxically, sildenafil has been reported in small series to be of prophylactic benefit in sickle cell and thalassemia priapism.^{87–89} Animal data suggests that sildenafil restores deficient production of PDE5 in the penis.⁷⁰ However, it is difficult to recommend sildenafil for this purpose until a clinical trial has been completed. Another prophylactic treatment with multiple anecdotal successes is injectable leuprolide, the gonadotropin releasing hormone antagonist.^{78, 90} However, extended use of leuprolide runs a substantial risk of longstanding hypogonadism, and priapism often returns immediately with its discontinuation.⁷⁸ Diethylstilbestrol showed some efficacy in a small clinical trial, but is rarely used for this purpose due to its feminizing side effects.⁹¹ Etilefrine, an adrenergic agent, has been used extensively for this purpose in Europe, but is not available in the United States. This and other agents with more limited anecdotal reports have been extensively reviewed, including flutamide and pentoxifylline.⁷⁸

Chronic, monthly red blood cell transfusion is sometimes attempted prophylactically, but there is no substantial published evidence of efficacy for prevention of priapism.⁷⁸ The medical management of recurrent or stuttering priapism is often difficult and frustrating, often involving sequential attempts with several different drugs, and clearly more rigorous clinical research is needed in this area. It is unfortunately common to have recurrent priapism subside only due to the development of impotence.^{4, 55–57}

Conclusions

Priapism is a frequent occurrence in males with SCD, but also seen in patients with other hemolytic disorders. Medical prophylaxis can be attempted in males with recurrent or stuttering priapism with hydroxyurea and pseudoephedrine, although supportive data are few. Etilefrine is not available in the United States, but there are reports of its prophylactic efficacy in Europe. There have been limited reports of effectiveness of leuprolide or diethylstilbestrol efficacy, but there are substantial reservations about their use. Previous dogmatic guidelines about medical management of acute sickle cell priapism have been questioned, and there is increased acceptance of early invasive urological management of acute severe priapism in SCD. Priapism is an important complication with substantial risk of long term consequences on sexual function. There are exciting recent advances in understanding its basic scientific mechanisms, but there still is a strong need for additional mechanistic research and cooperative clinical trials to improve the understanding, management and outcome of priapism.

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Table 1

Hemolytic anemias in which priapism has been reported.

Diagnosis	Citation
Sickle cell disease	2, 3
Thalassemia	23–28
Hereditary spherocytosis	92, 93
Paroxysmal nocturnal hemoglobinuria	52
Unstable hemoglobin disorders	29–31
Glucose-6 phosphate dehydrogenase deficiency	32, 33
Glucose-6 phosphate isomerase deficiency	34
Congenital dyserythropoietic anemia	35

Table 2

Risk factors and protective factors for sickle cell priapism.

Risk Factors	Citation
Low hemoglobin	61, 62
High LDH, bilirubin, AST, reticulocyte count	61, 62
High leukocyte and platelet count	61
High pulmonary artery pressure	49
Leg ulcers	65

Protective Factors	Citation
α -thalassemia trait	61
Greek or Saudi ethnicity	59, 60

Table 3

Preliminary genetic associations with sickle cell priapism.

Gene	Abbreviation	GeneID	Citation
Klotho	KI	83504	66
Transforming growth factor β receptor-3	TGFB3	21809	67
Aquaporin-1	AQP1	282653	67
Factor XIII	F13A1	134570	67
Integrin α_v	ITAGV	3685	67

Table 4

Mechanistic pathways potentially involved in sickle cell priapism.

Pathway	Animal Data	Human Data	Citation
Nitric oxide deficiency	Yes	Yes	62, 70
Excess penile adenosine	Yes	No	74, 75, 94
Obstruction of corpus cavernosa by sickled red cells	No	No	
Obstruction of corpus cavernosa by adherent cells	No	No	
Asplenia	No	Yes	25-31, 36, 37

Table 5

Medical management of sickle cell priapism.

Treatment	Quality of Data in SCD	Citation
Hydration, opioids, alkalization	Unsupported	
Exchange transfusion	Unsupported	95
Hydroxyurea	Case series	83, 84
Sildenafil	Case series	87, 88
Pseudoephedrine	Anecdote	78
Leuprolide	Anecdotes	78, 90, 96
Diethylstilbestrol	Anecdotes, small trials	91, 97-99
Etilefrine	Small trials	100, 101
Penile aspiration and irrigation	Extended series	82, 101