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Hydroxyurea therapy for priapism prevention and erectile function recovery in sickle cell disease: a case report and review of the literature

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Abstract

Prolonged ischemic priapism in patients with sickling hemoglobinopathies is a urologic emergency requiring immediate intervention to avoid irreversible anoxic penile injury, corporal fibrosis, and erectile dys-function. Therapeutic options, however, are limited and often ineffective. Here, we report recovery of erectile function with hydroxyurea therapy in an adolescent with

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hemoglobin SS following a prolonged episode of priapism and subsequent severe erectile dysfunction. This case suggests a potential role of hydroxyurea in reversing end organ damage in patients with hemoglobin SS and also supports basic science work indicating involvement of the NO-dependent pathway in the pathogenesis of sickle cell disease-associated priapism.

Keywords

Priapism; Impotence; Hydroxyurea; Sickle; cell anemia

Introduction

Priapism is a clinical disorder involving prolonged penile erection without sexual arousal or desire [1]. The predominant ischemic form often occurs in patients with sickling hemoglobinopathies and can occur as brief, repetitive, clusters known as stuttering or recurrent priapism, or as major events which are prolonged [1, 2]. Prolonged episodes cause penile tissue ischemia and a subsequent inflammatory reaction that promotes fibrosis of the spongy trabeculae, resulting in erectile dysfunction in severe cases [2]. Previous studies have demonstrated prevalence rates as high as 42 % in patients with sickle cell disease (SCD) [2]. Although the pathophysiology is incompletely understood, significant advances in recent years implicate aberrations in erection physiology regulatory signaling pathways that result in uncontrolled penile erections [2]. These derangements, predominantly that of the nitric oxide (NO) signaling pathway that is fundamental for regulatory penile erections [2, 3], have been demonstrated to be a molecular mechanism for priapic events [3]. Despite its prevalence in the SCD population, there is no consensus on the optimal therapeutic intervention for recurrent ischemic priapism. Here, we report a patient with SCD who developed complete loss of erectile function following a prolonged, severe priapism episode but then recovered erectile function after several months of hydroxyurea therapy. This observation suggested a possible effect of hydroxyurea on erectile function recovery after priapism resolution. We also review the scientific literature regarding the pathophysiology of this disorder and the proposed mechanisms of action of hydroxyurea therapy.

Case report

A 16-year-old male with homozygous SCD and recurrent priapism presented requesting alternative therapy to decrease his frequent hospital visits for monthly transfusion therapy. His recurrent priapism began at age 10, characterized by monthly episodes typically occurring on awakening from sleep and lasting approximately 1–2 h. These episodes often required periodic emergency room visits where they were managed conservatively with fluid resuscitation and pain control. At age 12 years, he was started on monthly transfusion therapy and although he experienced a concurrent decrease in the duration of priapism episodes, the frequency gradually increased to weekly episodes that occurred with sleep but lasted only about an hour. At age 15 years, a major episode occurred after 5 months off transfusion therapy but was resolved with an intravenous terbutaline drip and erythrocytapheresis. He subsequently resumed monthly transfusion therapy, and his

priapism episodes gradually decreased from 3 to 4 weekly episodes of about 1 h duration to no episodes of recurrent priapism.

At age 16, he was started on a daily, relatively low-dose, hydroxyurea (1000 mg) regimen. 4 months later, he developed a prolonged episode of priapism lasting 12–18 h and was admitted to the hospital where he reported being noncompliant with his regimen, commonly dosing weekly instead of daily. He was treated with terbutaline and intravenous hydration, and the priapism eventually resolved. Despite this episode, his erectile function remained intact. 3 weeks later, he was admitted with another episode of prolonged priapism. The episode did not resolve with hydration or multiple transfusions but instead progressively worsened until urination became difficult. After 72 h of unremitting priapism, a penile blood gas from the corpora cavernosa showed a pH of 6.86, pO2 of 4 mm Hg, pCO2 of 114 mm Hg, and bicarbonate of 20 mEq/L. He was urgently taken to the operating room for surgical drainage and irrigation of the penile corpora. Detumescence and pain resolution were achieved following the procedure, although the penis remained swollen. A medical decision was made to manage him with chronic transfusion therapy for 6 months following the surgical drainage, during which time he was continued on hydroxyurea for approximately 4–5 months with only a brief hiatus following his development of cholecystitis requiring cholecystectomy. Therapy was restarted once more at 6 months following the surgical priapism intervention. No additional episodes of priapism occurred; however, there was no erectile function present during this time period.

At age 19 years (18 months after hydroxyurea was restarted), the patient regained significant erectile functionality in terms of quality and firmness and also having the ability to ejaculate and orgasm normally. In follow-up over the subsequent 9 years, he did well on hydroxyurea without recurrent crises or other recognized complications of SCD, with his % hemoglobin F increasing from a baseline of <5 % to a peak of 16.1 % after the initial 18 months consistent with the effect of this therapy after long-term use. Notably, he continues to be successfully sexually active, having only slightly impaired erectile function but without requirement of treatment aids and no further episodes of painful priapism.

Discussion

To our knowledge, this is the first report of a patient with hemoglobin SS disease and erectile dysfunction secondary to a prolonged, 72-h long episode, who experienced return of erectile function 18 months later while on hydroxyurea. This case is notable for the episode duration and the recovery of function several months later. Although the natural history of disease can include spontaneous return of erectile function, potency preservation outcomes decline significantly with interventions during episodes lasting longer than 24–36 h [4]. Complete dysfunction typically occurs following episodes lasting longer than 48 h [4, 5], let alone 72 h [1], as in this case. Despite the often dismal outcomes, this patient remarkably experienced recovery while on low-dose, long-term hydroxyurea which may indicate that this therapy contributed toward the healing and tissue remodeling process that took place during this period.

Although priapism appears to be a relatively common problem in hemoglobin SS, the optimal therapy is unclear and the consequences can be severe. Hydroxyurea has been reported to decrease the number of stuttering priapism episodes in patients who retained erectile function [6, 7]. The beneficial effects may stem from its role as an NO donor, as hydroxyurea has been shown to interact with hemoglobin to form NO [8, 9]. Recent investigations exploring the use of NO donors have demonstrated their potential in reversing and correcting the pathological signaling that presents in priapism in animal models [10].

During hemolysis, free hemoglobin is released, which avidly scavenges intravascular NO, decreasing normal levels [11, 12]. Additionally, hemolysis releases the enzyme arginase into the plasma resulting in the degradation of L-arginine, a precursor to NO, and subsequently a decrease in NO bioavailability [11]. Chronically decreased NO bioavailability has been shown to promote disruptions in downstream molecular signaling in the penis as associated with priapism [3, 10]. Thus, more severe hemolysis leads to NO depletion and a consequently greater likelihood for priapic events. Despite these recent advances in our understanding of priapism, the etiologic factors that lead to recurrent events in a subset of patients are not entirely known. Hydroxyurea has been shown to induce increased hemoglobin F production and decrease hemolysis [13]. As such, it may also function in this capacity to improve deranged erection physiology regulatory signaling and potentially restore erectile function or prevent recurrent priapism.

Endothelin-1 (ET-1), a cytokine released by endothelial cells in the setting of cell injury, may play an important role in the corporal fibrosis and tissue remodeling process that takes place following anoxic injury and results in erectile dysfunction. While this peptide is commonly known to facilitate vasoconstriction, recent molecular work has demonstrated its significant role as a mediator of fibrosis in multiple organ and disease models [14, 15]. Increased ET-1 expression as seen in various pathologies such as pulmonary and hepatic fibrosis has been shown to increase promotion of fibrogenesis [14, 15]. Based on these findings and the significantly elevated serum ET-1 levels in patients with SCD [16, 17], we reasoned that the peptide is involved in the progression of corporal fibrosis and resulting loss of functional erectile tissue. Given that hydroxyurea has been shown to down-regulate ET-1 gene expression [18] and decrease ET-1 serum levels in children [19], it is possible that hydroxyurea therapy functioned in our patient to prevent the fibrosis-promoting function of ET-1 in the cavernosal bodies, which may have contributed to the recovery of erectile function.

Although we provide a potential molecular explanation for our clinical findings, we would be remiss to neglect to mention the sporadic and heterogeneous natural history of erectile dysfunction that occurs in these patients following a major episode. It is certainly possible that the recovery of erectile function may have occurred in the natural course of this patient's condition despite our medical intervention. Additionally, there is difficulty in evaluating the effectiveness of hydroxyurea therapy in preventing the patient's priapism relapse as being solely attributable to the patient's self-admitted noncompliance, due to the lack of any definitive studies assessing efficacy. Due to the challenges in determining these issues, future studies are certainly needed. This report suggests that hydroxyurea therapy may be

beneficial in preventing recurrent priapism in patients with hemoglobin SS and in restoring erectile function lost subsequent to a very prolonged episode.

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