CASE REPORT

Ischaemic Priapism and Glucose-6-Phosphate Dehydrogenase Deficiency: A Mechanism of Increased Oxidative Stress?

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ABSTRACT

Ischaemic priapism is a devastating urological condition that has the potential to cause permanent erectile dysfunction. The disorder has been associated with numerous medical conditions and the use of pharmacotherapeutic agents. The aetiology is idiopathic in a number of cases. There are two prior case reports of the association of ischaemic priapism and glucose-6-phosphate dehydrogenase (G6PD) deficiency. We report on a third case of priapism associated with G6PD deficiency and review recently described molecular mechanisms of increased oxidative stress in the pathophysiology of ischaemic priapism. The case report of a 32-year old Afro-Caribbean male with his first episode of major ischaemic priapism is described. Screening for common causes of ischaemic priapism, including sickle cell disease was negative. Glucose-6-phosphate dehydrogenase deficiency was discovered on evaluation for priapism. Penile aspiration was performed and erectile function was good post treatment. Glucose-6-phosphate dehydrogenase deficiency is a cause for ischaemic priapism and should be a part of the screening process in idiopathic causes of the disorder. Increased oxidative stress occurs in G6PD deficiency and may lead to priapism.

Keywords: Erection, glucose-6-phosphate dehydrogenase deficiency, oxidative stress, priapism

El Priapismo Isquémico y Deficiencia de Glucosa-6-fosfato Deshidrogenasa: Un Mecanismo de Aumento del Estrés Oxidativo.

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RESUMEN

El priapismo isquémico es una afección urológica devastadora que tiene el potencial de causar disfunción eréctil permanente. El trastorno ha sido asociado con numerosas condiciones médicas y el uso de agentes farmacoterapéuticos. La etiología es idiopática en un número de casos. Hay dos reportes de caso anteriores de la asociación del priapismo isquémico y la deficiencia de glucosa-6-fosfato deshidrogenasa (G6PD). Reportamos aquí un tercer caso de priapismo asociado a la deficiencia de G6PD, y hacemos una revisión de los mecanismos moleculares recientemente descritos en relación con el aumento del estrés oxidativo en la patofisiología del priapismo isquémico. Se describe el reporte de caso de un afrocaribeño de 32 años con su primer episodio de priapismo isquémico. El tamizaje de las causas comunes del priapismo isquémico, incluyendo la enfermedad de células falciformes arrojó resultados negativos. La deficiencia de glucosa-6-fosfato deshidrogenasa fue detectada al evaluar el priapismo. Se llevó a cabo la aspiración del pene, y la función eréctil fue buena posterior al tratamiento. La deficiencia de la glucosa-6-fosfato deshidrogenasa es una causa del priapismo isquémico, y debe ser parte del proceso de tamizaje en relación con las causas idiopáticas

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del trastorno. El aumento del estrés oxidativo tiene lugar cuando hay deficiencia de G6PD, y puede conducir al priapismo.

Palabras claves: Erección, deficiencia de glucosa-6-fosfato deshidrogenasa, estrés oxidativo, priapismo

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INTRODUCTION

Priapism, a disorder of erectile function, is a persistent and prolonged erection that continues beyond or is unrelated to sexual stimulation (1). Ischaemic priapism, a subtype of this disorder, is characterized by reduced to absent cavernosal blood flow. Ischaemic priapism is generally a painful disorder with rigid, tender corpora cavernosa on clinical examination. Cavernosal blood gas analyses in ischaemic priapism show hypoxia, hypercarbia and acidosis. Prolonged episodes of ischaemic priapism result in corporal fibrosis which clinically manifests with varying degrees of erectile dysfunction. Ischaemic priapism is a true urological emergency and the goal of treatment is to achieve detumescence and preserve erectile function.

Ischaemic priapism has been associated with a variety of medical disorders, erectogenic and non-erectogenic pharmaceutical agents. Sickle cell disease is highly prevalent in Jamaica, occurring in one in 150 births. Priapism is seen in as many as 42% of males with sickle cell disease (2). However, the aetiology of priapism is unknown in as many as 50% of cases. Recently, glucose-6-phosphate dehydrogenase (G6PD) deficiency has been reported to be associated with ischaemic priapism in two case reports (3, 4). We report an unusual presentation of ischaemic priapism associated with G6PD deficiency.

CASE REPORT

A 32-year old Afro-Jamaican male presented to the urology outpatient department with a history of sustained penile erection for 32 hours. The sustained erection was unrelated to sexual intercourse. He admitted to taking an energy drink a day prior to noticing the sustained erection. He denied any use of alcohol or illicit drugs. He had no chronic medical illnesses, malignancies or recent trauma. There was no use of a phosphodiesterase inhibitor, intracavernosal agent or any other pharmacological agent. This was his first episode of priapism. He reported very minimal pain, which was noted only on movement of his phallus laterally. Physical examination revealed very mildly tender and rigid paired corpora cavernosa. His blood pressure was persistently elevated at 155/100 mmHg.

His haemoglobin was 13.6 (normal range 11.5–16.5) g/dL. Haemoglobin electrophoresis showed AA_2 pattern. Blood film showed elliptocytes and occasional polychromatic cells. Renal function tests and electrolytes were normal. Qualitative analysis of his G6PD levels revealed a deficiency. Cavernosal Doppler ultrasound showed absent flow.

Winter's shunt (corpora-glanular) revealed thick, viscous blood, typically seen in ischaemic priapism. Aspiration resulted in the penis acquiring a semi-turgid non-tender state. The patient remained pain free and was subsequently discharged from hospital. Six weeks post admission, the patient reported normal erections and denied any further episodes of priapism.

DISCUSSION

This case report represents the third in the literature of ischaemic priapism presumed to be associated with G6PD deficiency. Evaluation of the patient failed to show any other associated cause of the priapism episode. Though sickle cell disease is presumed to be the leading cause of priapism in Jamaica, the patient failed to show positive results for the haemoglobinopathy.

Glucose-6-phosphate dehydrogenase deficiency, which results in a haemolytic anaemia, is reported to be the most common enzymopathy in man (5). It is an X-linked deficiency with over 300 allelic variants (5). Approximately 2.9% of the world population is genetically G6PD deficient (5). The disorder is prevalent in persons of African and Mediterranean ethnicity. The two previously reported case reports were of African American males and we now report on an Afro-Caribbean male patient. The incidence of G6PD deficiency in Jamaica is unknown; however, it is the commonest cause of neonatal jaundice presenting for hospital admissions in an urban hospital in Jamaica (6).

Glucose-6-phosphate dehydrogenase is considered the "house-keeping enzyme" of the red cell – vital for survival of the cell. The enzyme catalyses the reduction of nicotinamide adenine dinucleotide phosphate (NADP) to NADPH, which is the first step in the pentose phosphate pathway. This enzymatic reaction is the sole source of NADPH in red cells. Glutathione in its reduced form (GSH) protects vulnerable -SH groups of enzymes and the β chain of the haemoglobin molecule from the effects of oxidative stress. The reduced form of NADP – NADPH – regenerates reduced glutathione by the enzyme glutathione peroxidase. Since NADPH protects the red cell from oxidative stress, maintenance of adequate levels of G6PD is necessary for red cell integrity and survival. Under normal physiologic conditions, adequate levels of NADPH exist in the red cell. Glucose-6-phosphate dehydrogenase is regulated by the ratio

of NADPH/NAD. Exposure of the red cell to oxidative stress which reduces NADPH levels and reduces the NADPH/NAD ratio, results in activation of G6PD to produce more NADPH. Oxidative stress may be induced by commonly prescribed drugs such as acetyl salicylic acid, sulphonamides and nitrofurantoin, or substances such as fava beans. In G6PD deficiency where NADPH levels are reduced and not adequately increased in exposure of the red cell to oxidative stress, the consequence is an acute intravascular haemolysis. Further investigations have also revealed the central role of NADPH in many cellular processes including nitric oxide (NO) synthase and NADP oxidase activity (7). Preliminary data show an association between G6PD deficiency and diabetes mellitus, hypertension and cardiovascular disease (7).

Experimental evidence has proven that ischaemic priapism is due to dysregulation of the vasodilatory and vasoconstrictive molecular pathways in the corpora cavernosa. Additionally, ischaemic priapism in sickle cell disease is due to defective NO/cyclic guanosine monophosphate (GMP)/phosphodiesterase signalling, as a consequence of reduced tonic endothelial NO release (8). Increased oxidative stress is associated with the pathophysiology of sickle cell disease associated ischaemic priapism. Markers of increased oxidative stress have been demonstrated in two animal models of priapism [sickle cell disease and opiorphin-induced priapism] (9). Increased lipid peroxidation, glutathione S-transferase activity and oxidatively damaged corpora were seen in both priapism models. Musicki *et al* demonstrated that NADPH oxidase was the source of these reactive oxygen species (ROS). Sickle cell disease activates NADPH oxidase and inhibition of the up-regulation of this enzyme reduces oxidative stress (10). Lagoda *et al* demonstrated increased $gp91^{phox}$, a protein subunit of NADPH oxidase, in the penis of sickle cell patients with priapism but not in non-sickle cell patients (11). These findings support the theory that NADPH oxidase, which generates ROS and oxidative stress, may be a mediator of priapism in sickle cell disease. Oxidative stress may contribute to reduced NO signalling by reducing endothelial NO production, circulation and delivery or function (12). The corporal metabolic milieu in G6PD deficiency may similarly predispose to ischaemic priapism when there is exposure to oxidative stress. In G6PD deficiency, due to the weakened antioxidant defences, oxidative stress results in haemolysis, endothelial injury and NO depletion. A cofactor for NO synthesis, NADPH is reduced and further contributes to reduced and aberrant NO signalling. In light of these three case reports, further clinical studies would be required to elucidate these mechanisms.

The index patient had never reported a prior episode of stuttering or ischaemic priapism. The two previously reported cases had prior episodes of stuttering priapism. Uniquely, G6PD deficiency demonstrates unpredictable haemolytic episodes when individuals are exposed to agents causing oxidative stress (5). This variable haemolytic response in an individual or between individuals with the deficiency may be related to genetic factors or differences in G6PD variants. This could possibly explain the lack of prior stuttering episodes in our patient.

We are aware that a limitation of this case report is the absence of an arterial blood gas analysis of the corporal aspirate. However, the Doppler ultrasound findings and gross characteristics of the corporal aspirate were highly diagnostic of ischaemic priapism. We are unable to explain the atypical presentation with absent-mild pain in the patient which is unusual for ischaemic priapism. Additionally, this represents one of only three case reports on the association of G6PD deficiency and priapism. However, in light of the high prevalence of this enzymopathy, particularly in persons of African descent, we believe that G6PD deficiency must be evaluated in all persons with ischaemic priapism with negative sickle cell screening. Further preclinical and clinical studies are required in investigating the association of the two disorders.

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