Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency, a Rare Cause of Ischemic (Low Flow) Type of Penile Priapism: Case Report and Literature Review

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Abstract

Ischemic priapism (low flow) is a disastrous condition to present in urology care, holding the capability to cause erectile dysfunction. This condition is linked to several medical disorders and the use of different pharmacological drugs. In most cases, the etiology is idiopathic. In the literature currently, two case reports of ischemic priapism associated with glucose 6-phosphate dehydrogenase (G6PD) deficiency have been reported. To our best knowledge, a handful of case reports linking G6PD deficiency with priapism have been reported. The key point was the molecular changes that cause elevated oxidative stress activity in the ischemic type of priapism. Here we report a rare case of a 34-year-old male who is a known case of the recurrent ischemic type of priapism. All investigations, including sickle cell disease tests for this type of low-flow priapism, were negative. G6PD deficiency was discovered on evaluation for priapism. We did manage to get penile aspiration performed. G6PD deficiency is a cause of ischemic priapism and should be part of the screening process for idiopathic causes of the disorder. It's been observed that the elevated levels of oxidative stress in G6PD deficiency can cause ischemic priapism. Herein, we are describing a rare case of ischemic priapism due to G6PD deficiency.

Keywords; Priapism, G6PD deficiency, Ischemic, Low Flow

Introduction

Sickle cell disease (SCD) is common in Oman, but Priapism is a comparatively unusual clinical signs and symptoms secondary to SCD and occasional due to G6PD insufficiency. SCD is predominant worldwide with a 5.8 percent prevalence of sickle cell particularity among the Omani population, yet priapism was a fairly rare complication. Penile construction and detumescence are complex physiological processes that need neurological, hormonal, and cardiovascular system consequences.[1]

Ischemic Priapism is generally found with Sickle Cell Disease (SCD) in pretentious males, (42%) but uncommon in the sickle cell of less than eighteen (3.6%).[2] It has been observed that those patients with SCD who present with the painful ischemic type of priapism incline towards acute and severe, which may increase in hemolysis, cardiovascular disease, and repeated attacks of chest pain. The hemolysis process activates the arginine and free type of hemoglobin, which leads to decreases the nitric oxide (NO) levels. It is seen that nitric oxide and cyclic GMP are characteristically reduced in SCD, which can anticipate toward inhibition of penile erections and decreases the chance of priapism. It is thought that prolonged erections are a result of Corpus cavernosum smooth muscle activity potentially becoming more sensitive to NO and the GMP at levels that do not result in the initiation of the phosphodiesterase, [3] and this effect is

aggravated by oxidative stress. The commonest type of priapism seen is ischemic in nature and is triggered by the relaxation of arteries and smooth muscles of corpora cavernosa. If the detumescence becomes deferred, due to an incapability to oppose the arterial relaxations and smooth muscles immobility initiates the painful erection, which may lead to ischemic priapism. And this will cause an arterial inflow becomes slow towards the corporal tissue, resulting in a prolonged and rigid erection. This stuck blood results in a raised intracorporal pressure, leading to the painful crisis associated with hypoxia, cavernosal acidosis, and ischemic penile pain. On the other hand, patients usually do not develop tissue ischemia in high-flow priapism (non-ischemic), because of tangential arterial flow into corporal tissue without connected venous trapping. And thus, this presentation is usually painless.[4]

It is rarely observed the rigidity of the glans penis and corpus spongiosum, as these parts comprise different blood drainage (venous). Nitric oxide has an important role in normal erectile function. Phosphodiesterase inhibitors type 5, inhibit cyclic guanosine monophosphate (cyclic GMP) breakdown, leading to an increase and prolongation in intracavernosal smooth muscle relaxation. This extended relaxation usually causes an increase in blood flow and a rigid penile erection.[5] There are certain causes of pathophysiological changes like; Increases in the number of neurotransmitters shut down of venous drainage in the corpus cavernosum, (The powered blockage from SCD, lipids treatment, leukemia), detumescence disorders and an enhanced corpus cavernosal smooth muscle relaxations because of increased doses or more sensitive activity to the drugs are some of the underlying causes of Priapism.

Priapism is a painful erection for the duration of four hours, leading to pathophysiological abnormalities with penile corporal tissue destruction, normally seen after 6 hours.[6] When there will be more abnormalities or modifications in the smooth muscle after twelve hours of priapism, that will cause trabecular interstitial swelling.[6] There will be destruction on the cellular level after 24 hours of ischemic priapism, starting from skeletonization of the basement membrane, raised platelets aggregation, and endothelial damage of sinusoids. When there will be a formation of a thrombus in the spaces of sinusoids and causes injury to the corporeal smooth muscle, which causes the development of thickened fibrotic tissue and long-lasting erectile dysfunction after one and half day's duration time. Timely management to get early detumescence usually does not causes long-term erectile dysfunction and nearly 95% of the affected patients will be not able to perform satisfactory sexual activity.[7] A stuttering or recurrent priapism, commonly an ischemic type, isn't seen commonly. It has associated with SCD and, is also found in cannabis usage.[8,9] Repeated attacks of painful erections have been observed especially at late night, normally starting from some penile hardness and slowly progressing to a prolonged time. The particular physiological changes in the ischemic type of priapism are not fully understood, but it is hypothesized that an intra-cavernosal-controlling mechanism associated with phosphodiesterase 5 type. [10,11]

Sickle cell disease is highly prevalent in the Caribbean Sea area in Jamaica, with the type homozygous SCD affecting one, out of three hundred live newborns. Ischemic type of priapism was found approximately 45% associated with hemoglobinopathy. Newly, G6PD deficiency has been published in 2 case reports, found with an ischemic type of priapism.[12,13] Herein, we are reporting a rare case of Ischemic type of priapism due to the rare cause, i.e., G6PD deficiency. To the best of our knowledge, this case report will be first published in our country.

Case Report

A 34-year-old male with no past medical background came to the accident and emergency department in the early morning with a history of persistent painful erections for the last 3 hours. He had some episodes of painful erections in the last 3 months, which were managed conservatively with penile aspiration and intra-cavernosal phenylephrine injections. After the treatment of the first episode, he remained asymptomatic. He denies any sexual excitement activity, penile trauma, or drug taking. There was no history of blood disorders (Sickle cell disease, thalassemia, or leukemia). No family history of hematological conditions exists. There was no past surgical history. At the time of presentation on examination, the penis was hard and rigid, with severe pain on palpation of the tense corpora. The Glans penis and corpora spongiosum were soft on palpation. Both tests were normal, and there were no signs of infection. Approximately 100 mL of corporeal blood was aspirated with a 22-G butterfly cannula, and it revealed dark red blood. The corporeal blood gases show low oxygen and severe acidosis (ischemic flow type of priapism), and there was a minimal response with aspiration, so later on he was treated with an alpha agonist, phenylephrine (1 ml i-e 10 mg diluted in 19 ml of saline), for a total of 2 MLS (400 mcg were given on both lateral aspects of the cavernosa). During the injection, he was continuously monitoring his blood pressure clinically. After 30 minutes of intra-cavernosa injection, detumescence was achieved, and the patient felt comfortable and without pain. As we already explained the

patient that may he require additional procedure like distal shunting in case of failed medical therapy with phenylephrine, but no procedure required. He was discharged on antiandrogen medications: cyproterone acetate 50 mg once daily for 3 months. On discharge patient was made aware that there is no specific medication to prevent recurrent priapism secondary to the G6PD deficiency. We suggested some conservative measure like, regular physical exercise, use stairs and apply ice packs as an initial measure.

During his admission course we conducted all relevant investigations to determine the possible cause of this ischemic type of priapism. Laboratory test reports show: 1. G6PD screening test (value: deficient (30% activity)). 2. The thrombophilia workup reported all values within normal ranges; this includes a) the antithrombin function of 11A and inhibition for 20 seconds (1.253). b) Antithrombin function Xa inhibition: 20 seconds (1.37). c) Protein C Functional Chromatin and Protein C Functional Clotting (1.048 and 1.271, respectively). d) Protein S Functional and Antigenic (1.271 and 1.013, respectively). e) Proc Global/FV (1.12). f) Factor VIII chromogenic assays (0.982). 3) Molecular Hematology Tests: FV Leiden and PT II G20210A Mutation Analysis shows Methodology-Molecular H600 (GeneXpert FII and FV Assays). The other factors, like factor 5 Leiden and prothrombin II, are reported as being within a normal range. 4) S-protein results were within normal ranges for protein S activity. 5) Haptoglobin (HPT) value of 0.79 g/L (0.30–2.00). 6) LDH (Lactate Dehydrogenase) 290 U/L (135–250). 7) Autoimmune-antiphospholipid syndrome tests were included (Anti-B2 Glycoprotein 1, IgG). The other tests, like IgM, anti-beta 2 glycoprotein, and anti-cardiolipin antibodies (IgG and IGM), were within a normal range. 8) Extractable Nuclear Antigens (all were negative, except the anti-DFS70 value was weakly positive). 9) Coagulation: Lupus anticoagulant work-up: Lupus anticoagulants not detected. 10). Liver function tests: results were normal. 11) CRP (C-reactive protein 2) (0-5) 12) Bone profile (calcium, phosphate, albumin, alkaline phosphate) normal range 13) The coagulation profile was normal. 14) CBCs (complete blood counts), differentials, and blood films show all variables within a normal reference range. No further investigations were required as per hematology team.

On his regular follow-up, he remained asymptomatic and did not report a recurrence of priapism. On his last outpatient department visit six months ago, mentioned that he is taking PDE5I (Tadalafil) 5 mg as needed for his weak erection. On examination, we could not find any signs of priapism or the chordee. Advised the same conservative measures and his next follow-up next year in January 2024. We also suggested he keep following up with the Hematology team for any concerns. We were informed to report Emergency department if develop again priapism.

Discussion

G6PD is a genetic disorder that results in a hemolytic type of anemia because of the rapidly breaking down of red blood cells.[14] This abnormality is more prevalent in populations originating from the Mediterranean or Africa. The two previously published articles were case reports on male patients of Afro-Caribbean ethnicity. The prevalence of G6PD deficiency in Jamaica is not well known; nevertheless, it is the common etiology of neonatal jaundice and admissions in urban hospitals in Jamaica.[15]

Stuttering ischemic priapism is a rare nature of priapism considered by repeated attacks, which is most frequently understood in the circumstantial of sickle-cell trait or disease. Recently, Burnett et al12 reported the first known case of a young male with G6PD and with a history of recurrent priapism.[12] The main enzyme of the red blood cell, G6PD," is crucial to keeping the cell in proper formation and preventing breakdown. Initially, in the pathway of pentose phosphate, the Nicotinamide-Adenine Dinucleotide Phosphate (NADP) is converted to NADPH. NADPH is the NADP with hydrogen atoms present in the red blood cells (RBCs), and it is formed by this enzyme, i.e., G6PD.

The enzyme glutathione peroxidase regenerates condensed glutathione from the reduced form of NADP, NADPH. Hence, the later enzyme protects the RBCs from the process of oxidative stress (OS), and maintaining sufficient amounts of G6PD is crucial for red cell constancy and integrity. In typical physiologic conditions, RBCs contain sufficient amounts of NADPH. The ratio of NADPH to NAD determines the structure of G6PD deficiency. When the RBCs are unprotected from the OS process, that will cause decreases in the levels of NADPH, which ultimately lower the proportion of NADPH/NAD as G6PD is stimulated to form further NADPH enzyme. Routinely using drugs like acetylsalicylic acid, certain antibiotics, or fava beans in your diet, for example, can cause oxidative stress. Acute intravascular hemolysis is significant more when there is a deficiency of G6PD, where NADPH levels decrease and the contact of the RBCs with the OS process is lessened. Further research has revealed the importance of NADPH in

a variety of cellular functions, including the synthesis of Nitric Oxide (NO) and the movement of the NADP oxidase enzyme.[16] Ischemic priapism is caused by molecular-level abnormalities in the vasodilatation and vasoconstriction routes in the corpus cavernosum, as per experience-based evidence. Furthermore, low-flow priapism in a SCD due to the abnormality in nitric oxide, cyclic guanosine monophosphate, and phosphodiesterase signals results in decreased levels of Nitric Oxide in the endothelium.[17] When there is more OS, that will cause an ischemic type of priapism in SCD. Indicators of raised OS have been reported in animal models with different causes of priapism (e.g., SCD and opioid-induced).[18] In both priapism models, there were raised levels of lipid peroxidation activity, oxidative injury, corpus cavernosal activity, and glutathione S transferase activity. NADPH oxidase, as discovered by Musicki et al.[19], has observed the reasons for the reactive oxygen species (ROS). SCD initiated the activity in the pathway of NADPH oxidase, and inhibiting its activation reduces oxidative stress.[19] According to Lagoda et al [20], increased gp91phox, which is a subdivision protein molecule of NADPH oxidase, was found in the corpora of SCD patients.[20] The published data also reported that the raised levels of ROS due to the NADPH oxidase activity may lead to oxidative stress, which will cause the rigidity of the cavernosa in the SCD patients. The oxidative stress activity that leads to the decrease in the NO signals is contributed by less production of endothelial NO and circulatory problems. [21] When subjected to the OS, the corporeal metabolic environment in G6PD deficiency patients may contribute to the painful and ischemic types of priapism. Oxidative stress causes hemolysis, endothelial injury, and NO depletion in G6PD deficiency due to weakened antioxidant defenses. NADPH, which is a known associated factor for NO synthesis, becomes low, and that leads to decreased and abnormal NO signaling. More publication is needed to elucidate these complex activities based on the mentioned findings of the three previous case reports. G6PD deficiency, on the other hand, causes unpredictable hemolytic events once those are revealed to the mediators that lead the process of OS. So, overall, it was observed and identified that the hemolytic activity was likely due to hereditary aspects or alterations in G6PD modifications. Any patient reported to the department of emergency with painful priapism and negative sickle cell, he must investigate to identify G6PD deficiency. And further research will help to look for any association between these conditions.

Morrison BF et al [22] reported a case report and mentioned in their case report the limitation of the corporeal blood gas analysis, which was not done. In our case, arterial blood gases were done but they did the Doppler penile ultrasound that shows classical features of the low flow type of priapism. The authors also reported and mentioned that it's very difficult to explain the unusual clinical presentation with mild penile pain in a low-flow type of priapism. Furthermore, this signifies one of only three case reports on the connotation of G6PD deficiency and priapism. Nevertheless, in light of the high occurrence of these changes, predominantly in individuals of African origin, we believe that G6PD deficiency must be assessed in all people with ischemic priapism with negative sickle cell screening. Additional research publications are necessary to understand the exactly association of G6PD deficiency and priapism.[22]

Conclusion

To sum up, we are reporting a unusual presenting of low flow type of penile Priapism due to the rare cause i-e G6PD-deficiency One should consider to check this abnormality during work up for priapism, if no other causes identified.

Disclosure

We could not find any conflict of interest for this case report. Informed consent was taken from a patient.

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