Poorly Controlled Homocystinuria: A Rare Cause of Ischemic Priapism?

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ABSTRACT

We report on the 1st case of ischemic priapism secondary to poorly controlled homocystinuria. Homocystinuria is a rare, autosomal recessive, inherited disorder of metabolism that is caused by a deficiency of cystathionine synthase, leading to marked hyperhomocysteinemia. Arterial and/or venous thromboemboli are a major cause of mortality and morbidity in patients with homocystinuria. Untreated patients have a 50% chance of having a vascular event by 30 years of age. Increased homocysteine levels have been reported to upregulate prothrombotic factors and downregulate antithrombotic factors; in particular, increased homocystinuria has been found to downregulate nitric oxide (NO). Mice that are deficient in NO synthase in the cavernosal smooth muscles have a higher incidence of priapism. Decrease in NO synthase causes downregulation of cyclic guanosine monophosphate, phosphodiesterase type 5A, and Rho A/Rho-kinase. Because persistently increased homocysteine also downregulates NO, a similar mechanism could be proposed for priapism secondary to homocystinuria. In patients presenting with priapism, specific features of homocystinuria should be sought; in selected patients, screening with plasma total homocysteine might be appropriate. Ischemic priapism secondary to homocystinuria appears to respond well to the standard treatment options of aspiration, intracavernosal injection with phenylephrine, and, if required, a shunting procedure. **Johnson M, Murphy E, Raheem A, Ralph D. Poorly Controlled Homocystinuria: A Rare Cause of Ischemic Priapism? Sex Med 2018;6:171–173.**

Key Words: Priapism; Homocystinuria; Ischemic Priapism

INTRODUCTION

Ischemic priapism is a compartment syndrome of the corpus cavernosa. It is characterized by a persistent painful penile erection lasting longer than 4 hours that is not associated with sexual arousal. Inadequate or delayed treatment will result in permanent erectile dysfunction and penile shortening. Ischemic priapism is most often associated with sickle cell disease and can be caused by certain drugs, spinal injury, and malignancy. In addition, there are a significant number of men with idiopathic ischemic priapism in whom no cause is identified.[1] Identification of novel causes of priapism will aid our understanding of this potentially devastating condition.

To our knowledge, this is the 1st reported case of ischemic priapism that is likely secondary to poorly controlled homocystinuria. Homocystinuria is a rare inherited condition that results in an increased plasma homocysteine level, which is a significant risk factor for arterial and venous thromboemboli.[2] Ischemic priapism results from prolonged veno-occlusion and thrombosis of the corpus cavernosa.[1]

CASE REPORT

A 34-year-old man with poorly controlled homocystinuria presented to his local emergency department with a 24-hour history of ischemic priapism. This was the patient's 1st episode of priapism and his late presentation was attributed to his lack of knowledge of the condition. Successful detumescence was achieved with immediate corporal aspiration, washout, and intracavernosal injection of phenylephrine 400 μg. Cavernosal blood gas analysis was consistent with ischemic priapism (pH = 6.9, P_{CO_2} = 15.28 KPa, P_{O_2} < 1.3 KPa, lactate = 13.4 mmol/L [reference range = 0.5–2.2 mmol/L]). However, 3 hours after the initial intervention, his priapism recurred. Repeat aspiration, washout, and intracavernosal injection of phenylephrine were unsuccessful and he was taken to the theater and successfully underwent an emergency bilateral trans-glandular cavernosum-spongiosum shunt.

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After his discharge, the patient reported 1 to 2 episodes of stuttering priapism each week (self-limiting episodes of prolonged penile erection), which he managed conservatively with exercise. 2 months after his original presentation with priapism, the patient presented again with a painful 4-hour penile erection. This time successful detumescence was achieved with aspiration and intracavernosal injection with phenylephrine. Cavernosal blood gas analysis again showed an acidotic, hypoxic, and hypercapnic blood gas picture consistent with ischemic priapism. The patient was discharged with 1 month of cyproterone acetate 100 mg once daily (OD; antiandrogen) to prevent further episodes of priapism. After stopping the cyproterone acetate and despite these 2 episodes of priapism, the patient reported normal erectile function.

The patient has a background history of homocystinuria and asthma. His homocystinuria is complicated by bilateral aphakia, decreased bone mineral density, and lower limb varicosities. Prescribed medications included betaine 3 g 3 times daily, folic acid 5 mg OD, pyridoxine 100 mg OD, hydroxocobalamin 1-mg injection 3 times monthly, aspirin 75 mg OD, calcium and vitamin D supplements, and inhalers. However, he admitted long-standing poor adherence to all prescribed medications.

Biochemical testing at the time of his 1st episode of priapism was consistent with poorly controlled homocystinuria and included increased levels of plasma total homocysteine (382 μmol/L, normal range = 5−12 μmol/L), methionine (255 μmol/L, normal range = 13−40 μmol/L), and free homocystine (106 μmol/L, normally not detectable). Hemoglobinopathy screen, renal, liver, and bone profiles were normal. Secondary abnormalities included a low to normal vitamin B12 level (210 pg/mL, normal range = 197−771 pg/mL), a low serum folate level (<2 ng/mL, normal range = 2.9−26.8 ng/mL), and an insufficient total cysteine level (55 μmol/L, normal range = 200−350 μmol/L). Hemoglobin (144 g/L, normal range = 130−170 g/L) and mean corpuscular volume (94.1 fl, normal range = 80−99 fl) were normal.

DISCUSSION

Homocystinuria is a rare, autosomal recessive, inherited disorder of metabolism that is caused by deficiency of cystathionine β-synthase, leading to marked hyperhomocysteinemia. The clinical presentation varies, with some patients presenting with typical features in early childhood and others (particularly those with a vitamin B6−responsive form of the condition) remaining asymptomatic until adulthood. Typically, it is a multisystem disorder that can affect the (i) eyes (dislocation of the optic lens), (ii) skeletal system (marfanoid habitus, with excessive height and long limbs), (iii) vascular system (thromboemboli), and (iv) central nervous system (learning difficulties).[2]

Arterial and/or venous thromboemboli are a major cause of mortality and morbidity in patients with homocystinuria. Untreated patients have a 50% chance of having a vascular event by 30 years of age.[3] Patients who achieve consistent lowering of plasma homocysteine have a significant decrease in the number of vascular events experienced.[4] Current recommendations for treatment are to maintain plasma total homocysteine levels lower than 100 μmol/L lifelong.[2]

Venous thrombosis is the most common vascular event in homocystinuria. The exact pathophysiology of accelerated vascular disease experienced by these patients is unclear. Increased homocysteine levels have been reported to upregulate prothrombotic factors and downregulate antithrombotic factors. In vitro animal model data have shown that increased homocysteine levels (i) increase platelet activation and aggregation; (ii) block tissue plasminogen activator on the vascular endothelium, resulting in impaired fibrinolysis; (iii) bind to factor V, preventing deactivation of activated protein C; and (iv) downregulate nitric oxide (NO), thus lessening its bioavailability.[5]

Priapism results from prolonged veno-occlusion and thrombosis of the corpus cavernosa. It is proposed that blood in the erect penis (deoxygenated with increased carbon dioxide) causes ischemia, which in turn causes venous congestion in the sinusoidal space and increased viscosity.[6] Mice that were deficient in NO synthase in cavernosal smooth muscles had a higher incidence of priapism. Decrease in NO synthase causes downregulation of cyclic guanosine monophosphate, phosphodiesterase type 5A, and Rho A/Rho-kinase.[7,8] Because persistently increased homocysteine also downregulates NO, a similar mechanism could be proposed for priapism secondary to homocystinuria.

Emergency and/or uncommon conditions often lack good-quality evidence. Much of the evidence for ischemic priapism has been conducted in vitro or in men with sickle cell disease.[1] This case reports adds to the limited literature on this subject.

In patients presenting with priapism, specific features of homocystinuria should be sought; in selected patients, screening with plasma total homocysteine might be appropriate. Ischemic priapism secondary to homocystinuria appears to respond well to the standard treatment options of aspiration, intracavernosal injection with phenylephrine, and, if required, a shunting procedure.

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REFERENCES

1. Salonia A, Eardley I, Giuliano F, et al. European Association of Urology guidelines on priapism. **Eur Urol 2014; 65:480-489**.
2. Morris AA, Kozich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. **J Inherit Metab Dis 2017;40:49-74**.
3. Yap S, Boers GH, Wilcken B, et al. Vascular outcome in patients with homocystinuria due to cystathionine beta-synthase deficiency treated chronically: a multicenter observational study. **Arterioscler Thromb Vasc Biol 2001;21:2080-2085**.
4. Yap S. Classical homocystinuria: vascular risk and its prevention. **J Inherit Metab Dis 2003;26:259-265**.
5. Gatt A, Makris M. Hyperhomocysteinemia and venous thrombosis. **Semin Hematol 2007;44:70-76**.
6. Hinman F Jr. Priapism; reasons for failure of therapy. **J Urol 1960;83:420-428**.
7. Kheirandish P, Chinegwundoh F, Kulkarni S. Treating stuttering priapism. **BJU Int 2011;108:1068-1072**.
8. Champion HC, Bivalacqua TJ, Takimoto E, et al. Phosphodiesterase-5A dysregulation in penile erectile tissue is a mechanism of priapism. **Proc Natl Acad Sci U S A 2005;102:1661-1666**.