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Case Report

An Experience of Treating Stuttering Priapism

Ahmed Imran Siddiqi*

Diabetes & Endocrinology specialist trainee, London Hospital.

***Corresponding author:** Diabetes & Endocrinology specialist trainee, Department of Diabetes and Endocrinology, 3rd floor, 250 Euston Road, University College London Hospital, London. UK. NW1 2PG Email: Aims125@hotmail.com, Ahmed.siddiqi@nhs.net.

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Abstract

Priapism is a clinical manifestation of disordered erection physiology and results from a combination of disturbances involving the regulatory mechanisms governing penile tumescence and detumescence. I present here a case of stuttering priapism and its treatment for over 20 years. Antiandrogens were main stay of the treatment and helped to improve his symptoms and preserved his function. Over these 20 years other treatment options are available and antiandrogens are no longer first line treatment agents for such patients. I'll also review the newer options for treatment of this condition.

Keywords: Stuttering priapism; Antiandrogen; Cyproterone acetate.

Introduction

Priapism is a clinical manifestation of disordered erection physiology and results from a combination of disturbances involving the regulatory mechanisms governing penile tumescence and detumescence. First reported in 1845 by Tripe, priapism is defined as a prolonged and persistent penile erection, not associated with sexual interest or stimulation, lasting longer than 4 h [1,2]. Prolonged unwanted erections not only have adverse medical outcomes but can potentially have significant social and psychological implications on lives of such patients. Erectile dysfunction (ED) remains the most serious complication of the condition and urgent treatment is required to prevent it. Most patients will initially consult Urologist for urgent treatment but Endocrinologists' input is required for individuals with recurrent episodes of priapism, often termed as stuttering priapism.

Tumescence and detumesence is a sequence of complex neurochemical events regulating blood flow in and out of penis. Penis consists of three longitudinally oriented structures termed corpora. Two dorsolaterally located corpora are termed as corpora cavernosa and ventrally located corpora are termed corpus spongiosum. Corpora cavernosa are surrounded by thick tunica albugenia. Here lies the rich network of endothelial lined sinusoids and smooth muscles which plays a pivotal role in significant increase in blood influx (A). An increase in influx of blood with reduced efflux results in tumescence and the reverse leads to detumescence. Increase in blood flow is achieved by significant dilatation of these sinusoids mediated by release of a variety of chemicals. In flaccid state sympathetic nervous system predominantly control penile vascular tone but tumescence is achieved by parasympathetic dominance. This shift in autonomic nervous system releases predominantly cholinergic chemicals leading to significant influx on arterial blood. The rapid increase in influx of high pressure arterial blood leads to increase pressure on low pressure venous sinusoids. This increased pressure leads to reduced efflux of blood and mixed venous blood trapped in penis leads to tumescence. The influx will reduce once internal penile pressure is high enough to offset the pressure in penile artery, a branch of internal pudendal artery, a branch of internal iliac artery. Detumesecnce is achieved by change in internal neurochemical environment leading to reduce blood influx and increased efflux. Imbalance in this complex sequence of events leads to prolonged entrapment of mixed venous blood and complication.

Clinical Case:

A 23 years old man presented to Emergency department with painful prolonged erection for approximately previous three hours. He experienced it early morning without sexual stimulation during his sleep. He denied history of trauma, blood disorders, use of recreational drugs or over the counter medications. He had experienced episodes of prolonged erection of up to 2 hours with spontaneous resolution every now and then since his teenage. He experienced many of these episodes during sleep or without sexual stimulation. He could never find a precipitating factor for most of these episodes and did not seek medical advice as they used to resolve spontaneously. He noticed taking cold water shower occasionally helped to resolve his symptoms. He presented to

Emergency department on this occasion because this episode had been the longest and most painful so far. He had not noticed any change in his libido and was married for previous 2 years. He did not suffer from any other medical condition, did not take regular medications, no known drug allergies and no family history of note. He received the standard treatment by urology team with blood drainage from penis and pseudo-ephedrine injections. He was discharged following this treatment and he presented again with similar symptoms a few months later. This time he presented with 5 hours of erection. He experienced three more episodes of priapism during these months but did not present to Emergency department because all these episodes settled within three to four hours. On this presentation he was again treated with blood drainage and sympathomimetic injections. On this occasion he was offered urgent appointment in Endocrinology clinic for work up of his stuttering priapism. He attended Endocrine clinic 4 years later only after his ninth presentation to Emergency department with similar symptoms. He did not attend his previous appointments due to fear of possible major surgical procedure and adverse effects on his erectile function. During these 4 years he attended Emergency departments of different hospitals to receive emergency treatment but did not attend Endocrine clinic in any of those hospitals. By the time he presented to Endocrinology clinic he had completed his family and had two children, youngest 1 month old. On clinical examination his external genitalia was unremarkable with testicular volume 15 to 20 ml bilaterally, urethral meatus at normal site and no deformity of shaft or perennial area. His testosterone was 18.2 (7.8-31 nmoL/L), FSH 3.2, LH 2.1, SHBG 21 nmoL/L , Albumin 42, Hb 14.2 g/dL, haemoglobin electrophoresis excluded sickle cell disorder. His penile ultrasound Doppler confirmed normal blood flow between the episodes. Over these previous four years few other investigations were carried out. His ultrasound Doppler at the time of acute presentation on two occasions suggested features of ischemic priapismb (cavernosal blood flow was absent, with a high-resistance, low-velocity trace. Diastolic flow was low. The non-compressible sinusoids were engorged and demonstrated mixed echogenicity). His testosterone assessed on a few occasions during previous episodes was in range of 14.7 to 22.8 nmoL/L). His abdominal ultrasound and CT scan were unremarkable. These scans were carried out for investigation of his epigastric pain. Upper GI endoscopy confirmed peptic ulcer disease 1 year ago. Since he presented to different hospitals with acute presentation of priapism his emergency treatment was not much different during these presentations. He always received injections of sympathomimetic agents and drainage of penile blood to achieve detumescence. He did not complain of any problems with his erectile function. He used some herbal medications for a few months three years ago without any improvement of his symptoms.

He was commenced on cyproterone acetate for control of his stuttering priapism with a target testosterone at the lower end of normal range. His symptoms of priapism were reasonably well controlled with cyproterone acetate 50 mg four times a week with significant reduction in his Emergency department visits. He was advised to attend Emergency department if erections persist over 2 to 3 hours or if they are painful. He admitted he did not always follow this guidance. It was difficult for him to count the exact number of episodes of priapism he experienced but he attended Emergency department with Priapism only four times during subsequent 21 years. His testosterone remained around lower limit of normal range. His BMD was monitored with DEXA scan every 3 to 4 years and T-score always remained >1.0. Attempts were made to further reduce his cyproterone dose but could not be reduced with recurrence of symptoms. We managed to reduce it to 50 mg three times a week only 6 months ago. He was offered to change treatment but since his symptoms were well controlled he was not keen on the idea of changing treatment. His latest testosterone remains slightly below the normal range (5.6 nmoL/L) with no systemic symptoms. His DEXA scan showed T score at hip 1.3 and at spine 2.0. Despite mild dysfunction in his erectile function he is not keen on the idea of treatment change. We'll attempt further dose reduction with monitoring of his symptoms in due course.

Discussion:

Stuttering priapism is an uncommon but challenging medical condition. Understanding the pathophysiology is important to its treatment. There are two main groups depending on pathophysiology of the condition – low flow/ischemic and high flow/non-ischemic priapism. Stuttering priapism is very much a variant of ischemic priapism but is often classed as a separate group for its recurrent presentations and long term treatment needs. The exact pathophysiology for its recurrent nature has not been completely explored but acute treatment remains the same as for ischemic priapism.

Ischemic/low flow priapism is the most important and clinically most significant of all types of priapism presentations. Patients usually present with severe pain and intense prolonged erections. The persistent erection is marked by rigidity of corpora cavernosa with insufficient or no cavernous arterial inflow [1]. Both ischaemic and stuttering priapism share similar mechanism. It's an imbalance in local neurochemical environment and vaso-regulatory mechanisms, predisposing penis to an ischemic environment. The deregulation of vaso-regulatory mechanisms leads to entrapment of mixed venous blood in the penis, creating venous congestion. Insufficient or no arterial blood influx leads to tissue ischemia leading to pain and rigidity, classically seen with ischemic priapism. Studies have shown that ischemic priapism lasting longer than 24 h results in ED rates as high as 90% [7]. Therefore, ischemic priapism constitutes a true emergency that must be treated in a time-sensitive manner.

Non-ischemic priapism is a result of abnormal cavernous arterial blood flow [1]. The abnormal and deregulated arterial blood influx leads to tumescence but does not lead to entrapment of blood inside penis. Since the arterial blood is continuously flowing in it does not lead to an ischemic environment. These patients usually present late as they do not experience pain and erection is usually not as rigid as in cases of ischemic priapism [4]. They usually present with prolonged tumescence as their main presenting complaint. Such patients do not require emergency treatment as there is no tissue ischemia. Non-ischemic priapism can also result from congenital arterial malformations, iatrogenic insults, as a persistent high-flow state after shunt procedures for ischemic priapism and trauma creating a disruption in the cavernous arterial anatomy, resulting in an arteriolar-sinusoidal fistula [8].

Stuttering priapism, also termed recurrent priapism, is characterized by recurrent episodes of ischemic priapism. These episodes typically last less than four hours, prior to spontaneous remission [3,4]. The spontaneous remission differentiates these episodes from ischemic priapism as the mechanism of both stuttering and ischemnic priapism is the same. Sexual stimulation does not always have to be the precipitating factor. Prolonged erections commonly arise during nocturnal sleep or preceding or following sexual stimulation [5]. In many patients such episodes may increase in frequency and duration with time, compromising the patient's quality of life. Some of these episodes may last for longer with prolonged periods of erections without spontaneous resolution. These prolonged episodes are very likely to cause permanent damage similar to ischemic priapism [2]. Both stuttering and ischemic priapism, result in ischemic damage to the corporal tissue. Repetitive episodes combined with delays in treatment lead to cellular, molecular and morphological changes in the corpora cavernosa and its cumulative effect over time results in permanent ED [6]. Therefore, all episodes of recurrent priapism should be treated promptly, according to guidelines set for ischemic priapism [2]. Ultimate goal of the treating urologist/Endocrinologist should be to prevent recurrent stuttering priapism by using pharmacotherapies which address the underlying pathophysiology of the disease state.

A variety of hormonal agents have been suggested for treatment of stuttering priapism. To date there has been only one randomised controlled trial for treatment of patients with stuttering priapism using synthetic oestrogen, diethylstilbestrol (DES). The results were promising that all the patients showed resolution of their symptoms but symptoms recurred in more than 50% of these patients following discontinuation of the treatment [11]. In the absence of randomised controlled trials case reports and individual approaches have been used to treat such patients using hormonal agents. It terms of symptoms control Antiandrogens, 5α-reductase inhibitors, and gonadotropin-releasing hormone agonists with or without sympathomimetic agents are effective therapeutic options. [5,1,2]. There are reports available on use of these agents in treatment of stuttering priapism. Cyproterone acetate (CPA)also known as 1,2α-methylene-6-chloro-δ6-17α-acetoxyprogesterone is a synthetic, steroidal antiandrogen, progestin, and antigonadotropin [9]. It is primarily used in the treatment of androgen-related conditions by virtue of its ability to suppress androgenic activity in the body, an effect it mediates by preventing endogenous androgens from interacting with the androgen receptor and by suppressing androgen biosynthesis [10]. There concerns regarding safety of long term use of antiandrogen agents. Prolonged use of antiandrogens in young men desirous of fertility is not recommended. Antiandrogens in such patients are expected to cause clinical features of hypogonadism and can potentially cause psycho-social problems in such patients. Such agents should particularly be avoided in young men around puberty [1]. Use of such agents could lead to long term consequences on body composition, bone mineral density and final height.

Since priapism is believed to be a result of imbalance between influxes an efflux of blood mediated by abnormal penile vascular responses, medications believed to affect these blood vessels should be helpful. Phosphodiesterase 5 (PDE 5) inhibitors have shown promising results in small studies in patients with stuttering priapism and sickle cell disease mediated ischemic priapism. These studies used different PDE5 inhibitors and beneficial effects were noticed with all of them. Patient noticed improvement in priapism without affecting their normal erectile function. Studies used Sildenafil in 25 mg which was then increased to 50 mg OD. The timing of the medication is important particularly in patients with SCD. Patients should take the medicine midmorning at a time when no sexual stimulation is expected. Patient should not take it at night as it is likely to exacerbate priapism early morning particularly in patients with SCD (B).

Terbutaline, a beta agonist showed good results in pharmacologically induced priapism. Terbutaline intracavernosal injections achieved good results in a study comparing its use with phenylephrine and placebo. The success rate was significantly better than placebo (C). Ketoconazole, Digoxin, Gabapentin and baclofen have all been used in treatment of stuttering priapism with variable success (D). One has to choose the most appropriate agent depending on patient's clinical features and condition. Randomised controlled trials will allow establishing clinical effectiveness, safety and selection of most useful agent in treatment of this condition. At the moment the data size in these studies is not large enough to conclusively advise on the clinical efficacy and safety of these agents in treatment of stuttering priapism.

This case is an interesting example of carefully monitored treatment keeping testosterone in lower normal range with suf-

ficient symptom control without noticeable adverse effects of hypogonadism. With the availability of newer medications anti-androgens would not qualify to be first line agents in stuttering priapism but in resistant or uncontrolled cases these agents may still have a place in treatment regimen.

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