

Case Report

The increased cellular permeability syndrome manifesting as severe idiopathic type urinary incontinence

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Summary

Purpose: To evaluate the efficacy of treatment with dextroamphetamine sulfate for severe idiopathic urgency urinary incontinence refractory to treatment with the selective beta 3 adrenergic agonist, mirabegron. **Materials and Methods:** Dextroamphetamine sulfate extended release capsule was started at 9.4 mg and increased to 15.7 mg in a woman with two years of severe urgency urinary incontinence. **Results:** The urgency urinary incontinence completely resolved, as did the fibromyalgia, headaches, and chronic fatigue syndrome. The symptoms have remained eradicated for over one year while treatment continues. **Conclusions:** Idiopathic urgency urinary incontinence (neurogenic bladder) has been found to be another manifestation of the increased cellular permeability syndrome. Similar to the other chronic disorder associated with the increased cellular permeability syndrome, idiopathic urgency urinary incontinence responds well to dextroamphetamine sulfate treatment despite failure to respond to standard therapy.

Key words: Idiopathic urgency urinary incontinence; Neurogenic bladder; Dextroamphetamine sulfate; Increased cellular permeability syndrome; Dopamine.

Introduction

Urinary incontinence may occur in 37.5% of women aged 30-50 [1]. Women with this condition will usually seek help from a urologist or urogynecologist.

The two most common types of incontinence are stress and urgency incontinence. Stress incontinence is usually caused by increasing parity, vaginal birth or obesity [2-4]. This can be due to injury to the pelvic floor musculature and connective tissue, or nerve damage from labor and delivery, or even from the enlarged uterus of pregnancy. Both vaginal and caesarean delivery increase the risk of urinary incontinence, but vaginal delivery poses the greatest risk [5].

Stress incontinence can be related to hysterectomy [6]. This is probably related to damaging the pelvic floor muscles. Weakening of the pelvic floor muscles can lead to other conditions besides urinary incontinence prolapse of the bladder (cystocele) or prolapse of the rectum or uterine prolapse [7]. Stress incontinence is characterized by involuntary loss of urine following events that can increase intra-abdominal pressure, e.g., coughing, sneezing, high impact exercise, heavy lifting, or constipation [8].

The main etiology of stress incontinence is a poorly functioning urethral closure mechanism leading to urine leakage when raising intra-abdominal pressure from coughing or

sneezing or exercise as mentioned above. In contrast, urgency incontinence is characterized by a sudden desire to urinate that is difficult to hold, and occurs with little or no warning. Though this type of urinary incontinence may be related to a neurologic disorder, e.g., spinal or pelvic nerve injury, or Parkinson's disease, multiple sclerosis or diabetic neuropathy, most cases are idiopathic [9].

A selective beta-3 adrenergic agonist called mirabegron is one of the most commonly used treatments today for idiopathic urgency type urinary incontinence (sometimes referred to as a neurogenic bladder) [10-14].

A case is presented of a woman with severe idiopathic urgency incontinence who failed to improve despite mirabegron treatment, but demonstrated marked improvement with the sympathomimetic amine dextroamphetamine sulfate, a very effective drug for a variety of conditions that are part of the increased cellular permeability syndrome [15, 16].

Case Report

At age 44 a woman developed symptoms of urinary urgency. Unfortunately, when the urgency manifested, she could not control her urination and make it to the bathroom. She consulted a urologist who performed a cystoscopy, and there was no evidence of interstitial cystitis. A urodynamic study was performed. She

demonstrated positive detrusor overacting at small volume and of significant amplitude. The opinion of the urologist was that she had a neurogenic bladder.

She was started on mirabegron 25 mg daily which did not help. Her symptoms became increasingly worse. Increasing the dosage of mirabegron to 50 mg per day, though it seemed to help her somewhat initially, she still had to wear adult diapers. However, after one year, the symptoms became markedly worse.

She no longer had urgency followed immediately by urinating. She would keep urinating without any warning at all. She worked as a dentist, and had to stand most of the day. Embarrassing in the middle of dental procedures, she would be leaking urine down her legs. The urologist suggested that she have a neuromodulator placed in her back, known as an "Ultrastim", which would be hooked to her bladder this would hopefully alert her that she needed to get to the bathroom immediately to urinate. It would cost her \$10,000 out of pocket with no guarantee to work.

After two years from the initial diagnosis, the woman developed other symptoms including severe chronic fatigue syndrome, and generalized aches and pains, especially on the right hip, thighs, and legs, and migraine headaches. Her dental hygienist, who was aware through friends that had been treated for the increased cellular permeability syndrome successfully with dextroamphetamine sulfate, referred her to the authors' practice [15].

She was started on amphetamine salts 15 mg extended release capsules (approximately 9.4 mg dextroamphetamine sulfate) which was increased to 25 mg extended release capsules (approximately 15.7 mg dextroamphetamine sulfate). This treatment has not only resulted in complete eradication of her urinary incontinence, and eradicated other urinary symptoms, e.g., urgency or frequency, but has also markedly improved her headaches, chronic fatigue, and fibromyalgia.

Discussion

The increased cellular permeability syndrome is the etiologic factor for a wide variety of chronic conditions that are refractory to standard therapies that have in common very good improvement following treatment with dextroamphetamine sulfate [15, 16]. The conditions that improve include pelvic pain of various types, with or without the presence of endometriosis, and migraine headaches, chronic fatigue and fibromyalgia (as seen in the patient described), neuromuscular disorders, bowel motility disorders (e.g., achalasia, gastroparesis, or pseudointestinal obstruction), chronic urticaria, arthritis, and chronic regional pain syndrome.

The theory explaining the syndrome is as follows: related to increased cellular permeability unwanted elements that are normally precluded from entering tissues are able to permeate the tissues leading to either inflammation causing pain or muscle dysfunction related to unwanted chemicals getting into mitochondria leading to their dysfunction. Dextroamphetamine sulfate is believed to improve the various manifestations of this syndrome by releasing dopamine from sympathetic nerve fibers. One of the functions of dopamine is to decrease cellular permeability [15, 16].

Dextroamphetamine sulfate has been found to be highly effective for treating interstitial cystitis [17, 18]. Sometimes the interstitial cystitis can be an isolated event, and some-

times may be associated with other pathological entities associated with the increased cellular permeability syndrome [19].

There is little question, based on the phenomenal response of the patient described, that dextroamphetamine sulfate can be highly effective for idiopathic urgency urinary incontinence, at least when it is associated with other manifestations of the increased cellular permeability syndrome. Hopefully, this case will motivate other clinicians to corroborate its efficacy, not only in other cases of idiopathic urgency incontinence, even those not necessarily associated with other entities described to increase cellular permeability. Perhaps dextroamphetamine therapy may even prove useful for urgency urinary incontinence related to neurological disorders, e.g., Parkinson's disease, and multiple sclerosis, or even cases of stress urinary incontinence, especially cases refractory to standard therapy.

The urethral closure mechanism requires both functioning musculature and nerve innervations to accomplish the normal urethral closure mechanism. The tenets of the hypothetical way that the increased cellular permeability causes disruption of normal organ function, and in this case the urethral closure mechanism, is that toxic elements permeate these tissues, which is improved when more dopamine is released by sympathomimetic amine therapy [16]. Sometimes pain or organ dysfunction occurs, after an injury, theoretically leaving the affected individual with a permeability disorder, which may also respond to dextroamphetamine sulfate, even when other treatments are ineffective [16]. Thus, it seems reasonable to try dextroamphetamine sulfate, even for cases of stress urinary incontinence that may have been the result of injury from vaginal delivery or hysterectomy.

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