The sympathetic neural hyperalgesia/edema syndrome, a common cause of female pelvic pain, manifesting as a pseudopheochromocytoma with marked clinical improvement with sympathomimetic amines

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Summary

Purpose: To show that a common but not well-known disorder of the sympathetic nervous system can present with symptoms suggesting a pheochromocytoma. *Materials and Methods:* The standard treatment of this disorder (which is characterized by an abnormal water load test), i.e., sympathomimetic amine therapy, was given to a woman with paroxysmal tachycardia and hypertension. *Results:* Over a period of six months, the treatment eradicated the paroxysmal symptoms to which all other therapies had failed. *Conclusions:* This condition recently named as sympathetic neural hyperalgesia edema syndrome can present with symptoms of a pheochromocytoma and will respond to therapy with low dosages of dextroamphetamine sulfate.

Key words: Pheochromocytoma; Sympathomimetic amines; Hypertension; Paroxysmal tachycardia.

Introduction

A condition predominantly involving women was described over 50 years ago in which women would experience unexplained edema and weight gain [1]. Typically the edema was worse in the feet and legs at the end of the day and involved the face and hands in the morning. Other symptoms included abdominal distention and nocturia [1]. The edema had remissions and exacerbations and the cause was unknown. Thus the condition was named idiopathic orthostatic cyclic edema [1].

A defect in the sympathetic nervous system was found to be etiologic in this condition [2]. The explanation for the edema, especially in the feet and legs which worsened with standing and improved by lying down, was that to compensate for the increase in hydrostatic pressure that occurred with standing, hence fluid would tend to leak from intracapillary to extracapillary sites. Thus to maintain intravascular volume, a signal is sent via the sympathetic nervous system to a pre-capillary sphincter causing the sphincter to contract and preventing leakage of fluid from intravascular to extravascular spaces [2].

Though treatment with standard diuretics, spironolactone, converting enzyme inhibitors, and bromocriptine have been proposed as therapies, their efficacy pales in comparison to the treatment with the sympathomimetic amine dextroamphetamine sulfate as far as control of the edema and weight gain are concerned [3].

Subsequently it has been determined that this disorder of the sympathetic nervous system may be the etiologic factor for various health problems, especially in women [4]. This disorder frequently presents with chronic pelvic pain, dysmenorrhea, dyspareunia, and/or mittelschmertz which is usually attributed to endometriosis. Whether endometriosis is present or not by laparoscopy, the pain responds better to treatment with sympathomimetic amine therapy than any other therapeutic measures including surgery [5-7]. Similarly, pain from interstitial cystitis, vulvodynia, and vulvovaginits also responds quickly and effectively following treatment with dextroamphetamine sulfate [8].

Several gastrointestinal syndromes not only associated with pain but also with diarrhea and malabsorption, e.g., esophageal pain, gastroparesis, and pseudointestinal obstruction, have been demonstrated to respond very well to sympathomimetic amine therapy, despite having failed to respond to previous standard therapies [9-11]. In fact recently a woman with a 12-year history of severe Crohn's disease involving her entire colon, with complaints of about ten severely painful daily bowel movements, who had failed to respond to all conventional therapies, responded within one week to sympathomimetic amine therapy. Soon after therapy she had 90%

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improvement and within one month was 100% relieved of all symptoms [12]. She has remained symptom-free for three years, including spontaneous closure of two perianal fistulas [12]. Other pain syndromes helped by sympathomimetic amines which had previously failed to respond to conventional therapy include: backaches [13], headaches [14], joint pain allegedly secondary to rheumatoid arthritis [15], carpal tunnel syndrome, and fibromyalgia [2, 4].

Other conditions that respond and improve considerably with sympathomimetic therapy that were resistant to other treatment include urticaria [16, 17] and chronic fatigue syndrome [18]. Vasomotor symptoms can be one of the presenting symptoms of a pheochromocytoma. Two cases were presented of women with severe vasomotor symptoms not responding to estrogen therapy whose symptoms were eradicated by treatment with dextroamphetamine sulfate. Biochemical testing failed to show evidence of a pheochromocytoma or carcinoid syndrome [19, 20].

The authors present a case of a woman who was incapacitated by episodes of severe tachycardia and hypertensive episodes resistant to other therapy but who responded to therapy with sympathomimetic amines.

Case Report

A 44-year-old woman presented with the main complaint of frequent paroxysmal episodes of severe tachycardia and severe rise in blood pressure associated with profound weakness, chest pain, shortness of breath, light headedness, and sweating that would leave her incapacitated. These symptoms had been present for several years. The frequency and severity of symptoms were so severe that she was house-ridden.

She had a history of hypertension dating back to her mid-twenties that was well-controlled on losartan. During pregnancy she was switched to alpha methyldopa. After her first pregnancy, her blood pressure normalized and no medication was taken.

At the age of 40 she re-developed hypertension but also sinus tachycardia. Her blood pressure and resting heart rate were both slightly high but there would also be paroxysmal episodes of sinus tachycardia with heart rates up to 200 beats per minute (BPM). Her blood pressure would markedly rise at this time with documented pressures of 165/120 mmHg. A referring cardiologist tried beta blockers but could not find one that she could tolerate (nausea, fatigue, and depression). Lisinopril 20 mg/day did not control the blood pressure adequately.

On physical examination, the patient had a blood pressure of 160/100 mmHg with a weight of 77 kg and pulse of 108 BPM. Otherwise, her physical examination was unremarkable. Neck evaluation revealed the absence of any thyroid enlargement or tenderness or carotid bruits. The lungs were clear, both anteriorly and posteriorly and with symmetric chest wall expansion. Cardiovascular examination revealed regular rate and rhythm, without any murmurs, rubs, or gallops. She had no peripheral edema.

Her laboratory tests were as follows: free thyroxin normal at 1.36 ng/dl (nl – 0.8-1.8 ng/dl), thyroid-stimulating hormone (TSH) normal at 1.36 mIU/ml (nl = 0.425 to 3.0), serum insulin 11.2 μU/ml (normal < 20 μU/ml). Her morning serum cortisol was normal at 9.7 mcg/dl and her 24-hour urine for fractionated metanephrines, was metanephrine 160 mcg/24 hours (nl = 58-203), normetanephrine 365 mcg/24 hours (nl = 88 - 649), and total metanephrine was 525 mcg/24 hours (nl = 182/739). The vanillylmandelic acid levels were very slightly increased at 6.2 mg/24 hours (nl = ≤ 6). One year later these tests were all normal.

Two years later, during an episode of paroxysmal tachycardia and hypertension, the total metanephrines were slightly elevated at 847 mcg/24 hours, with top normal fractionated metanephrine and normetanephrine (203 and 644 mcg/24 hours). During this time, urinary epinephrine was normal: eight mcg/24 hours (nl = 2 - 24), as were norepinephrine 94 mcg/24 hours (nl = 15 - 100), and dopamine with a level of 430 mcg/24 hour (nl = 52 - 480). A dexamethasone suppression test ruled out Cushing's syndrome.

A computed tomography (CT) scan of her abdomen without contrast was performed to evaluate for pheochromocytoma, and this demonstrated a 0.8 x 0.8 cm left adrenal adenoma. Magnetic resonance imaging (MRI) of the abdomen with and without gadolinium found a small lesion on the left adrenal with normal abdominal vascular structure. A repeat CT of the abdomen without contrast one year later found no growth of the left adrenal lesion.

A 24-hour heart monitoring found the minimum heart rate to be 67 BPM with a maximum of 156 with only two atrial premature contractions and 13 premature ventricular contractions. By examination the fastest heart rate ever documented was 200 BPM.

The woman performed a water load test where she excreted 50 of the 48 ounces of water ingested over a four hour time period, while supine but only 24 ounces erect. Based on this abnormal water load test, the woman was started on dextroamphetamine sulfate extended release capsules 25 mg/day.

When she was evaluated after eight months of taking the extended release capsule of dextroamphetamine sulfate, she was asked: what was the major benefit of taking the dextroamphetamine sulfate? She stated that she had almost complete elimination of any of the tachycardia paroxysms associated with the other aforementioned symptoms. She stated that she still suffers from general fatigue but on a scale of 0-10 she rated the improvement as a six. Nevertheless her blood pressure was still increased despite taking irbesartan and diltiazem.

Her fatigue improved with further treatment with dextroamphetamine sulfate. However one of her four children developed T-cell lymphoblastic leukemia and she was not able to return to the office for prescriptions. She continued the irbesartan but stopped the diltiazem because of side-effects. She reported a return of the paroxysmal tachycardia and the rest of the syndrome within one week of stopping the dextroamphetamine sulfate. The paroxysmal symptoms were much improved to almost non-existent within ten days of restarting the medication. It has been 18 months since restarting and she once again has been able to return to a functional life.

Discussion

It is unclear if the effectiveness of sympathomimetic amines in this patient was through diminishing vascular permeability; perhaps some toxic substance was thwarted from absorbing into the heart, thereby preventing irritation of the sinoatrial (SA) node, or by inhibiting edema of the heart and thus altering pressure on the SA node. The possibility of a toxic factor absorbing into heart tissue because of increased permeability related to a defect in

sympathetic nervous system is supported by the quick response to sympathomimetic amines in certain conditions before any improvement in edema is seen or in cases where there is no apparent edema [4, 8, 12, 14]. Possibly, the sympathomimetic amines work in some other way. Her seven-kg weight loss supports the possibility of the edema mechanism.

It is disappointing that the dextroamphetamine sulfate did not lower her generalized hypertension and only helped the paroxysmal symptoms. Perhaps the main abnormality was the paroxysmal tachycardia and the "fright" response triggered the other symptoms.

These data suggest that a pseudopheochromocytoma can be added to the list of various obscure treatment refractory conditions that seem to be related to a defect in the sympathetic nervous system and responds to sympathomimetic amine therapy. In this case, the defect in the sympathetic nervous system caused the paroxysmal symptoms, but the sustained blood pressure elevation was probably just essential hypertension.

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