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New Insight into the Understanding of the Pathophysiology of the Postural Orthostatic Tachycardia Syndrome (POTS) and a Description of a Potential Novel Highly Effective Treatment

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ABSTRACT

Rationale: *There are data supporting the concept that the etiology of idiopathic orthostatic edema is related to a delayed response by the sympathetic nervous system to secrete more dopamine from sympathetic nerve fibers to diminish cellular permeability of the capillaries in humans when changing from supime to an erect position to inhibit transudation of intravascular fluid to the extravascular space. This physiologic change is related to the increased hydrostatic pressure that occurs by standing. Evidence supporting this theory is that this clinical entity, manifested by edema of unknown origin and weight gain, is usually ameliorated by treatment with the sympathomimetic amine dextroamphetamine, which is known to increase dopamine release. We hypothesized that postural orthostatic tachycardia syndrome (POTS) may be caused by a more severe transudation of fluid from intravascular to extravascular space which results in light headedness and/or symptoms from hypovolemia related to transient inadequate blood supply to the brain, before compulsory mechanisms are triggered by the renin-angiotensin-aldosterone axis. Tachycardia is related to the need to increase the heart rate to allow the required 5 liters of blood per minute.*

Objective: *To determine if dextroamphetamine could improve a severe case of POTS.*

Findings: *A woman with severe treatment resistant POTS, with multiple syncopal episodes, had a great response to 60mg dextroamphetamine sulfate, which completely eradicated her POTS.*

Conclusion: *At least one form of POTS can have a good response to dopaminergic drugs e.g., dextroamphetamine, which also corrected other associated conditions e.g., dysmenorrhea, dyspnea on exertion, chest pain, headaches, chronic fatigue, brain fog, depression, and fibromyalgia.*

Keywords

Dextroamphetamine sulfate, Dopamine, Increased cellular permeability syndrome, Postural orthostatic tachycardia syndrome.

Introduction

In a recent review by Sebastian et al. Postural Orthostatic Tachycardia Syndrome (POTS) was defined as a condition that is characterized by an increase in heart rate upon standing associated with light-headedness, chest pain, shortness of breath, and brain fog [1]. They state that the etiology of POTS is largely unknown and often debilitating [1]. Other reviews e.g. by Iser and Arca include headaches as another condition associated with POTS [2]. Ray et al. also concluded that headaches may be associated with POTS as did Mueller and Robinson-Pupp [3,4].

Another condition that has been found to be associated with POTS is chronic fatigue [5]. There has also been an association also of gastrointestinal disorders with POTS syndrome [3,5]. There are

many hypotheses about the pathophysiology of POTS, and it is possible that there is more than one etiology. Thus, possibly different forms may require different treatments [1-5]. Some consider POTS as part of an autoimmune nervous system imbalance associated with numerous conditions, not only including the aforementioned conditions described above, but also associated with autoimmune conditions e.g., fibromyalgia, memory loss, and hearing dysfunction [6].

Sebastian et al. discussed three major hypotheses about the pathophysiology of POTS: 1 autoimmunity, 2) abnormally increased sympathetic activity and 3) sympathetic denervation leading to central hypovolemia and reflex tachycardia [1]. Thus, Sebastian et al stated, "given its heterogeneous nature, it is crucial to understand each component of POTS with more emphasis incorporating a multidisciplinary approach to control the symptoms. Future works should focus on better understanding the POTS pathophysiology and discussing randomized controlled, trials for implementing effective therapy."

In the aforementioned December 2022 review of POTS by Sebastian et al, there were two other co-authors and experts in the field of POTS, and by their description, we are just scratching the surface in finding an effective treatment [1]. Realistically, randomized controlled trials (RCTS) are only going to happen when a pharmaceutical company has discovered a new drug that, if effective, could be brought to market. There is a drug already that is a generic that can be very effective in some very severe cases of POTS that will be presented in this case report. This drug has a very good long-term safety profile. In addition, the generic form of this drug is very inexpensive.

Case Report

A 42-year-old woman presented with a long-term history of 25 years of a large variety of symptoms including POTS, dysmenorrhea, dyspnea on exertion, chest pain, headaches, chronic fatigue, brain fog, fibromyalgia, and depression. Over the 25 years, she had multiple hospital admissions to attempt to diagnose her problem, but also to treat head injuries and bone fractures from multiple sudden syncopal episodes. Though she had been under the care of physicians of various specialties, including family practice, gynecology, psychiatry, neurology, and cardiology, her main treating physician was her cardiologist. The attempted treatments that were rendered for most of these conditions are too numerous to mention, but they all failed to improve her symptoms, with the exception of various anti-depressants that she used over the years which allowed a moderate improvement of her depression. For the POTS syndrome she had been treated with fludrocortisone and midodrine but she gained no improvement at all with these medications.

On her initial visit, her supine blood pressure was 118/72 dropping to 108/58 with standing and her corresponding heart rate was 76 supine and 110 standing. She had symptoms of a urinary tract infection, and we sent her to the bathroom to collect a urine specimen. Because she seemed to be in the bathroom for a longer time than expected, my nurse was sent to check on her status, and to wait for her and accompany her back to the consultation room. Through the door she said she was fine and would be right out. She exited the bathroom, and was talking to the nurse, and after taking a few steps fainted and slammed her head on the floor. Fortunately, there were no injuries from this fall and she had no evidence of a concussion.

The multitude of symptoms can occur from a common disorder, but not welk-known condition, called the increased cellular permeability syndrome [7]. Because of a high likelihood that her symptoms of pelvic pain, chronic fatigue, memory impairment, brain fog, fibromyalgia, chest pain, and dyspnea on exertion, and depression would improve following treatment with dextroamphetamine sulfate [8-11], we started her on this drug to improve her quality of life [7]. However, her most life threatening and most debilitating condition was the POTS; it was hoped that dextroamphetamine sulfate would help the POTS part of the syndrome, however, we never had a case of POTS so severe [11]. All of her symptoms markedly improved, including the POTS, even before taking her final dosage that had slowly been incremented of 30 mg of amphetamine salts am and noon. In the two and a half years of treatment she has only had one syncopal episode that occurred after drinking a moderate amount of wine and failing to take the second dosage of dextroamphetamine in the afternoon. Previously she had at least 4-5 episodes of syncopal episodes per week. The only medication she was taking besides the dextroamphetamine sulfate was fluoxetine for her depression.

Discussion

The initial academic interest for the lead author was cancer immunology. Since there seemed to be a similarity between cancer and the fetal semi-allograft, e.g., rapid proliferation of cells, invasion of normal tissue, and evasion of immune surveillance, a series of research studies trying to determine the mechanism involved in embryo implantation and the methods employed by the fetal semi-allograft to escape immune surveillance were conducted. These studies did in fact, lead to some interesting discoveries resulting in novel treatments that have shown marked palliative benefits and increased longevity even in patients with very advanced cancers who no longer have any standard treatment options [12].

A series of other studies, which have been summarized suggested that intrinsic to successful implantation is the need to establish an autoimmune reaction against certain of the thick-walled uterine arteries during the luteal phase to create thin-walled spiral arteries to allow nutrient exchange between mother and fetus [13,14]. This model suggests that to enhance the cellular immune reaction, one of the roles of early progesterone (P) secretion by the corpus luteum is to block dopamine. One of the roles of dopamine is to decrease cellular permeability. The model suggests that progesterone blocks dopamine leading to infiltration of irritants, which evokes a cellular immune reaction [14]. To prevent these cellular immune cells from attacking the fetal semi-allograft and cause implantation failure, while these inflammatory events are occurring, progesterone

stimulates immunomodulatory proteins from the embryonic cells, mesenchymal cells, trophoblast cells, and gamma delta T-cells e.g., the progesterone induced blocking factor (PIBF), which reduces the killing potential of these cellular immune cells by day 6 from conception. This allows successful invasion of the fetus and trophoblast into the endometrium [15-18]. These proteins that are products of membrane progesterone receptors are vital also for malignant tumors to escape immune surveillance [19]. With the thought process that cancer cells may be able to proliferate using a mechanism related to the survival of the fetus, to allow progression to the pathological state of cancer, possibly certain pathological conditions may occur related to a sympathetic fetal survival mechanisms requiring increased cellular permeability to allow absorption of irritants into the endometrium during the luteal phase to stimulate an increase of cells of the cellular immune system to cause an "autoimmune state" to allow remodeling of some of the thick walled uterine arteries to make spiral arteries to allow nutrient exchange between mother and fetus [17]. This led to the hypothesis that perhaps the initial etiologic factor for most autoimmune conditions certain tissues may for various reasons (infection, genetics, trauma) become more permeable leading to infiltration of irritants leading to an inflammatory response. If chronic conditions may be caused by a relative dopamine deficiency, a logical concept is that possibly drugs that release more dopamine may improve symptomatology of certain medical conditions specially those that may have an autoimmune etiology. This hypothesis was formulated, and the search for a dopaminergic drug to test this hypothesis began around 1980. The dopaminergic drugs available on the pharmaceutical market at that time were levo-dopa or dextroamphetamine sulfate. The former had too many side effects, so suspected cases of relative dopamine deficiency were treated with dextroamphetamine sulfate, an off-label use. Clinically many of these conditions responded to dextroamphetamine sulfate. Nevertheless, we were searching for one case that would leave little question of the efficacy of dopaminergic drugs for a variety of pathological states. Thus, the first case we reported was a woman who had total body chronic urticaria over a seven-year time period who showed no response to standard treatments. Her urticaria completely disappeared shortly after treatment with dextroamphetamine sulfate and never returned as long as she remained on the drug [20]. This was published in 1984. The second case report of improving a seemingly treatment resistant condition with dextroamphetamine sulfate was achalasia [21].

Subsequently, many other case reports showed marked efficacy of dopaminergic drugs for treating a variety of medical conditions, which was first summarized in 2011 [10]. Since dextroamphetamine sulfate is in a class of drugs called sympathomimetic amines, we referred to the dextroamphetamine as a sympathomimetic amine, and did not use the term dopaminergic drug until we could prove that dopamine is the main neurotransmitter responsible for the observed efficacy. Though we used dextroamphetamine because it releases more dopamine from sympathetic nerve fibers, we could not be sure that it may work in some other manner. When it became clear that other dopaminergic drugs e.g., cabergoline, can also treat some of these same conditions, we felt justified in using the term dopaminergic drug [22]. Indeed, Sebastian et al. mentioned that POTS has been associated with brain fog and chest pain. Brain fog is a synonym for the term used for attention deficit disorder (ADD) and the on-label use for dextroamphetamine sulfate is ADD, for which it is very effective. Chest pain was also mentioned by Sebastian et al., and as mentioned, dopaminergic therapy was found effective for chest pain related to achalasia [1,19]. The reviews by Iser and Area, Ray et al., and Mueller and Robinson. Papp found that headaches were frequently found in patients who also had POTS [2-4]. Dextroamphetamine sulfate have been found to be very effective for idiopathic migraine headaches of unknown origin, along with a variety of different headache conditions including trauma [23-28]. Frequently these headaches may be associated with other conditions without POTS that also responds to dopaminergic drugs [29-32].

The aforementioned summary articles have found that gastrointestinal disorders have been seen in a greater frequency in patients with POTS [1-4]. Treatment with dextroamphetamine sulfate has been found to markedly improve various gastrointestinal disorders that were refractory to standard therapy [33-39]. Wu et al. found a higher frequency of the chronic fatigue syndrome in patients with POTS [5]. Treatment with dextroamphetamine sulfate was found to be very effective for treating the chronic fatigue syndrome [40-42]. Malkova and Shoenfeld mention other conditions e.g., fibromyalgia and hearing loss associated with POTS [6]. Treatment with dextroamphetamine sulfate has been found to be effective in treatment refractory cases of fibromyalgia and autoimmune hearing loss [43,44].

A condition had been described by George Thorn in 1965 describing women who had an unknown condition of generalized edema. The edema was orthostatic and sometimes women needed to wear larger size clothing by the end of the day [45]. He believed that the condition may be psychosomatic and related to depression. Thus, he treated these women with the main antidepressant in those days, e.g., dextroamphetamine sulfate, and many responded very well [45].

We had noted that many of the patients with orthostatic edema also had these various disorders successfully treated by dextroamphetamine sulfate. We found that dextroamphetamine sulfate not only relieved the edema, but it fared much better than thiazide diuretics, converting enzyme inhibitors, or spironolactone [46]. Inhibiting the edema led to weight reduction without dieting [46,47]. This edema manifestation of this syndrome fits in with the hypothesis that the increase in hydrostatic pressure that occurs with sitting or standing erect in the human species would cause a fluid shift from intravascular to extravascular sites were it not from triggering an increase stimulation of the sympathetic nervous system, hypothetically, releasing dopamine. The increase in dopamine by this theory would diminish cellular permeability of the capillaries, which maintains the intravascular fluid volume and prevents leakage to extravascular sites. Studies from David Streeten following

injection into patients of radioactive albumen found that patients with orthostatic edema, taking dextroamphetamine shortly before the injections of rasioactive albumen corrects the leak and keeps the albumen in the vascular system, whereas when tested before dextroamphetamine sulfate was given thus, showed evidence of leaking of the albumen out of the vascular system [48].

For idiopathic orthostatic edema there is a transient diminished intravascular volume that is quickly compensated to restore intravascular fluid volume through the renin-angiotensin aldosterone system [47,48]. The theory as to the etiology of at least one mechanism of POTS is that the permeability of the capillaries is too great for immediate restoration of intravascular volume, leading to hypovolemia, with transient diminished blood supply to the brain with subsequent light headedness or syncope. Also, because of less blood flow to the heart, there is a diminished ejection fraction leading to the need for an increased heart rate (tachycardia) to maintain the required 5 liters of blood flow per minute.

Thus, a milder form of vascular insufficiency related to orthostatic changes is common, and manifests more likely with edema and inability to lose weight even by dieting, but much less commonly presents as POTS. Nevertheless, both respond to dopaminergic drugs. At one time related to the common presentation with edema, but also pain related to insufficient release of dopamine from sympathetic nerve fibers allowing irritants to infuse into various tissues causing inflammation and pain, this condition was termed the sympathetic neural hyperalgesia-edema syndrome [7]. However, because not all people with this condition have pain (e.g., chronic fatigue) and not all have edema, we changed the name of this condition that we have described to the increased cellular permeability syndrome [7].

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