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Editorial Article

Changing the name of a syndrome: sympathetic neural hyperalgesia edema syndrome becomes – the increased cellular permeability syndrome

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Summary

Purpose: To provide examples of other conditions that are improved following treatment with dextroamphetamine sulfate that would not involve hyperalgesia and/or edema. Thus elucidation of such conditions would demonstrate the need to change the name from the sympathetic neural hyperalgesia syndrome to a name that would cover all conditions responding to sympathomimetic amine therapy. *Materials and Methods:* Cases of chronic fatigue syndrome and various skin and neurologic disorders and temperature regulation conditions are provided as examples of conditions responding well to dextroamphetamine sulfate that do not involve either pain or edema. *Results:* Examples are provided that show that inherited permeability defects in certain tissues or inherited sympathetic nervous system hypofunction produce symptoms other than pain or swelling yet respond to dextroamphetamine sulfate. *Conclusions:* Though lacking "pizzazz", the new name given to this condition refers to the main hypothesized defect whether inherited or acquired, and that is increased cellular permeability. Thus, the new name is the increased cellular permeability syndrome in lieu of the sympathetic neural hyperalgesia – edema syndrome which had replaced the name idiopathic edema.

Key words: Sympathetic neural hyperaglesia syndrome; Increased cellular permeability syndrome; Idiopathic edema; Sympathomimetic amines; Dextroamphetamine sulfate.

Recently I wrote an editorial entitled "Sympathomimetic amines are a safe, highly effective therapy for several female chronic disorders that do not respond well to conventional therapy" [1]. Since we have written a large number of case reports and a previous editorial on treating pelvic pain, hopefully some of our readers have tried this therapy even before the last editorial. If not, from these past case report studies, hopefully the last editorial has convinced you to try this therapy for a variety of female disorders [1]. If you have tried it, I know you and your patients are very satisfied.

This condition is not limited to women but seems to be more common (similar to autoimmune disorders). In fact, I think this condition, that we have referred to as the sympathetic neural hyperalgesia edema syndrome, plays a critical role in most autoimmune disorders. A large majority of so-called autoimmune diseases are much more effectively treated by dextroamphetamine sulfate rather than glucocorticoids and/or biological immunosuppressives with far less risk and much less expense when compared to the biologicals.

This condition is extremely common, yet it is unknown to most clinicians with the exception of the readership for Clinical and Experimental Obstetrics & Gynecology. The reason for this is that it is not being promulgated by large pharmaceutical companies because dextroamphetamine sulfate is available as a generic drug. Furthermore, the plethora of published articles would prevent a large pharmaceutical company from obtaining a patent even if they made some slight modifications to the formulation.

Probably the first name given to a form of this condition was provided by George Thorn (who was the head of endocrinology at Harvard Medical School) over 45 years ago and he used the name "idiopathic edema" [2]. He also called it "periodic swelling" [2]. Since the condition became worse from morning until evening, and it was clear that standing erect made the condition worse, I sometimes referred to the condition as idiopathic orthostatic edema [3].

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Since Dr. Thorn noticed there were times the edema seemed to be worse, and then would get better (but not associated with the menses), thus sometimes the condition was called idiopathic orthostatic cyclic edema [2].

Many of these women with the idiopathic edema (hypothyroidism, renal and hepatic disease, and congestive heart failure excluded along with drugs that could cause edema) were thought by Dr. Thorn to have a psychosomatic basis, so they were treated with the main anti-depressant 47 years ago, dextroamphetamine sulfate [2]. The considerable improvement in their edema seemed to support the hypothesis. Significant improvement of depression was associated with improvement in the edema. However, physiological studies by David Streeten *et al.* suggested that dextroamphetamine sulfate helps the edema by a different mechanism, i.e., correcting a defect of increased capillary permeability allowing intravascular fluid to leak into the extravascular space related to the increase in hydrostatic pressure that occurs in the orthostatic position. Streeten *et al.* had already previously determined that the diminished intravascular fluid volume was compensated through the renin angiotensin system causing secondary hyperaldosteronism [4]. Subsequently Streeten performed studies confirming the theory of increased capillary permeability. He took female volunteers who were injected with albumin labeled with radioactive iodine. Albumin is a large enough particle that when in circulation, when a person is standing, the capillary pore size is sufficiently small that the albumin stays intravascular and thus one will recover the radioactive iodine diluted by blood volume. However, women with idiopathic edema would lose a significant amount of albumin following injection in the standing position [5]. Interestingly ingestion of dextroamphetamine sulfate corrected the defect, i.e., there was much less loss of the radioactive labeled albumin [5]. This showed that the mechanism of action of dextroamphetamine sulfate in correcting the edema was not improving depression, but correcting a vascular permeability defect [5].

George Thorn had developed a water load test to diagnose the condition. If a woman ingested 1,500 mL of water over 30 minutes, she was diagnosed with idiopathic edema if she excreted less than 55% of the ingested water load in four hours. In 1985 we presented our data at the American Society of Obstetrics and Gynecology, and showed that if one used a cut-off of 75% instead of 55%, one could detect this condition as common, not rare, and thus a common cause of women who cannot lose weight despite dieting. In 1995 we published a randomized study comparing treatment with dextroamphetamine sulfate versus three other therapies used for idiopathic edema, including standard diuretics, spironolactone, and converting enzyme inhibitor. Dextroamphetamine treatment showed marked superiority to the other drugs [6].

Despite this publication, and the previous work by George Thorn and David Streeten, the condition known as idiopathic edema is not well known. As mentioned, the condition of sympathetic neural hyperalgesia edema syndrome is not restricted to women, even the pure edema form. One 40 year old man, who was 2.13 meters tall and weighing over 181 kg, was admitted for 1.5 months in the hospital for severe unexplained edema with severe stasis dermatitis. Despite a plethora of specialists including vascular specialists, cardiologists, nephrologists, and endocrinologists he was discharged basically disabled to return to his job as a vice principle of a high school. As an outpatient he was seen at our medical center and within one month his edema was completely cleared as was his stasis dermatitis following treatment with dextroamphetamine sulfate. He has remained edema free for three years while he continues therapy. Interestingly, a recent expert review on idiopathic edema was published and it was clear that the authors have no experience using dextroamphetamine sulfate since it was merely mentioned in passing [7].

Some of the associated conditions with the idiopathic edema had been thought to be related to the edema itself. However, I considered that there may be a generalized permeability defect related to all tissues not just capillaries. A woman had been covered with urticaria over her entire body for seven years. She was initially suicidal since antihistamines or glucocorticoids failed to provide any relief. She had seen a multitude of specialists and decided to try a reproductive endocrinologist. I considered that maybe she had this permeability defect in the vesicles containing histamine, thus allowing leakage. We treated her two weeks on and two weeks off with dextroamphetamine sulfate. Within one day of this therapy, all of her hives disappeared only to return in one day after cessation of therapy. This phenomenon was repeated several times showing remission with treatment and exacerbation with stopping. She remained on therapy with sympathomimetic amines and her urticaria has remained in complete remission for over 30 years [8]. Another woman who was similarly affected by severe treatment refractory urticaria had not had one hive for 22 years while on treatment. She lost her prescription so had to wait one month for another prescription. Though stopping suddenly did not result in any withdrawal symptoms or evidence of dependence, her hives returned full force within three days only to disappear again within three days when her therapy was resumed. Both of these women had edema also, and the latter woman lost 41 kg on therapy. However, subsequently we have helped many women with severe urticaria who showed no evidence of edema.

I had been treating this condition of idiopathic edema for about eight years and had observed many other symptoms, e.g., headaches and joint pain improve, and thus I considered that edema in a closed place like the skull could cause pain. But I also considered that the permeability defect may be present in other cells not just capillaries, I considered that chronic urticaria may be related to increased permeability of the vesicles containing histamines, and dex-

troamphetamine sulfate may control the urticaria by diminishing cellular permeability, thus stopping the leakage. If so, the possibility existed that a cellular permeability defect could allow infusion of chemicals and toxic material into various tissues, thus leading to inflammation and pain.

It was not until 1986 that I treated one woman for menstrual irregularity that led me to publish my second case report on this condition of increased cellular permeability. Though not the reason for consulting me, her history revealed not only orthostatic edema but a chronic severe type of chest pain diagnosed by her brother, the chief of gastroenterology at a major well known medical school, that she had achalasia [9]. However, none of the treatments rendered provided relief. I advised her that dextroamphetamine sulfate could relieve her edema and could possibly help her chest pain since I had observed many different pain symptoms improve, though I had not been presented before with any patient with her type of chest pain. Not only did her edema improve but her chest pain completely dissipated [9]. One would think that her brother, the gastroenterologist, and her father, a specialist in internal medicine, would be happy about her continued relief of the chest pain, but instead admonished her for taking "such a dangerous drug" and begged her to stop. She did not listen to them and enjoyed complete relief for 2.5 years. Then I received a strange phone call. This young lady said she is sorry for missing her last appointment because she was admitted to a psychiatric hospital. She stated that with constant pressure from her father, brother, and pharmacist, she stopped the dextroamphetamine sulfate and her pain returned in a week. They got her to voluntarily be admitted to the psychiatric hospital to explore "why she has this psychosomatic condition". She said over the phone that after being there a week she realized that the only crazy thing about her was allowing her family to influence her to stop therapy. She resumed dextroamphetamine sulfate, and her chest pain immediately ceased. I decided that it may be important to make other physicians more aware of this condition. One of my patients was a first year fellow in gastroenterology and I asked him if he would like to get published in a gastroenterology journal and help write the case report, and it was published in 1990 [9].

At this point in time I decided that I would write other case reports when I saw ones that were convincing such that the patient had long-term suffering, failed standard therapy, but responded quickly and effectively to treatment with dextroamphetamine sulfate. It became clear that many patients who responded to dextroamphetamine sulfate did not have edema. Some even with edema passed the water load test, so we dropped this cumbersome test in making the decision as to who to treat with dextroamphetamine sulfate.

When we published our first case report on improvement of treatment resistant headaches with dextroamphetamine sulfate, the woman who showed this response also improved her edema which was evidenced by weight loss [10]. Thus we considered that the case may have been a vascular permeability defect with fluid in the closed-space, i.e., the skull [10]. However, we subsequently found a woman who may have had both headaches and edema but achieved immediate relief from the dextroamphetamine sulfate without losing a gram of weight. This made us more suspicious that the permeability defect may involve the tissues of the skull and brain and not necessarily a vascular permeability defect leading to edema causing the pain. I considered that there must be a direct effect of possibly unwanted toxic elements entering certain tissues causing inflammation and pain without the edema [11]. Thus, as of 2011, our thoughts were that the syndrome was related to a certain tissue weaknesses, i.e., cells more prone to permeability coupled with a generalized sympathetic nervous system hypofunction which would compound the problem. We thus started calling the condition the sympathetic hyperalgesia edema syndrome, since most patients had pain and/or edema [12].

As we submitted the second manuscript using the new name of sympathetic neural hyperalgesia edema syndrome entitled "Sympathetic neural hyperalgesia syndrome, a frequent cause of pelvic pain in women, mistaken for Lyme disease with chronic fatigue", I realized that she did not have hyperalgesia, and furthermore she did not have edema either [13]. Even our first case report using the new name had vasomotor symptoms that improved, thus the new name for this syndrome did not take into account the improvement of her vasomotor symptoms [12]. In fact, in a previous publication where dextroamphetamine sulfate improved vasomotor symptoms, the old term of idiopathic orthostatic cyclic edema was used, and yet she did not have edema [14]. The name coined in 2011 "The sympathetic neural hyperalgesia edema syndrome" simply did not encompass improving vasomotor symptoms [14,15].

Other conditions improved by dextroamphetamine sulfate did not involve pain either [16-22]. Thus we considered other names. We did not want to call the syndrome sympathetic dystrophy because it would sound too close to the condition that had been called reflex sympathetic dystrophy, which is now called chronic regional pain syndrome. Incidentally we have successfully treated chronic regional pain syndrome that failed to respond to ketamine with dextroamphetamine sulfate [23]. Another important factor in deciding to change the name change was the question as to whether there is always sympathetic nervous system hypofunction, or are there circumstances where the tissue or cellular permeability defect becomes worse where normal sympathetic tone cannot prevent the infusion of unwanted chemicals or toxins but where increasing the sympathetic tone above normal can inhibit infusion of these toxic elements? Thus, a reason to eliminate "sympathetic neural" from the name because the problem may be with a defect on the tissue and not the sympathetic nervous sys-

tem.

There seems to be a strong hereditary component to this condition in many cases. Sometimes specific tissue defects seen are familial, e.g., "pain from endometriosis" in mother and daughter, or inheriting the edema component. So one question was should hereditary be included in the name? Interestingly we presented at the 2015 American Association of Clinical Endocrinologists an interesting case of a man whose brother was diagnosed with hereditary spastic paraplegia (and was already paraplegic) and this man started himself with spasticity and he was dragging his right leg [24]. Within one month of treatment with amphetamines he was no longer spastic or dragged his right leg. He was once again able to participate in strenuous activity using his legs following treatment with dextroamphetamine sulfate. However, he had neither pain and nor edema. Furthermore he was a male indicating that men too can improve various medical conditions with sympathomimetic amine therapy, yet not have any of the classic symptoms of the sympathetic neural hyperalgesia edema syndrome [24]. Thus, though the condition seems to be more common in women, it is clear that men also can suffer from the problem and thus "female" should not be included in any name change.

Since so many cases seemed to be familial, I considered that possible hypo-function of the sympathetic nervous system may be a common link between the various presentations of the condition. Another case that we presented at the American Association for Clinical Endocrinologists convinced me not only that this condition can be acquired, but that one does not necessarily need sympathetic nervous system hypofunction. A 22-year-old male developed daily severe headaches occupying 70% of each day that was not greatly relieved by strong analgesics. However, the etiology was not obscure since the headaches started after his 7th concussion from playing collegiate ice hockey [25]. On 30 mg amphetamine salts extended release capsules, he rarely gets a headache. He takes no other headache medication [25]. Prior to the concussion he neither suffered from headaches nor had any other symptoms suggesting sympathetic nervous system hypofunction.

This case suggested that acquired trauma, as opposed to strict inheritance, can create a permeability defect in that tissue allowing unwanted foreign material to enter the cells of that tissue leading to inflammation and pain. This case also suggests that even when a tendency for sympathetic nervous system hypofunction (and thus insufficient production of the sympathomimetic amine dopamine which may be the main factor to diminish cellular permeability) does not seem to be present, and where trauma seems to be the cause of increased cellular permeability, increasing dopamine by treating with dextroamphetamine sulfate can diminish cellular permeability and improve symptomatology. Interestingly, I recently submitted a manuscript to Clinical and Experimental Obstetrics and Gynecology 2 cases of severe headaches from concussion that happened to two teenage girls following a school bus accident following treatment with amphetamines, but also completely corrected a severe stuttering problem that also resulted from this head trauma.

Conditions associated with smooth muscle dysfunction have also responded very well to amphetamines [26, 27]. Thus, I decided that the common denominator for all these conditions is increased cellular permeability, no matter what the cause. Thus, I propose a new name "the increased cellular permeability syndrome". I would refer to this name for all conditions (including attention deficit disorder) that dramatically improve following treatment with dextroamphetamine sulfate. As mentioned, the drug may operate by stimulating more dopamine from sympathetic nerve fibers thus reducing cellular permeability. Of course, this name could change again if the hypothesis that best fits the explanation for the dramatic improvement with dextroamphetamine sulfate proves to be inaccurate and some other mechanism is found. Our fellow in reproductive endocrinology/infertility thinks the name lacks "pizzazz", but for now, I will be referring to the new name as the "increased cellular permeability syndrome". To narrow down the tissue involved, one could mention the headache variety of the increased cellular permeability syndrome or the "pelvic pain variety", "the edema variety", or "the Crohn's disease variety", etc. When multiple organ systems are involved one could simply state the patient has the increased cellular permeability syndrome with multiple manifestations. The name could replace the term autoimmune disease since increased permeability can explain many of these entities, and can explain multiple systems involved with these conditions. Dextroamphetamine sulfate is much safer than the immunosuppressives used for these disorders, and in many instances, we have found it to be superior to immunosuppressives in relieving symptoms.

When women have dysmenorrhea that has a premenstrual component that is getting worse with age that may be associated with mittelschmerz or dyspareunia, most gynecologists would describe the woman as probably having endomtriosis. This could be confirmed by laparoscopy; but what if endometriosis is not found on laparoscopy as has happened to us so many times in the past? Are there white or clear lesions lost in the light so the endometriosis was missed from laparoscopic surgery? If we find one spot of endometriosis, is our presumptive diagnosis confirmed? How can one spot of endometriosis cause so much pain, and yet some infertile women without pelvic pain having a laparoscopy may be found to have extensive endometriosis? Why does removing endometriotic implants frequently fail to provide long lasting relief for those women whose implants were removed and has the same degree of pain in their very next menses what happened? Did it grow back that fast or did we miss lesions? My contention is that endometriosis is not the cause of the syndrome, but menstrual

tissue implants in the wrong place may merely be the result of the increased permeability defect; but why do some women, in a minority of cases have long-lasting relief? Could it be the surgical procedure itself can sometimes result in diminishing cellular permeability? Does estrogen contribute to cellular permeability, and lowering it can sometimes, but not always, diminish cellular permeability of the pelvic tissue, leading to improvement of inflammation and pain? Thus, in my opinion, stating that a woman has endometriosis pain is a misnomer because of the implication that it is the cause of the pain syndrome. I would prefer to tell the patient that she has the pelvic pain variety of the increased cellular permeability syndrome [28-33].

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