

## Dopamine Agonist Therapy to Treat Erythromelalgia-Case Report

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### Abstract

Erythromelalgia manifests with pain and erythema in the hands and feet. It is exacerbated by warmth. Many treatments have been tried, but none have demonstrated a high efficacy. Many treatments refractory dermatological and neurological disorders have had marked ameliorative benefits following treatment with dopamine agonists, especially the sympathomimetic amine dextroamphetamine sulfate. The hypothetical mechanism of how the dopamine agonist works is to correct increased cellular permeability allowing the infusion of irritants across the mucosal barrier causing inflammation and pain, but sometimes improving other physiological disturbances. In the case presented, treatment with dextroamphetamine resulted in complete relief of the symptoms of erythromelalgia in a short period of time which has persisted for almost 20 years. Thus, this is the first case report of treating erythromelalgia with a dopamine agonist. Though only one case, it seems more effective than the myriads of other therapies that have been tried.

**Keywords:** erythromelalgia; dopamine agonists; increased cellular permeability syndrome; edema; chronic fatigue

### Introduction

Erythromelalgia is a condition in which patients experience episodes of pain in the hands and feet which appear erythematous if the extremities get too warm [1]. The pain and redness may be relieved by cooling [1-2].

The primary form is related to variants in the SCN9A gene [possibly as many as 15 gene variants] that increase activity of the NaV 1.7 voltage-gated sodium channel [3,4]. Evidence also suggests that this disorder may also affect SCN10A and SCNA coding genes for NaV 1.8 and NaV 1.9 neuronal sodium channels [5].

There are various treatments that have been tried for erythromelalgia including pharmacological therapy for certain pathogenetic variants, e.g., mexiletine for the P.L858F/H variant and carbamazepine for the V400m, S241T, and the 1234T variants [3]. Topical agents that have been tried include: iloprost, misoprostol, topical amitriptyline-ketamine, and lidocaine [6]. Chemical lumbar sympathectomy has also been tried [6]. The two agents that worked the least for pain reduction, cooling scores, and temperature regulation in a review by Argarml et al were iloprost and misoprostol given orally [6]. The topical use of amitriptyline-ketamine reduced pain in 75% of the patients [6]. Other therapies have included epidural infusion, sympathetic ganglion block, sympathectomy, pulsed radio frequency,

spinalcord stimulation, dorsal root ganglion stimulation, brain stimulation, transcranial magnetic stimulation, and botulinum toxin injection [7]. As stated by Lee et al, "Both successful and unsuccessful outcomes have been reported. Although these procedural interventions extend the therapeutic options for erythromelalgia, the evidence for their use is limited. Case reports and small series comprise most of the evidence [7].

Whenever there are so many different options for treating a condition, e.g., erythromelalgia, it is usually indicative that no single effective treatment has been found for a given pathological condition. We present here another case report of a highly effective medical treatment option that has never been previously reported for the treatment of erythromelalgia and that is treatment with the dopamine agonist dextroamphetamine sulfate.

### Case Report

A 61-year-old woman consulted our reproductive endocrinology practice in 2005 for hormonal therapy for vasomotor symptoms and inability to lose weight despite dieting. Her review of symptoms was positive for frequent headaches and edema of the feet and calves. Furthermore, she stated that she had frequent episodes over the last two years of a burning pain especially in her hands and feet associated with redness of the skin. She consulted a dermatologist who referred her to a neurologist, and both concluded

that these symptoms were consistent with a rare condition called erythromelalgia. This was later confirmed by genetic testing in 2018 to be a monogenic autosomal dominant mutation.

Though she had been given oral estrogen by her gynecologist, it had not relieved her vasomotor symptoms sufficiently. However, she was reluctant to increase the dosage of estrogen for fear of breast or endometrial cancer and also a short trial of higher dosages of estrogen intensified her headaches. Evaluating her food intake, evaluating total calories, and carbohydrate percentage, her diet seemed appropriate and should have helped her lose weight. Instead, she had gained 15 pounds in the last year.

She stated that she had been prescribed various topical agents by both the dermatologist and neurologist but they provided no relief for the erythromelalgia, and so she stopped them. She could not recall what were the names of these topical medications. At that time, we were focused on treating the vasomotor symptoms, the edema and the weight loss. In fact, we had not even heard of erythromelalgia. Her only relief was provided by keeping her hands and feet as cool as possible.

She was advised that we have treated unexplained edema of the feet and legs associated with inability to lose weight despite dieting, and vasomotor symptoms also with the sympathomimetic amine dextroamphetamine sulfate (DS) [8-11]. Previous visits to an internal medicine specialist found no evidence of cardiac, renal, or hepatic disease. Our research suggested that this drug mostly works by releasing dopamine from sympathetic nerve fibers correcting problems of increased cellular permeability [12-14]. We explained that the increased weight may be related to an improper response by the sympathetic nervous system to release dopamine when a human is in the orthostatic position to diminish capillary permeability related to the increase in hydrostatic pressure causing fluid to shift from intravascular to interstitial spaces [9]. In fact, in a less common, more severe problem of increased cellular permeability at the capillary level syncope with compensatory tachycardia may ensue and this condition of postural orthostatic tachycardia syndrome also can respond well to dopamine agonists e.g., dextroamphetamine [15]. She was advised that although we had never heard of erythromelalgia at her initial appointment, it would not be suppressing if improvement was found in that conditions also by treatment with DS since so many different types of treatment resistant conditions

in women and men have been ameliorated by treatment with DS [13-17].

The patient was initially treated with oral amphetamine salts extended-release [ER] capsule 15mg providing 9.4mg of the actual active ingredient DS. This was eventually over 3 months increased to 30mg with the 30mg ER capsule. There had been almost complete eradication of the vasomotor symptoms. She also lost 25 pounds within 3 months of treatment at this dosage.

Furthermore, she no longer had episodes of erythromelalgia which previous to this therapy was present daily during late spring, all summer, and early fall and would occur at least once per week during cooler weather. Complete relief of the erythromelalgia lasted for 5 years on the 30mg ER capsule of amphetamine salts. Her insurance changed so she had to switch to the immediate release tablet for insurance coverage taking 15mg IR tablet twice daily [morning and noon]. Her vasomotor symptoms remained absent. She had lost 25 pounds from 210 pounds to 185 after the initial 6 months of therapy, which remained stable for 5 years. With the change to the IR tablet of amphetamine salts, she gained 5 pounds in one month.

The change in therapy occurred in mid-April. Her erythromelalgia returned twice per week for April and May increasing to about 15 times per month in June. She was increased to 30mg IR tablet AM and noon. Within 2 weeks, despite the summer heat, she had no more episodes of erythromelalgia. She also lost the 5 pounds that she had gained.

This woman now, aged 81, is still treated with 60mg amphetamine salts without any side effects. Her weight has also been stable over the 20 years of treatment and she still weighs 185 pounds. She stopped estrogen therapy at age 67, and she no longer has vasomotor symptoms.

Related to shortages of amphetamine salts over these 20 years of treatment, she would be off treatment for a week to one month. There were no withdrawal symptoms from sudden cessations during these respites she would gain a few pounds related to edema and would have the erythromelalgia would return.

Her internal medicine specialist, not understanding the safety and efficacy of DS, has been strongly advising her to stop this therapy. She has refused to stop because she has had no adverse side effects, her blood pressure and heart rate have been normal for all 20 years, and the internal medicine specialist could not offer her an alternative therapy other than just

keeping her hands and feet cool. She advised him that she would not stop mostly because he has no idea how painful is this condition.

## Discussion

Erythromelalgia is a rare condition. Thus, it is unlikely that a large case series or a randomized controlled trial evaluating a particular therapy or therapies would be initiated. Thus, a treating physician faced with a case of erythromelalgia and looking for a therapy for erythromelalgia may have to rely on case reports or very small series. In choosing the best therapeutic option the physician needs to take into account the degree of success of a given therapy in a case report versus actual or potential side effects, costs of therapy, potential long-term complications and nature of administration. The fact that it is an autosomal dominant disorder does provide the opportunity to evaluate multiple afflicted siblings, which could provide a small series at least.

The patient reported was first seen by her family physician and her internal medicine specialist, who then referred her to a dermatologist who in turn referred her to a neurologist because even at that time data suggested that erythromelalgia could be considered a small fiber neuropathy related to abnormalities in neuronal sodium channels [5]. Nevertheless, in establishing the diagnosis it is likely that the type of physician to get the first referral may be the dermatologist since this is a rare syndrome probably unfamiliar to pediatricians, family physicians, and internal medicine specialists. Once diagnosed, some of the other mentioned therapies would be more restricted to neurologists and some topical agents to dermatologists [6]. Leroux considers erythromelalgia a cutaneous manifestation of neuropathy [18].

The dermatologist may be more likely to be familiar with treatment with DS since publication of its efficacy for dermatologic conditions can be found as early as 1984 [19]. Over the years there have been many more reports showing the benefit of DS for a large variety of treatment refractory dermatologic conditions including but not limited to urticaria [19-27].

The case of treating dystrophic epidermolysis bullosa with an amphetamine similar to DS i.e., lisdexamfetamine, warrants mentioning. She had a 30-year history of painful blisters from this autosomal dominant disorder. Her 30 years of the continuous presence of this disorder cleared up within two weeks

of lisdexamfetamine therapy. The marked amelioration has persisted for 2.5 years. This genetic disorder is related to producing a defective type of collagen responsible for anchoring the dermis to epidermis [27]. The deficit allows a greater susceptibility to bruising, and this allows an unwanted excessive infiltration of irritants into the bruised tissue leading to pain. The dopamine agonists provide marked amelioration by preventing the leaking of irritants into those more susceptible areas. In addition, her dysmenorrhea dissipated and her infertility was corrected [27].

The increased cellular permeability syndrome is a polygenic disorder with various manifestations which all have in common that they are all successfully treated by sympathomimetic amines that release more dopamine from sympathetic nerve fibers. This is exemplified by a recent publication of 4 siblings who all had recurrent aphthous stomatitis (RAS) all of whom had complete correction of the RAS with DS [28]. One sibling had 20 years of very severe RAS. She also had unexplained weight gain. The DS helped her to reduce unexplained weight gain by correcting peripheral edema [8,9]. In addition, her chronic fatigue markedly improved [29-31]. Another sibling corrected both the RAS and gastrocolic reflux [16]. Another female sibling had RAS., dysmenorrhea, and diminished oocyte reserve with both the RAS and dysmenorrhea corrected by DS [28]. Pelvic pain is a common symptom in women with the increased cellular permeability syndrome and may occur as the sole symptom or be associated with other conditions which all respond to dopamine agonists [32-35]. The fourth sibling, a male, is very interesting. He not only had RAS but would have frequent episodes where he felt that his whole body was on fire. Indeed, his skin on most parts of the body would be very hot to touch. His only relief was to strip off his clothes and sprinkle himself with cold water. Not only did the RAS resolve with DS, but so did his temperature regulation problem [16, 28, 36]. Two siblings did not have any evidence of RAS or other manifestations of the increased cellular permeability syndrome. One could speculate that in the 4 siblings' cases with RAS, the RAS could have been related to an autosomal dominant disorder which was lacking in the two RAS free siblings. Alternatively, they may have the autosomal dominant disorder but lack the genetic predisposition for the increased cellular permeability syndrome, so the defect potentially manifested by the autosomal gene for RAS remains clinically silent.

Another previously published case report seems prudent to mention in context with the present case. An 89-year-old man presented with excruciating post-herpetic neurological pain [possible small fiber neuropathy] that had not responded to various anti-neuropathy oral medications, glucocorticoids and very high dosages of opiates. He wanted to enter into hospice and end his life. He was pain free within 1 month of treatment with DS and died peacefully in his sleep at age 94, having 5 years of no pain [37]. The physicians involved in the health management of the patient in this present case report wanted her to stop DS because of her age. Yet they did not have any “safer” suggestive therapy for her erythromelalgia other than referral to a dermatologist or neurologist to try a different therapy. They were unaware that alternative therapies would be more likely to be less effective with more side effects.

With over 45 years of treating hundreds of patients with DS, we have found it not only be a very safe and effective therapy with no long-term consequences (e.g., steroids and other immune suppressive drugs), but we have found it non-addicting in the dosages used. We cannot state for sure that DS would work for all cases of erythromelalgia. However, based on its rarity, despite the myriads of treatment options, it is these authors' opinions that DS is probably more effective than any of the other treatments, has less immediate and long-term side effects, is less expensive than most of the other treatments, and has the advantage of not only treating the erythromelalgia but improving other symptoms e.g., the edema and weight gain and vasomotor symptoms experienced by this patient.

For some reason amphetamines have the reputation to be dangerous drugs with a class II narcotic restriction thus making it somewhat difficult to obtain. Also, just like all medications, sometimes a given patient may have side effects to DS or other amphetamines. If the concept is true that its main benefit in treating these disorders is not its release from sympathetic nerve fibers of epinephrine and norepinephrine but the release of dopamine, one should also find amelioration of these disorders with more pure dopamine agonists. Indeed, there have been reports of the dopamine agonist cabergoline ameliorating various symptoms of the increased cellular permeability syndrome [40-42]. One recent case report showed that though the improvement of symptoms of the increased cellular permeability syndrome may be better with DS vs cabergoline,

another dopamine agonist, carbidopa levodopa may be equally as effective as DS [43].

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