

## Two New Clinical Manifestations of the Increased Cellular Permeability Syndrome Responding Well to Dopaminergic Drugs: Carpel Tunnel Syndrome and Sesamoiditis

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### ABSTRACT

There is evidence that the final pathway leading to various pathological states a common link between a wide variety of seemingly different disorders is increased cellular permeability resulting in infiltration of unwanted elements into various tissues and organ systems which in turn leads to inflammation and pain or physiological dysfunction through these various disorders may have different etiologies. There seems to be one universal treatment that can correct most of the symptoms and that treatment is the use of drugs that release more dopamine from sympathomimetic nerve fibers. One major function of dopamine is to decrease cellular permeability. A recent perspective listed the various conditions to date that appear in the literature that showed good response to dopaminergic drugs despite failing to show significant improvement with conventional therapy.

This perspective did not include carpal tunnel syndrome (CTS) or sesamoiditis. In this case report, we describe two women with CTS who responded very well to two different dopaminergic drugs (dextroamphetamine and cabergoline) saving them suggested surgery. A third case is described of a woman with sudden onset severe sesamoiditis who had total resolution of this extremely painful condition with a very small dosage of dextroamphetamine saving her from the treatment suggested by her physician and that was high dosage glucocorticoids.

**Keywords:** Carpel tunnel syndrome, Dopaminergic drugs, Increased cellular permeability syndrome, Sympathomimetic amines, Acute sesamoiditis

### INTRODUCTION

#### Carpel Tunnel Syndrome

Carpel tunnel syndrome (CTS) is caused by entrapment of the median nerve at the level of the wrist. The median nerve begins in the axilla, traverses the forearm and ends in the palm of the hand. The entrapment of the median nerve is generally at the level of the transverse ligament of the wrist which is considered the carpel tunnel and thereby provides the origin of the name [1].

The CTS is usually more common in women by 2-5-fold [2,3]. It occurs more commonly after the woman is middle-aged but there are a lot of exceptions [2,3]. The most common complaint is tingling, numbness and burning pain in the hands and fingers and it is common for the pain to spread proximally along the outer part of arm to the elbow and sometimes as high as the shoulder [4]. Typically, the

pain in the hand involves the thumb and forefinger and lateral half of the middle finger but sometimes all fingers are involved. Prolonged use of the hand can exacerbate the symptoms [4]. CTS is a common problem occurring in about 4% of the population [5].

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Treatment of CTS can be surgical especially for severe cases [6]. However, there are a variety of non-surgical therapies for mild to moderate cases. These various non-surgical treatment methods have varying degrees of success and side effects. These treatments include, but are not limited to wrist splints, oral non-steroidal inflammatory drugs, oral glucocorticoids, and local corticoid injections into the carpal tunnel [7-11].

A recent perspective suggested that most chronic medical conditions, including, but not limited to pain syndrome, may all have as a common etiologic factor, an increase in cellular permeability which leads to an infusion of unwanted irritants thus causing inflammation and pain [12]. Evidence to support this hypothesis was that many reported cases of chronic pain syndrome had a great quick ameliorative response to dopaminergic drugs. Dopamine is known to decrease cellular permeability [12-15].

An extensive literature search failed to find any mention of using dopaminergic drugs as a non-surgical treatment of CTS. Furthermore, the aforementioned perspective on treating a large potpourri of chronic disorders with dopaminergic drugs did not mention any cases of CTS that were treated with these agents [12]. Thus, the present manuscript describes 2 cases of severe CTS that responded to 2 different types of dopaminergic drugs.

### Sesamoiditis

Sesamoiditis is an inflammation of the sesamoid bones in the ball of the foot and the tendons that are embedded in it. It is usually caused by overuse, especially by dancers, runners, and athletes who frequently bear weight on the balls of their feet. It is usually treated with rest and anti-inflammatory medicines.

Sometimes in severe cases oral glucocorticoids or glucocorticoid injections directly into the injured tissue are given to relieve pain and inflammation. Surgery is only used in rare cases of chronic sesamoiditis. Removing one but not both of the sesamoid bones can bring relief. Mild cases may resolve in days while more severe cases can take months. Surgery will prolong recovery time. If one does not treat immediately, chronic sesamoiditis and permanent damage is more likely to ensue.

Many pain syndromes will respond quickly to dopaminergic drugs. The theory on why using dopaminergic drugs is so helpful for a large number of seemingly different disorders is that the end pathway allows infusion of irritants into a given tissue because of increased cellular permeability [12-15]. Dopamine diminishes cellular permeability and thus drugs that release more dopamine inhibit the infiltration of the tissue with irritants.

In the recent summary of all of the publications and the different organ systems involving clinical manifestations of the increased cellular permeability syndrome, sesamoiditis

was not on the list. A case is described with severe acute sesamoiditis with extremely quick pain resolution by treating with a very small dosage of the dopaminergic drug dextroamphetamines sulfate.

### CASE REPORTS

#### Carpel Tunnel Syndrome-Case Report #1

A 56-year-old woman whose job requires a lot of computer work and telephone calls developed pain in her wrist radiating up the arm from the thumb side to the elbow. She also had numbness and tingling in the hand from the thumb to the middle finger.

She consulted a well-known orthopedic specialist who after performing various tests concluded that she had severe entrapment of the median nerve causing CTS. They advised her that surgery would be her only option because of the severity of the nerve entrapment and that surgery was needed to prevent permanent nerve damage [16,17].

She consulted our group because she previously had severe backaches related to herniated disks and the dopaminergic drug dextroamphetamine sulfate provided her with complete relief of pain, so she avoided the recommended surgery [18]. She was hoping that the same therapy could relieve her pain and allow her to avoid surgery once again.

Though she was advised that we had never treated CTS with dopaminergic drugs, it was certainly worth a try. Within 2 days of taking amphetamine salts 15mg am and noon (equivalent to 9.4mg dextroamphetamine sulfate am and noon), all of her symptoms disappeared. She remained on the drug for 2 months and decided to stop the amphetamine salts after a brief treatment period since previously her backaches never returned after stopping the drug. The discomfort did return when she stopped the dopaminergic drugs, but the symptoms were much milder and bearable, so she has elected to not treat with the amphetamine for now unless symptoms become severe again. She had no side effects to the amphetamines.

#### Carpel Tunnel Syndrome- Case Report #2

A 74-year-old woman feeling "absolutely perfect" the day before. When she woke up the next day, she could not move related to severe bilateral arm pain. The pain was so bad in her arms that she could not apply enough pressure to push herself out of bed. She could not raise her arms above her head.

Eventually with difficulty she was able to get out of her bed. However, this extreme pain persisted for 2 weeks. She consulted an orthopedist who was not sure of the diagnosis.

Eventually she consulted 3 more orthopedic specialists and the last one after performing electromyography (EMG) concluded that she has very severe bilateral CTS. They gave her cortisone injections into both carpal tunnels and in her cervical spine, which resulted in only mild relief for 2 days.

They concluded she had both a pinched nerve in her cervical neck region and bilateral CTS. They suggested that she consider surgery on both carpal tunnels. She was mostly confined to her home. Five months later she came to our office for her annual gynecological check-up with the lead author. She told him that she almost cancelled the appointment because of the pinched nerve and bilateral CTS but a friend drove her to our office. Furthermore, she was aware from previous conversations, and also treating her daughter for pelvic pain, that the lead author may have an alternate suggestion for treatment.

Her daughter had marked improvement of severe pelvic pain with dextroamphetamine sulfate treatment. The lead author informed her that he did have one case of CTS that responded very well to that dopaminergic drug. However, she was advised that there had been a change in the interpretation of a law in the state of New Jersey. This state had an old law that restricted prescribing schedule II drugs off-label. However, her daughter was able to get the prescription in the state of Pennsylvania by the lead author because there was no such restriction in that state.

Nevertheless, for unknown reasons, the attorney general of New Jersey recently interpreted the law that a person could not even acquire the drug outside the state because, in his opinion, when the patient would re-enter the state of New Jersey they are technically breaking the law. She was advised that although an opinion received from a former attorney general of Connecticut and a former attorney general of New Jersey considered that interpretation as unconstitutional, nevertheless, our hands were tied.

However, she was advised that we have seen cases of treating pain syndromes with another dopaminergic drug that has no restrictions, i.e., cabergoline, which we mostly use for New Jersey residents [19, 20]. She started on 0.25 mg cabergoline 2 times per week before bedtime with food. After 2 months she was feeling slightly better. She was increased to 0.5mg 2 times a week and in her evaluation 2 months later she was feeling much better. She now had good movement in her wrists, and she could drive the car. In fact, her only issue was some pain in the hands and fingers only in the morning. Upon reassessment 3 months later, she stated that she is 100% better. It is not clear if the symptoms of this case 2 were solely from CTS or did she also have a pinched nerve in her cervical vertebrae?

### Sesamoiditis- Case Report #3

A 61-year-old woman suddenly developed pain that started at the ball of her left foot. She did not remember any activity or injury that could have prompted the pain. Within 2 days the pain intensified to such a degree that she could not walk on that foot. With the pain continuing with severe intensity, she was evaluated by a physician who concluded after testing that she had sesamoiditis. The physician recommended a short course of high dosage glucocorticoids

for at least a week followed by a gradual reduction in dosage with the strong possibility of maintaining a lower dosage of glucocorticoids for a prolonged period of time. However, since she developed psychogenic side effects and edema in the past when taking high dosage corticosteroids for another condition, she sought a second opinion from our practice.

In lieu of corticosteroids, she was treated with amphetamine salts 15mg (equal to 9.4mg dextroamphetamine sulfate daily). Within one day her pain was much reduced. By 2 days she could put pressure on her left foot. At the 3<sup>rd</sup> day mark, the pain was completely gone, and she is now able to walk without any pain. The plan is to stay on this dosage for at least 1 month and then she will be reassessed as to whether she should try stopping it or not.

### DISCUSSION

Carpal tunnel syndrome and sesamoiditis can now be added to the long list of chronic conditions that may be associated with pain, (but some with just some type of physical dysfunction, e.g., fatigue, constipation, diarrhea, or a neurologic disorder) that improves tremendously with dopaminergic therapy [12]. In the 2 cases of CTS described, they were both saved from having surgery (which is not always successful).

These cases would have fit into the category of conditions more common in women, but sometimes seen in males. Since the publication of that perspective another condition that responded well to dopaminergic therapy was reported and that is polymyalgia rheumatica [12,21]. The lead author had been treating the various manifestations of the increased cellular permeability syndrome for over 40 years. The large majority of cases have been treated with dextroamphetamine sulfate because at that time the only choice of dopaminergic drug was levodopa, which of course, had more potential side effects. Despite extensive use no patient has even been hospitalized for a serious complication, certainly no deaths and no addictions. In fact, the drug is usually stopped abruptly without any withdrawal symptoms in those where it is decided to stop the medication, e.g., women taking it for infertility and/or miscarriage when they frequently abruptly stop after the first trimester.

Case 1 is the exception rather than the rule. Most cases may need to take the drug for the rest of their lives, or the symptoms will usually return. However, in some cases, if one breaks the cycle after several months of treatment either the symptoms do not return at all (i.e., the previous history of backache in Case no. 1) or to a milder degree (i.e., the CTS in Case no. 1).

It is not clear why the attorney general of New Jersey interpreted an existing law in such a way that had such devastating negative effects on so many New Jersey inhabitants by making all New Jersey residents stop the drug immediately and allow them to suffer immensely from the return of their conditions. As mentioned, this was considered

unconstitutional by 2 former attorney generals when asked their opinions. One could think that New Jersey is just very strict about potential addiction to drugs not realizing its benefit and lack of risks because of their lack of medical training and understanding the difference between conventional dosages and illicit dosages. However, what is confusing is the state of New Jersey allows the purchase of marijuana and even psychedelic mushrooms from stores without even an evaluation by a physician.

Patients usually did so well with dextroamphetamine we were reluctant to try other dopaminergic drugs that subsequently came onto the pharmaceutical market e.g., cabergoline. If there is any silver lining, the New Jersey strange interpretation of the law has forced our New Jersey office to evaluate cabergoline. We have found this drug also in general to be effective. It seems that cabergoline must be given at least at a dosage of 0.5mg 2x per week and frequently 3 times per week to achieve clinical benefit. Though, in general, it seems somewhat less effective than dextroamphetamine, it has the advantage of having no prescribing restrictions. In the United States, patients treated with dextroamphetamine must be evaluated every 3 months whereas cabergoline only once per year. We plan on evaluating case 2 only once per year in conjunction with her annual check-up.

There are other states in the United States, e.g., California, that are very restrictive about the use of amphetamines but liberal about marijuana. Also, there are some countries other than the United States with great restrictions on the use of amphetamines. Furthermore, frequently there seems to be shortages of amphetamines and patients have to stop therapy for a period of time and frequently symptoms return. Thus, a good evaluation of cabergoline should be conducted as an alternative or to be used when there is a shortage of amphetamines, so patients do not have to abruptly cease dopaminergic therapy.

A search of the literature failed to find any previous cases of sesamoiditis treated with any dopaminergic drugs, and thus this is the first case report of the successful use of dextroamphetamines for this condition. The patient's presentation was so severe that the first treating physicians not only recommended not walking or putting any pressure on the foot for at least a week, but to start high dosages of methyl prednisone with quick tapering over a week to 10 days. Previously the patient had significant side effects with this treatment for a different condition, so she sought a second opinion from our group having knowledge of our use of dopaminergic drugs for various pain syndromes.

This case is unique because most other cases that we have treated have been relatively chronic with symptoms for at least a month before they received treatment. This is the first case where we actually treated a pain condition that was only 2 days old. The extremely good response to this type of drug (which is not considered an analgesic) further supports

the hypothesis that most pathological conditions, though manifesting in different ways and in different organ systems related to different etiologies, eventually cause the symptoms by allowing irritants into tissues which would otherwise be precluded, which then leads to the symptoms. Thus, there seems to be one universal type of treatment, dopaminergic drugs, e.g., dextroamphetamine and also cabergoline (although there has been less experience with this drug)[12, 19, 20]. Unfortunately, despite the long term high successful treatment with dopaminergic drugs in a variety of different conditions that were not responding to "standard" therapy (which in most cases used treatment that had a much lower safety profile than dopaminergic drugs), this benefit is not well known amongst treating physicians. It is hoped that by publishing interesting novel case reports, that this discovery could be corroborated by other physicians and could hopefully lead to more randomized controlled trials, which if confirming the beneficial aspects of dopaminergic therapy, will make this concept even more credible.

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