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Identification and Treatment of Complex Regional Pain Syndrome-Not Otherwise Specified (CRPS-NOS) with Peripheral Sympathetic Nerve Blockade: A Case Series

Case Series

Carden E[1], Fanning MT[2]*, Sparley K[2] and Horrigan J[2]

[1]*Southern California Academic Pain Management Institute/RSD Institute USA*

[2]*Tactical Sports Medicine Department, Southern California University of Health Science (SCU) USA*

***Corresponding author:** Michael T. Fanning, Tactical Sports Medicine Department, Southern California University of Health Science (SCU) USA E-mail Id: MichaelFanning@scuhs.edu

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Abstract

Introduction: Complex Regional Pain Syndrome (CRPS) is a pain condition that is often controversial in definition and treatment approach. While early identification of the disease process is important for treatment, current diagnostic criterium is particular on qualifying signs and symptoms. The restrictive nature the different consensus criterium may leave a patient without a diagnosis, and without effective treatment.

Methods: This case series details twelve patients that do not fall into the typical CRPS-I and II case presentation, diagnostic criteria and might not otherwise receive a CRPS diagnosis. These patients would more likely fall into a CRPS-NOS (not otherwise specified) diagnosis because they do not meet all of the criterium. Not considering CRPS-NOS as a diagnosis could ultimately lead to an inaccurate diagnosis, ineffective treatment, and poor long-term outcomes.

Results: During a fourteen-month period, patients that were experiencing multiple symptoms of CRPS were identified and referred to a CRPS specialist for confirmatory diagnosis and treatment. Each of the patients underwent a series of peripheral sympathetic nerve blocks which ceased, or at least significantly decreased, patient symptomatology.

Conclusion: This case series is a small sample size of patients that were successfully treated with a series of peripheral sympathetic nerve blocks and adjunct therapy for CRPS. CRPS is a difficult disease process to manage, often with invasive means of treatment such as sympathetic ganglion blockade, intrathecal pump, spinal cord stimulator and/or pharmacologics. Peripheral sympathetic nerve blockade can be a powerful diagnostic and treatment tool for patients suffering from CRPS.

Keywords: Complex Regional Pain Syndrome; CRPS, neuropathic pain; Sympathetic nerve blockade; Pain management

Introduction

Complex Regional Pain Syndrome (CRPS) is a pain condition that is often controversial in definition and treatment approach [1,2]. While early identification is important for appropriate and effective management [3, 4] there are different methods of diagnosis which may yield different diagnostic conclusions [5].

The most accepted diagnostic criterium is developed by the International Association for the Study of Pain (IASP), the "Budapest Criteria". The nature of this consensus criterium is to set a framework and standard for diagnosing CRPS [3, 4]. The challenge for clinicians is those patients who do not fit into typical CRPS presentation. These patients could be left without a diagnosis, or effective treatment, leading to long-term disability [6, 7].

The IASP Budapest Criteria states for a diagnosis of CRPS to be made patients[3]:has continuing pain which is disproportionate to any inciting event. The patient reports at least one symptom in three or more categories below, displays at least one sign in two or of the categories below and no other diagnosis can better explain the signs and symptoms. Categories include:

1. Sensory: allodynia and/or hyperalgesia
2. Vasomtor: temperature asymmetry, skin color changes/ asymmetry
3. Sudomotor: edema and/or sweating.
4. Motor/Trophic: decrease range of motion, trophic changes such as hair, nail, skin and motor dysfunction such as weakness, tremor, dystonia.

CRPS has two categories, CRPS-I and CRPS-II. Both present similarly but the precipitating event is different. CRPS-I usually develops after a noxious event and pain is often disproportionate to the inciting event with no specific nerve injury. CRPS-II is often precipitated after injury to specific nerve. In CPRS-II, an ephapse (neuroma) can often be identified [8]. Both types often have similar symptoms [2, 3, 4, 7].

CRPS should be viewed as a "disease on a spectrum rather than a binary option" [5, 7].

For patients who may not meet the strict diagnostic criteria of "Budapest" CRPS-I or CRPS-II, there is a third category: CRPS-NOS (not otherwise specified)[3]. CRPS-NOS includes patients that have some of the typical CRPS symptoms but may not meet all of the qualifying signs and symptoms, and there is no other explanation for their pain.

Furthermore, CRPS has two pain types: sympathethetically maintained pain and sympathetically independent pain [9]. "CRPS sympathetically maintained pain occurs together with swelling, hyperesthesia, allodynia, burning dysesthesia, and temperature, color, and trophic changes to the extremity. These signs and symptoms may be inconsistent, presenting not at all, alone or in any combination. However, any pain which is relieved by and is responsive to sympathetic blockade is by definition sympathetically maintained pain [9] ."

"CRPS sympathetically independent pain patients will present with classic symptoms and signs (CPRS)but will be unresponsive to sympathetic blockade. Although not entirely understood, a potential explanation for this phenomenon is that the disease process has become centrally maintained only [9]."

Lastly, CRPS can further be defined as "warm" or "cold": warm CRPS is characterized by a warm, red, edematous, and sweaty extremity while cold CRPS is characterized by a cold, blue, and less edematous extremity [10]. Warm CRPS is often associated with an acute bout of the disease process while cold is associated with chronic CRPS [10]. However, early stage cold CRPS findings are often associated with poor clinical outcomes [11].

The onset of CRPS has a distal predominance and is more common in females (4:1) compared to men. CRPS onset can be due to fractures, surgery, repetitive sprains/strains, burn injuries, limb immobilization (casting), penetrating injuries, or infection [2, 4].

Most common treatments for CRPS include sympathetic ganglion blocks, spinal cord stimulator, intrathecal pump,ketamine, gabapentin among other pharmacologics, and occupational therapy/ physical therapy [5]. Other, less conventional methods, include dextrose hydro dissection of effected nerves [20].

Methods

Patient data was obtained retrospectively from electronic health records review at the Southern California University of Health Sciences (SCU) Tactical Sports Medicine Clinic. The period of patient-clinician interaction began October 1, 2021, and ended May 1, 2023. All of the patients were diagnosed with CRPS-NOS at SCU and referred to the office of Edward Carden, MD (Carden). Per direct communication with Carden, he is a trained anesthesiologist and has specialized in treatment and management of CRPS for over forty years.

Utilizing the most common symptoms of CRPS, using Budapest Criteria as a guide, a clinical diagnosis of CRPS-NOS was made when a patient displayed two or more of the following: pain disproportionate to precipitating injury, temperature differences at the site of injury compared to the contralateral side(temperature was ascertained via an infrared thermometer, IP22 model FT-F41),poor range of motion at the affected limb, burning pain, hypersensitivity or allodynia, deep throbbing pain which often wakes at night, edema or swelling, discoloration, previous trauma, fracture and/or immobilization, trophic changes [2, 3, 5, 7, 9] mirroring pain [12], detection of possible ephapse was considered and could be helpful in diagnosis of CRPS-II [8].

An ephapse is a site, typically in the peripheral nervous system, where an abnormal, pathological synapse occurs between the somatic nervous system and the autonomic nervous system. The theory of an ephapse, or neuroma, is that it may generate ectopic activity to the dorsal horn [8]. Though this theory of CRPS is controversial, it should not be overlooked entirely.

CRPS pathophysiology has many hypotheses including an inappropriate inflammatory response, altered cutaneous innervation, central and peripheral sensitization, altered sympathetic nervous system function, and/or an increase in local circulating catecholamines [2, 9, 13]. These many hypotheses suggest that a multifaceted approach to care is imperative for mitigation of symptoms and treatment of the disease.

This case series highlights the importance of identifying the presence of CRPS-NOS in our patients, no matter how subtle the signs and symptoms. Once CRPS-NOS has been identified, an appropriate referral is made to a chronic pain management specialist for further evaluation. Each patient was then treated via peripheral sympathetic block with saline solution and a dilute Marcaine solution. The location of the sympathetic block was determined based on the suspected origin site of CRPS.

Administering location for each peripheral sympathetic block was

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determined by Carden based on each individual case presentation and his clinical evaluation. The injection was performed with a 27-gauge needle, ultrasound guidance and electrostimulation for needle placement. Unless otherwise specified, each injection contained 10 cc of saline and 0.025% Marcaine solution.

Adjunct therapy for the patient varied but included oral alendronate (75mg) [14, 15], clonidine patches (.1%) [16], and followed with manual therapy and therapeutic exercise when appropriate. Instituting therapeutic exercise into the management plan was approached judiciously as aggressive active care can often increase patient symptomatology [2, 4].

Results

Patient 1

A 25-year-old male presented to the office with right lateral ankle pain of five years. He reports chronic right ankle pain that has undergone three failed surgical procedures (1. syndesmosis repair, 2. anterior talo-fibular ligament repair and 3. exploratory surgery), pain management (cortisone injection, platelet rich plasma), acupuncture treatment, joint manipulation, and physical therapy. The patient would take 5000mg of ibuprofen per day to help alleviate his pain. The patient reported waking every night due to throbbing pain, he suffers burning pain, allodynia at the ankle, intermittent swelling and sweating at the ankle with atrophy of the right lower leg.

Examination findings include direct palation of the ankle led to immediate edema, perspiration and became cold to touch. The patient had restricted ankle range of motion compared to the uninvolved side. Additionally, light pressure palpationto a small area inferior to the fibula referred pain proximal to anteromedial thigh (possible phapse). Due to these findings, a referral was made to Carden.

Carden confirmed the diagnosis of complex regional pain syndrome with a peripheral sympathetic block on the right femoral nerve at the groin. Following the patient's initial injection, the treatment gave the patient 24-hours of complete pain relief, which was the first relief he had experienced in years.

The patient underwent a series of injections, in conjunction with oral alendronate (70 mg)once per week and 0.1%mg clonidine patches about the suspected ephapse, with management of symptoms. This patient's symptomatology drastically reduced, allowing him to sleep through the night and return to normal activities of daily living. He intermittently returns to receive a peripheral sympathetic block which can produce one full month without symptoms.

Patient 2

A 45-year-old female who had been under our care for a left fibular fracture began developing significant pain after she was taken out of a hard cast. The patient was in a hard cast for six weeks total. Once out of the cast CT imaging with 3D construction was performed. The CT revealed: "distal fibular oblique fracture demonstrating findings of partial nonunion. There is approximate 60% of healing at the fracture site." The patient was now experiencing pain disproportionate to a typical bone healing timeline.

The patient suffered nighttime throbbing pain, burning pain, and a sensation of swelling. Examination findings included focal allodynia about the site of previous fracture, while her symptomatic ankle was 31.1°C compared to 34.2°C on the contralateral side. Lastly, a suspected ephapse[1]was located that mirrored pain to the contralateral ankle [12]. Due to these findings, a referral was made to Carden where a sympathetic blockade was performed at the posterior tibial nerve.

Following the injection, the pain in the ankle reduced to 0/10 and the patient was then allowed to get up and leave. At that point, she had full range of motion in the toes, feet, and the ankle. She underwent a total of twelve injections, in conjunction with oral alendronate (70 mg) once per week and 0.1%mg clonidine patches about the suspected ephapse.

The patient remains symptom free 18 months later.

Patient 3

A 35-year-old male developed burning pain ten weeks post-left Achilles tendon debridement. The patient was placed in a hard cast for six weeks following surgery, and then placed in a controlled ankle motion (CAM) boot. During the time he was in a CAM boot, and beginning post-operative therapy, burning pain developed.

Clinical examination included discovery of an ephapse about the surgical incision site, direct palpation to this site mirrored his pain to the contralateral ankle [19]. The patient's left ankle temperature was measured at 31.2°C compared to 34.6°C right. Due to the increased pain level, burning pain and temperature difference, a referral was made to Carden.

Carden provided a diagnostic sympathetic block to the left ankle at the posterior tibial nerve, following the procedure, the patient reported eight hours pain free. The patient underwent a series of peripheral sympathetic blocks to the left posterior tibial nerve, with each injection giving the patient progressively longer periods pain free until the pain resolved.

The patient's management with Carden included oral alendronate (70 mg) once per week and local 0.1%mg clonidine patches. The patient's pain remained minimal, and he was able to participate in a full post-operative rehabilitation program.

Patient 4

A 29-year-old female presented to this facility with right upper extremity pain. The patient was involved in a motor vehicle accident (MVA) where multiple injuries were sustained. She was initially treated by another provider for cervical spine instability, concussion, and left rotator cuff strain. Due to her ongoing right shoulder pain, she was referred to this facility for a clinical work-up.

The patient had right shoulder burning pain, poor shoulder range of motion, specifically flexion and described "pain" at the right shoulder with light touch. During the examination, allodynia at the upper arm was found, the right shoulder temperature was measured at 32.4°C compared to the contralateral side of 34.1°C. Due to the dystonia, allodynia and temperature difference, a referral was made to Carden.

Just prior to her initial consult with Carden, she did undergo

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an MR Arthrogram of the shoulder and the most relevant findings included:

1. Mild to moderate supraspinatus tendinosis with small, focal low grade articular sided tearing at the posterior supraspinatus and anterior footprints. No full thickness tear or retraction is evident. Preserved muscle bulk. 3. Mild glenohumeral joint capsulitis. The patient reported that her symptoms increased after the gadolinium injection.

Carden provided diagnostic confirmation and treatment of CRPS with a right sided interscalene sympathetic block to the brachial plexus. The pain in the right upper extremity ceased while performing the injection. Immediately following the injection, the patient was able to perform full shoulder flexion.

She was given Alendronate 70 mg, one tablet weekly and Clonidine Transdermal Patch 0.1% mg, one patch weekly. The patient underwent a total of five interscalene blocks and thepain resolved as did the dystonia.

Patient 5

A 34-year-old female presented with chronic left knee pain. After a comprehensive history, physical examination, and MRI, the patient was diagnosed with Grade III jumper's knee [17] and posterolateral corner instability. She was referred to an extremity orthopedic surgeon and concurrently commenced care consisting of manual therapy, rehabilitation and PRP injection of the patellar tendon. The patient did not respond well to conservative care and ultimately required surgery to repair the patellar tendon and posterolateral capsule of the knee. During the post-operative rehabilitation process, the patient's passive and active knee flexion did not improve past 100° in the subsequent weeks and she began to complain of "extreme sensitivity" at the medial incision site with burning pain.

The physical examination revealed allodynia along the medial aspect of the left knee, and direct palpation to the incision site referred pain proximal (ephapse). The aforementioned dystonia of the left knee was present. Surface temperature of the left knee was 31.5° C and the contralateral side was 33.0° C. The patient was then referred to Carden.

Carden confirmed the diagnosis of CRPS by blocking the infrapatellar branch of the saphenous nerve with 3 cc saline/0.025% Marcaine solution. The patient did not have immediate improvement in the symptoms. However, at the next visit for post-operative therapy, the patient had a significant improvement in knee flexion to 120°, she reported a decrease in pain and symmetric temperature from right to left knee. The patient's CRPS symptoms did not return after one treatment.

Patient 6

A 34-year-old female developed post-operative "stinging" pain 10 weeks after left ankle arthroscopy to repair occult instability. The patient was placed in a hard cast for six-weeks post-operatively. Once removed, she was placed in a CAM boot for six additional weeks with little to no post-operative therapy. Once therapy began, during isometric exercise, she reported "stinging" pain at the lateral ankle about the incision site. This was closely monitored over a two-week period; however, the "stinging" pain began to wake her at night. She also reported an increase in pain after rehabilitation therapy.

The clinical examination revealed there was a temperature difference of 32.7° C and the uninvolved side was 34.1° C, and the left ankle was cold and clammy to the touch. Due to the increase in pain with exercise, "stinging" pain and temperature differences, a referral was made to Carden where a peripheral sympathetic block was performed to the posterior tibial nerve.

Immediately after injection the pain level reduced and remained absent for six days before returning, but at a lower level than previously. The patient commenced a series of six sympathetic blockades to the posterior tibial nerve. The patient was also be placed on Alendronate 70 mg, one tablet weekly and Clonidine Transdermal Patch 0.1% mg, one patch weekly through resolution of symptoms.

Patient 7

A 26-year-old male developed an abnormal amount of pain six weeks post-right knee arthroscopy. Prior to that development, the patient had been progressing on a normal post-operative trajectory. The knee range of motion was adequate, and he showed no signs of infection. The patient had ceased taking pain medication and completed the full course of doxycycline.

The patient began waking at night due to deep, throbbing pain. Allodynia followed at the anteromedial aspect of the knee, and his range of motion began to regress which is indicative of dystonia. In addition to these findings, his symptomatic knee was measured at 32.1°C compared to the contralateral knee at 34.6°C. A referral was made to Carden, due to the suspected diagnosis of complex regional pain syndrome.

Carden confirmed the diagnosis of CRPS with a peripheral blockade at the ipsilateral femoral nerve with a 20cc solution. Immediately following the procedure, the patient was able to ambulate normally without pain from the knee distal to the plantar aspect of the foot.

This patient underwent a series of thirteen peripheral sympathetic blocks utilizing the saline solution. It was observed that each block adehada compounding therapeutic effect, meaning each treatment typically lasted longer than the previous injection. The treatment began as oncer per week and evolved to oncer per month. The patient was placed on oral alendronate (70 mg) oncer per week and 0.1%mg clonidine patches about the suspected ephapse (ipsilateral knee).

Patient 8

A 45-year-old male developed deep, throbbing pain at night only, six weeks post-left knee arthroscopy. During the post-operative rehabilitation process, he successfully gained adequate range of motion at the knee. We closely monitored his symptoms once he informed us of his night pain. He also developed tingling about the knee.

During a re-examination a likely ephapse was located at one of the incision sites, it referred pain proximally to the anterior hip. Additionally, there was hypersensitivity about the infrapatellar branch

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of the saphenous nerve. No temperature difference was detected. The deep aching night pain was most problematic. Pain medication did not help with this pain. A referral was made to Carden.

Carden confirmed the diagnosis of CRPS with an injection to the posterior tibial nerve at the popliteal fossa. Following this injection, he stated the knee tingling, and the throbbing in the leg ceased immediately, and the numbness in two or three of the toes on the left side also disappeared.

Additionally, the patient was placed on oral alendronate (70 mg) once per week and 0.1%mg clonidine patches about the suspected ephapse. The patient underwent five peripheral sympathetic blocks and reported complete solution of symptoms.

Patient 9

A 54-year-old female developed intermittent burning pain four weeks post-right cubital tunnel release. The patient was undergoing successful post-operative therapy, which included manual therapy and range of motion exercises when she began to regress in her care. She then reported poor sleep due to deep, throbbing pain that would wake her at night. These symptoms did not improve with over-the-counter pain medication.

The patient began to experience abnormal hair growth and allodynia at the site of incision. She could no longer partake in post-operative therapy as most motions increased her pain level significantly. Her right forearm was 32.0°C while her left arm was 34.1°C.

The patient then began to report mirroring pain, consisting of the same symptoms in the asymptomatic arm. The patient was referred to Carden for evaluation.

Carden provided an ipsilateral inter scalene brachial plexus blockade. Immediately after the injection, the pain ceased inthe arm, elbow, wrist, hand and thereby confirming the diagnosis of complex regional pain syndrome.

Additionally, the patient was placed on oral alendronate (70 mg) oncer per week and 0.1%mg clonidine patches about the suspected ephapse. The patient underwent five peripheral sympathetic blocks and reported resolution of symptoms.

Patient 10

A 36-year-old male developed dystonia and a cold sensation at the right second finger post-traumatic distal phalanx amputation. During a motor vehicle accident, the patient suffered an amputation at the right second distal interphalangeal joint. The patient's wound was appropriately cleaned and managed with a prescription of anti-biotics at the emergency room. In the subsequent months, the patient developed burning pain, throbbing pain at night and difficulty flexing the entire finger.

Examination revealed that his right index finger was 33.1°C while the contralateral finger was 35.1°C. Dystonia was present in the affected finger. These findings coupled with the subjective findings warranted a referral to a chronic pain specialist.

Carden confirmed the diagnosis of CRPS with an ipsilateral brachial plexus blockade. Immediately post-injection the pain in the right hand diminished with improvement in range of motion of the digits of the hand. He could now close his fist while prior to the injection he could not.

The patient required two peripheral sympathetic blocks before resolution of symptoms.

Patient 11

A 44-year-oldfemale presented with sharp burning pain and swelling on the anterolateral left foot. The patient's ankle pain began after standing on her feet for a sixteen-hour shift. The patient has a history of a gunshot wound at the foot, and the bullet fragments were removed surgically two years prior.

Clinical examination revealed areas of hyper pigmentation and swelling of skin around anterolateral ankle. The right foot was 33.4^0C while the right foot was 32.1^0C.A likely ephapse was present at the dorsum of the foot at the 1-2 metatarsal space which radiated proximally to the lateral ankle with direct palpation. The patient was then referred to Carden for an evaluation and sympathetic blockade to the posterior tibial nerve at the knee.

Following peripheral sympathetic blockade, the patient reported complete resolution of pain. She underwent a series of these injections to the left posterior tibial nerve; each injection provided the patient longer periods pain relief.

The patient is currently undergoing continued care with Carden, which includes posterior tibial sympathetic nerve blocks once per week, oral alendronate once per week and local clonidine patches. The patient is now getting up to one week of full pain relief with each peripheral sympathetic block.

Discussion

This case series illustrates a repeatable method of clinical diagnosis, and a minimally invasive approach to confirm the diagnosis and manage CRPS. The first and most important aspect of the case series is clinical recognition of a patient with CRPS. Not confining our clinical judgment by the strict Budapest Criteria, each patient was clinically diagnosed with CRPS-NOS if they displayed two or more of the following: pain disproportionate to precipitating injury, temperature differences at the site of injury compared to the contralateral side, poor range of motion at the affected limb, burning pain, hypersensitivity or allodynia, deep throbbing pain which often wakes them at night, edema or swelling, discoloration, previous trauma, fracture and/or immobilization, trophic changes, mirroring pain [12], and/or presence of an ephapse.

The specifics of the peripheral sympathetic blockades are outlined with each patient interaction discussed above. The sympathetic blockade relieves symptoms of CRPS "by reducing circulating nor epinephrine" which "in turn (reduces) tone and output of the mechanoreceptors" [9]. With a decrease in mechanoreceptor output, there is now decreased input at the dorsal horn and spinal cord.

Adjunct therapy of Alendronate was taken once per week. While not fully understood, alendronate has been shown "effective in improving pain, physical function and oedema in patients presenting"

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with CRPS [14, 15]. Mani court et al. proposed the alendronate reduces "local acceleration of bone remodeling, (alendronate) might relieve pain by effects on nociceptive primary afferents in bone" [15]. Clonidine patches are placed around the suspected site of origin of CRPS as the "peripheral nerves generate ectopic impulses, which are sensitive to adrenergic agonist. These nerve terminals are inhibited from releasing norepinephrine upon adrenergic agonist binding" [16].

This is not a novel approach, thus have been multiple case studies published that document the efficacy of a peripheral nerve block for treatment of CRPS [18, 19]. Moreover, "Lam, Reeves and Cheng" utilize a dextrose hydro dissection method that has shown to be efficacious in treatment of CRPS [20].Prior to more invasive approaches to treating CRPS, we postulate that a less invasive route be explored for management of the disease.

Conclusion

Complex Regional Pain Syndrome can be debilitating for patients that suffer with the disease process, who often go years without an accurate diagnosis which can lead to long term disability and poor quality of life. We do not contest that utilizing the Budapest Criteria as a framework to help diagnose but recognize the strict nature and rigid adherence to it may leave patients without an accurate diagnosis. The signs and symptoms of CRPS can often be subtle. This case series outlines a group of patients with CRPS-NOS that have been managed via a series of peripheral sympathetic nerve blocks and adjunct pharmacologics followed by manual therapy while under the peripheral sympathetic block.

Treatment of CRPS is limited and the diagnosis is often contentious unless it meets the standards of the Budapest Criteria. Often, management of this disease process can be invasive with treatment such as pharmacologics and/or spinal cord stimulator. We postulate that treatment options for patients with CRPS symptoms should include a more conservative approach utilizing peripheral sympathetic nerve blockade as described in this case series.

While the literature is scant for this type of treatment method, high-quality research is needed to further demonstrate its efficacy.

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