Chronic Regional Pain Syndrome (CRPS) and Reflex Sympathetic Dystrophy (RSD) for Primary Care Professionals. How to Diagnose and When to Refer to a Pain Specialist

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Statement of Need

The frequency of occurrence of CRPS is unclear. A 2005 study of patients with fractures of the distal radius reported that CRPS type I developed in 18% of the cases. Another study of 162 soldiers wounded in the Iraqi war who were seen in pain clinics reported that 4.3% suffered CRPS type II and 1.9% from CRPS type I. In 1997, there was a study that looked at what percentage of the population suffered from neurogenic pain. The result was that approximately 1% of the population have neurogenic pain. A 2006 study indicated an overall incidence rate of CRPS at 26.2 per 100,000 person years (95% CI: 23.0-29.7). A 2003 study by Stanton-Hicks noted that women make up between 60-80% of the cases and the mean age at diagnosis is 42-years-old.

Misdiagnosis stems from a misunderstanding of the symptoms and the fact that there is no conclusive test to confirm or rule out the presence of CRPS. While there are several emerging therapies that show promise for treating CRPS, there are no universally accepted guidelines for what therapies should be used for which cases. These therapies include, but are not limited to immuno-inflammatory modulation, platelet rich plasma injection, spinal cord stimulation (SCS), sacral nerve root stimulation (NRA), hydrotherapy, and complementary and alternative medicine (CAM), Several new drugs including analgesics, calcitonin, and sympathomimetics have also been tried. This wide range of treatment options makes treating CRPS even more difficult.

Thus, clinicians need to know the signs and symptoms of the disorder and the impact early diagnosis and intervention can have for patients.

Intended Audience

This CME/CE activity is intended for practicing physicians, nurses, and other health care professionals who deal with primary care.

Learning Objectives

Upon completion of this activity, the participant should be able to:

1. Identify the clinical findings of CRPS (RSD).
2. Differentiate the classical stages of RSD from the continuum of clinical presentations that occur in CRPS.
3. Identify potential perpetrators or comorbid factors that may be associated with CRPS.
4. Assess the rationale for medical approaches to CRPS, including medication management, procedures, and physical therapy.
5. Identify new/upcoming therapies for treating CRPS.

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Background

Reflex Sympathetic Dystrophy (RSD), also known as Complex Regional Pain Syndrome (CRPS) Type I, is a chronic condition characterized by burning pain and abnormalities in the sensory, motor and autonomic nervous systems. [1] This chronic pain condition is believed to be the result of dysfunction in the central, sympathetic, or peripheral nervous systems. [1]

The sympathetic nervous system supplies all of the body structures — including muscle, tendon, ligament, dura, disk, synovium, bone, and even the internal organs. When one of these sites receives an injury, it's the sympathetic nervous system's job to monitor the injury and tell the spinal cord or the brain about it. Sometimes the sympathetic nerves forget to stop monitoring the injury.

This can be compared to a car engine that keeps on running (or dieseling), even after being turned off. When this happens to the sympathetic nerves, a very painful syndrome called Reflex Sympathetic Dystrophy (RSD) can develop. While Chronic Regional Pain syndrome (CRPS) is another term that is often used to describe this syndrome not all cases of CRPS involve the sympathetic system. RSD is anything but simple. Anyone afflicted with sympathetic pain should obtain a medical opinion and consult a doctor with specialized interest or training in sympathetic pain syndromes and obtain a medical opinion.

Introduction

When spraining an ankle, the first impulse is a sharp electric pain, and then that pain is replaced by a burning pain. While the sharp pain comes from the fast pain fibers, and the burning pain comes from the sympathetic nerve fibers. Normally the burning pain stops over time [3, 4]. Sometimes, however, the burning will not stop. In addition, the painful part may always feel cold, and sensitivity to cold temperature, rain, or falling barometric pressure can occur. If the condition becomes more severe, then the skin can become sweaty, change colors, and become painful to move. Patients develop a natural tendency to avoid touch by anyone or anything. This condition is Reflex Sympathetic Dystrophy (RSD) Stage 1.

With RSD there is a decrease in the local blood flow to the injury site (especially the structures in the surrounding skin), even after it should have healed. If allowed to persist, then the cold, sweaty, and swollen skin progressively gets worse until there is loss of range of motion or even loss of muscle mass. This is called Stage 2. In some cases the bones may thin as well (Stage 3).

RSD almost always begins after an identifiable event such as a crush injury, torn ligament, or fracture [5]. The initial injury may seem minor, or be severe. Since most health care providers are not familiar with the proper diagnosis of sympathetic pain, it is important for anyone with these complaints to be aware of it.

In most cases of RSD, the sympathetic nerve is felt to be overactive. Again think of it as if an engine was dieseling. In this case the sympathetic nerve stays on, even when the injury itself is old and no longer represents a new injury.

Diagnostic studies required for this disorder require a special expertise, so most doctors perform a sympathetic block to prove the diagnosis. This block is supposed to stop the dystrophic nerve fibers from dieseling, decrease pain, and increase blood flow, and decrease pain [6, 7].

Using sympathetic block as the sole diagnostic criteria, however, leaves a lot to be desired. Many people suspected of having RSD still complain of pain, even after the block has been performed. While doctors may display have a tendency to blame psychological factors when relief does not occur, there are clearly those who demonstrate no psychological overlay. They have obvious physical signs of injury and others who have persisted with their complaints in a consistently reliable manner over time. One explanation for this discrepancy is that sympathetic skin response studies, such as infrared medical thermography, are rarely used to assess the condition before, during or after a block is performed. As a result there may be no objective evidence that the intended block was in fact successfully accomplished.

Due to the lack of a gold standard for in diagnosis [4], and since diagnosis is difficult due to the possibility of symptom overlap [2], a complete medical history and physical examination are mandatory. The two diagnostic tests used to objectify the presence of RSD are three phase bone scans and medial infrared thermography (sympathetic skin response studies). While a positive bone scan is felt to be more specific for the diagnosis of CRPS/RSD, but the thermogram is more sensitive. Thermography measures sympathetic skin response by monitoring infrared recordable change in skin temperature. Skin Temperature is supposed to be within one degree centigrade from opposing sides of the body. When a significant, “asymmetric” pattern exists, the test is said to be positive. Although skin temperature is felt to be under the control of the sympathetic nerve fibers, a positive thermogram only means that there is an abnormal physiologic response to injury [8]. While it is readily discernable which anatomic injuries correlate to unique thermal asymmetry patterns, as with all objective physiological studies infrared medical thermology studies do not explicitly tell what structures are involved the underlying injury is that generated the response [9-12].

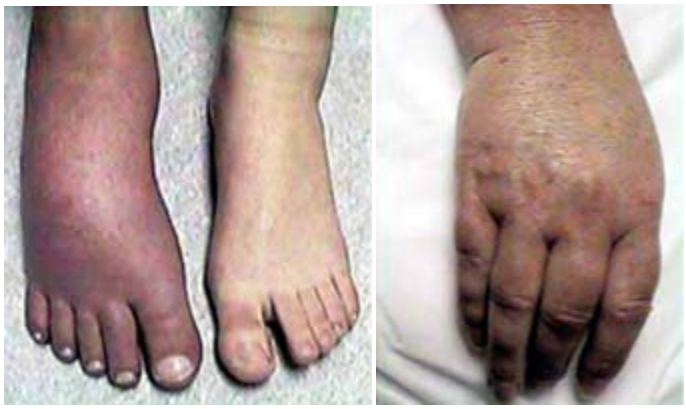
Quantitative sensory testing (QST) can also provide information about the sensory symptoms profile using psychophysical testing of thermal, pain and vibratory thresholds. Inherent limits to QST include limited distribution of measurement and patient response participation. However, there is no sensory profile that is characteristic for CRPS [4]. On the other hand, sympathetic skin response studies that allow the examiner to map the entire distribution of skin temperature changes measurements determine vascular function and may be helpful both in the diagnosis of CRPS/RSD and in ascertaining the generator of the abnormal sympathetic response. Due to the

wide diversity of sympathetic pain syndrome presentations it should not be assumed that there is a singular sensory or thermal profile that is characteristic for CRPS/RSD [4].

Determining the source, or generator of that asym sympathetic abnormality, can be a very complex task. If you believe you have a minor or major form of sympathetic pain, it is wise to seek the assistance of a medical doctor with specialized training in RSD. Once the type of RSD is diagnosed, and an investigation of possible underlying perpetrators is investigated has been completed, the reasons for its perpetration are discovered, there are many effective non-surgical and non-addicting interventions available that can provide relief.

Symptoms

Below are some typical presentations of patients with RSD.



RSD is typically classified into the following three classic stages and newly recognized non-classic stages: [2]

Stage 1	Stage 2	Stage 3
Lasting 1 to 3 months*	Lasting from 3 to 6 months*	Progression to point where changes to tissue are irreversible
Severe, burning pain	Pain intensifies	Pain is continuous, unyielding
Cold hyperalgesia- cold hurts. The afflicted feels excessive pain to cold.	Edema- swelling of the affected body part can occur.	Sudeks Atrophy - bone loss or thinning can occur
Rapid hair growth	Hair growth decreases	Mobility severely limited
Vasomotor changes - color changes. Red or blue skin color changes occur.	Nails become cracked, brittle, grooved, spotty	Contractions of muscles and tendons (limbs may be twisted)
Muscle spasms	Joints stiffen	Irreversible changes to skin and bone
Joint stiffness	Bones soften	
Sudomotor changes - sweating of the affected body part can occur.	Contracture - loss of range of motion, muscles atrophy (the muscles waste away).	Muscle atrophy
Sensitivity to cold, rain and barometric pressure	**Non-Classic stages that are now recognized**	
Sympathetic fiber hyperactivity - the sympathetic nerves are irritable or easily aroused.	1. Visceral somatic convergence – as a result of excess activity coming from the sympathetic nerves supplying the muscles, tendons, ligaments, or other tissues affected; there may be internal organ involvement (cardiac, ophthalmic, dental abnormalities can occur).	
Scleratomally mediated pain; the pain does not follow the pattern of a particular sensory or motor peripheral nerve or nerve root.	2. Motor Form of Dystrophy - movement disorders in the affected body part can occur.	
Thermogaphic change - infrared medical thermography can map the distribution and presence of skin temperature changes.	3. Spread - there may be spread of symptoms from the original body part affected to other body parts.	
Mechanical hyperalgesia - excessive pain to movement. Movement stimulates pain. Pressure from touch hurts.	*Most experts no longer feel that staging is time dependant	

Diagnosis

CRPS/RSD is diagnosed primarily through observation of the signs and symptoms. A high index of suspicion is required. But because many other conditions have similar symptoms and since most doctors are not expert in sympathetic pain syndromes, it can be difficult for doctors to make a firm diagnosis of CRPS/RSD early in the course of the disorder. W when symptoms are few or mild. Sympathetic skin response studies (thermology) are the most sensitive, objective measurement that can validate early changes. Or, for example, Even if thermographic abnormalities are present the search for other more easily treatable conditions should not be abandoned. A simple nerve entrapment can sometimes cause pain severe enough to resemble

CRPSRSD but may in fact represent a simpler case of CRPS. CRPS, if properly treated early, one can either arrest the painful response or, in cases with more severe or chronic disease, symptoms can be greatly reduced. Diagnosis is further complicated by the fact that three phase bone scans require up to 30% bone loss to be positive and relying upon sympathetic blocks ignores the presence of false negatives outcomes. Even more confounding is the fact that physical exam alone is not felt to be reliable and that rather progressing, some mild cases can people will improve gradually over time without any treatment [13].

One of the most important roles for diagnostic testing is to help rule out other more easily treatable conditions. Often there are several. For example there may be associated ligamentous strain in the presence of peripheral vascular disease and occult infection. Depending upon the case, Electrodiagnostic studies, Diagnostic Musculoskeletal Ultrasound, Physiologic and Duplex vascular examinations, MRI and laboratory can all be important.

Treatments

Because there is no singular cure for CRPS/RSD, doctors frequently focus treatment on alleviating the pain rather then trying to correct the root cause. Since CRPS/RSD patients are a subset of chronic pain patient's judicious use of opiates, with an eye directed toward their pitfalls, should be employed. Typical non opiate pharmacologic treatments include: [1, 15]

- Topical analgesics
- Antidepressants
- Corticosteroids
- Antiepileptics
- Antihypertensives & other cardiovascular related medications
- Hormonal agents
- Anti infectives
- Immunomodulating medications
- Atypicals

Other non-pharmacologic treatments may include (but are not limited to):

- Physical therapy – to restore ROM and function to the afflicted limb or body part and reduce hyperalgesia
- Psychotherapy – cognitive treatments that address the whole patient
- Sympathetic nerve block – anesthetics to block receptors or restore sympathetic nerve function
- Peripheral nerve block – for localized pain relief
- Trigger Point Injection- to relieve muscle related pain
- Joint Injection- to reduce intra articular sources of "C" fiber response
- Prolotherapy- to restore underlying ligamentous or tendon injury
- Platelet Rich Plasma (PRP) grafting – to induce an intensified, local wound healing reaction that may both restore normal anatomy and sympathetic physiology

As a last resort even more aggressive (and more controversial) treatments have included:

- Spinal cord stimulation – application of pleasant, tingling sensation to the painful area
- Intrathecal drug pumps to deliver opioids and local anesthetic agents via the spinal cord

- Surgical sympathectomy
- Ketamine coma induction

In conflict with these generally accepted treatment strategies, BMC Neurology recently published the findings of a group of Dutch researchers in their quest to develop multidisciplinary guidelines for treatment of CRPS [16]. The group (Perez R. et al.) found insufficient evidence that paracetamol, NSAIDS, oral opioids, morphine injection, local anesthetics, some anti-convulsants, anti-depressants, capsaicin, muscle relaxants, Botox, sympathetic block, amputation, TENS, multidisciplinary treatment or psychological treatment work.
Perez further uses Level 3 evidence to propose that:

- IV ketamine or corticosteroids might work
- Gabapentin might work in the first 2 months
- Two months of daily DMSO or NAC cream might help
- Calcium-channel blockers have some effect in acute CRPS
- Surgical sympathectomy can help some patients as can spinal cord stimulators
- Physiotherapy and occupational therapy probably help

Prognosis

While spontaneous remission can occur in certain individuals, most experience unremitting, crippling, and irreversible pain [1]. Patients should be counseled that the goals of treatment include quality of life management, aggressive intervention to prevent a worsening of condition or spread, and a hopeful eye toward reversing the lasting effects of chronic pain. Notwithstanding the above, with a greater understanding of the pathology, types, variants and subsets of sympathetic pain that are now identifiable (as per the ensuing content in this article) more patients can look forward to both pain reduction and symptom resolution.

Sympathetic Pain vs. RSD

There are many kinds of nerve fibers. Two that are easy to understand are the motor fibers, which let us move, and the sensory fibers that let us feel. Another important group of fibers that is harder to understand includes the sympathetic nerves. These nerves arise from ganglia, which are collections of the fibers located outside of the spinal cord. The ganglia function independently (automatically) from the rest of the nervous system.

The sympathetic nervous system is ubiquitous. From the ganglia sympathetic fibers travel to many places, including internal organs, coverings of the spinal cord (dura), intervertebral disks, muscles, tendons, joints, ligaments, skin and blood vessels. The job of the sympathetic system is to provide an independent neural network for functions that are intended to occur automatically and to provide the central nervous system with another mechanism of feedback.

Typically something goes wrong following an injury. The injury may be major or minor in severity. When you sprain an ankle, first you feel a sharp electric pain, and then you feel a burning pain. The sharp pain comes from the fast pain fiber, and the second burning pain comes from the sympathetic nerve fiber. Usually, over time, this burning pain will stop. This type of sympathetic pain is entirely normal.

Sometimes the burning will not stop. When this happens, people often have a hard time describing where their pain begins or ends, but usually can tell you that the cold or shifts in the weather make it worse. They may have noticed that since becoming hurt, the painful part always feels cold. As it becomes more severe, their skin can become sweaty, and they don't want to move the painful part (stage 1). When it is more severe still, they do not want anyone (or anything) to touch the involved area.

While most cases of CRPS/RSD begin in the limbs, the face and trunk can also be presenting sites. More commonly recognized examples of sympathetic pain syndromes in the head and neck include cluster headaches and atypical facial pains. Barre-Lieou describes a sympathetic pain syndrome including head and neck pain associated with nausea, vertigo, dysphagia and trouble swallowing. This syndrome is most commonly due to a traction injury of the posterior cervical sympathetic chain (and is hence sometimes referred to as the Posterior Sympathetic Pain Syndrome of Barre-Lieou).

When health care practitioners hear patients complain of weather sensitive or excessive pain (allodynia or hyperpathia) they should at least think about sympathetic pain syndromes as the underlying diagnosis. Since not all CRPS cases involve the sympathetic system, depending upon the full clinical and diagnostic work up a diagnosis of RSD (including mild to more severe cases) versus CRPS can be made.

Making the diagnosis of CRPS/RSD is important. Besides the significant impact upon quality of life, the potential physical deterioration that can occur is note worthy. In true RSD, there is a decrease in the local blood flow of the injured part. If allowed to persist, then the cold, sweaty and swollen skin of stage 1 can get progressively worse until there is loss of range of motion, or even loss of muscle mass (stage 2), or bones thinning as well (stage 3). As the disease progresses medical costs increase and the likelihood of maintaining employability falls dramatically.

Not all cases of RSD are alike. Subsets exist. In addition to the classically describe scenario where an overactive sympathetic system decreases blood flow to the skin in the area involved another subset where blood flow is increased exists. This has been referred to as the Angry Backfiring C (ABC) Syndrome. It occurs when the “C” nerve fiber type backfires and spits out excess histamines and other inflammatory cytokines. It is felt to be due to a back firing calcium dependant potassium channel. Thermographic studies show localized areas of warm, vasodilated skin.

Another variant is referred to as the Triple C Syndrome (CCC). In this instance the patients presents with Cold hypesthesia (they cannot readily differentiate between cold and pain), cold hyperalgesia, and cold skin. The CCC syndrome is felt to be due to hyperexcitability of the fast potassium voltage gate. Thermographic studies show regional areas of hyperintense cold skin.

Differentiating between subsets of RSD is important. For example, sympathetic blocks will not work, and may even make the pain worse, when the ABC (vasodilated) subset is present. Different pharmacologic regimens should be employed depending upon which presentation

exists. At least one kind of block, Electric Sympathetic Block, has been described that allows differentiation of the type of sympathetic block based upon the subset of sympathetic pain involved.

Despite the above, even among pain practioners today it is still common to perform sympathetic ganglion block to confirm the diagnosis of RSD. Since the block is supposed to shut the sympathetic system down, blood flow should increase and pain should decrease. If the expected response does not occur then the patient is frequently said to have psychological overlay. Many patients are labeled as having pain behavior to begin with. When it comes to measuring outcomes for patients with sympathetic pain this approach, by in large, has been a failure.

Diagnosis based upon response to sympathetic block alone fails to account for those patients who still complain of pain, have obvious physical signs of injury, and present in an entirely consistently reliable manner over time.

The most specific tests used to diagnose RSD remains the three phase bone scans. Because it is not very sensitive however many false positive cases for sympathetic pain occur if this method of measurement alone is used.

In order for a bone scan to be positive, there must be up to 30% bone loss. In addition there must be enough vasoconstriction (decreased blood flow) in the bone related tissues for it to be seen. Three phase bone scans may miss those address cases of RSD that do not involve non bone related tissues and will be falsely negative in early detection or mild disease.

Clearly, waiting for a positive bone scan is far too late to identify the majority of patients with sympathetic pain and early detection is preferred. While still underutilized, multiple types of sympathetic skin response testing including infrared medical Thermology, have increased our understanding of CRPS/RSD disorders, facilitated early diagnosis, provided valuable information for treatment strategies and filled the gaps inherent in other diagnostic methods. Fortunately there is now awareness that not all sympathetic pain patients have classical RSD and not all CRPS cases are due to RSD. There is also greater understanding of how to use diagnostic studies to categorize what type of sympathetic pain exist [17].

RSD with Dystonic Features

RSD with dystonic features represents yet another special category of sympathetic pain. In this case the patient develops both features of reflex sympathetic dystrophy and dystonia, a movement disorder. In mild cases there may be only a complaint of decreased balance or dexterity. In moderate cases there may be visible contractions of a single muscle (like a writer's cramp) and in more severe cases an entire limb may move about uncontrollably. These movements can be paroxysmal or continuous. They most often stop while asleep.

Signs of Motor Form of Dystrophy:

1. Decreased coordination and dexterity – Reduced skill in using one's hands or body. This is involuntary; it cannot be intentionally controlled. It is not the same as a "Tremor" — shaking you can feel and may or may not see.
2. Focal Myodynia – A form of dystonia (abnormal muscle tone). It is when a smaller groups or even individual fibers of muscle contract and then relax.
3. True Motor Dystrophy – Constant or rhythmic contraction of large muscle groups.

While no one really knows what causes dystonia, or why RSD patients get motor form of dystrophy, possible explantations include C fiber over-activity that results in "cross talk" to neighboring motor nerve fibers, the creation of peripheral muscle spindle/sympathetic efferent fiber reflex arcs (a feedback loop between muscle and nerve), defects in the brainstem routing allows reflex arc formation between peripheral muscle spindle and sympathetic nerve fibers, central biasing creates overflow of central activity and improper routing. When motor form of dystrophy is present, electromyographic (EMG) examination is helpful to identify which muscles are firing abnormally.

Sympathetic blockade rarely offers relief or, only temporary or minor at best when dystonia is present. Treatment instead must first be directed toward stopping the movement disorder (which itself causes further vasoconstriction, fatigue, and pain in the involved limb). Anti-Parkinson drugs, muscle relaxers, non-steroidal anti-inflammatory medicines, and Botulinum (denatured botulinum toxin) are best suited for this. Once the movement has been controlled, treatment of the underlying sympathetic response is more likely to be successful [18].

RSD and Spread

In the past it was controversial to suggest that RSD can spread from within the same body part or to different body parts [6,1]. One side of the camp feels quite strongly that spread is not uncommon. The opposite camp not only believes that spread cannot occur but that CRPS/RSD only presents as a localized syndrome that only affects the hand or upper extremity (this is clearly not the case).

Like most debates that have extreme points of view, the truth lies somewhere in the middle. More often then not if previously diagnosed CRPS/RSD patient complains of migrating pain the problem is due to something else and they have no objective evidence of sympathetic spread. Likewise there are clear cut cases where clear evidence for spread does exist. To simply assume that spread does not or has not occurred is a disservice both to the patent and treating physician.

Whenever RSD spread of any kind is suspected an aggressive clinical approach is warranted. It important to stop RSD from progressing and to identify what would otherwise be considered common pathology. The clinician should looks for objective findings such as vasomotor or sudomotor instability, edema, contracture, or at least hyperalgesia and weather sensitive pain [6, 20]. In the absence of convincing evidence in this regard, the new symptoms, while noteworthy, do not necessarily represent spread.

Probably more important than the debate of whether there is true spread of RSD is the

discussion of why these new symptoms are occurring.

A few notable explanations include:

- Neuro-humeral mechanisms (via transmitters such as epinephrine from both the nervous system and the adrenals)
- Increase regulation of both central and peripheral NMDA receptors [21, 22]
- Immune response to hidden infection (that once activated has no reason to stay localized to the injury site)
- Fascial winding (when the fascia either winds up on itself or in some fashion gets pulled, just like a tablecloth, and causes effects in distant places).

In those cases where co-morbid medical disease is found to be the etiology of the new complaint it should be treated in the typical fashion for that diagnosis. If spread of RSD has occurred treatment should be aggressive so as to contain the progression from one stage to the next and to minimize the distribution of involvement [17].

RSD, Fibromyalgia and Spread

While RSD and fibromyalgia are clearly distinct syndromes there can be overlap between the two disorders. Confusion as to the diagnosis can occur. Especially when there is an early stage sympathetic pain syndrome that presents with spread. Likewise, at the extremes the two diagnoses are rarely confused. Apart from having weather sensitive pain the typical stage III RSD patient with localized bone loss (Sudek's atrophy), contracture, muscle loss and trophic skin changes simply looks nothing like the non localizing, chronic fibromyalgia patient.

But what about the early or stage one CRPS/RSD patient whose chief complaint is weather sensitive pain that never shows progression through the classical stages? With few objective physical findings there can be confusion between their presentation and a fibromyalgia patient, especially if they start to complain their RSD has spread. In the end there may in fact be some convergence of the two syndromes as the vast majority of fibromyalgia patients suffer from weather sensitive pain as well.

Despite the overlap of presenting symptoms in this situation the two diagnoses for the most part can still be differentiated. The RSD patient's chief complaint will center around abnormal pain response to changes in barometric pressure, moving weather fronts and extremes in temperature (in the vast majority of RSD cases cold is much more problematic then warm, but some cases of warm sensitivity do exist). While the RSD patient with spread may share signs of "brain fog", difficultly sleeping and even report somato visceral complaints, their chief compliant still centers around pathology that can be traced back to an abnormally functioning sympathetic, or "C" , nerve fiber.

In contrast the fibromyalgia patient will only have weather sensitivity as a feature in their overall presentation. They may be able to clearly state that they have weather sensitive pain, but it will be just one of a plethora of complaints. Other differentiators for the fibromyalgia patient include the typical absence of an inciting event that is almost universally present in the RSD patient, and the dominance of another typical fibromyalgia characteristic such as sleep disorder,

emotional issues, an underlying form -fruste immunological complaint or associated visceral symptoms.

The fact that overlap between RSD & fibromyalgia does exist is simply another good reason to aggressively evaluate the RSD who complains of spread, even if they only have mild disease. To further confuse the situation, over time it is not uncommon for sympathetic, C fiber related symptoms to finally burn out, even in RSD patients. While this creates a sympathetic independent pain syndrome that can remain localized (and still meets the criteria for CRPS) if complaints become global the patient for all intensive purposes shares the typical presentation of a fibromyalgia patient. None the less, once an RSD patient has been given a diagnosis of RSD they always carry that diagnosis.

It should also be recognized that a Fibromyalgia patient's symptoms might progressively worsen to the point that sympathetic pain becomes their dominant complaint. In such an instance the fibromyalgia patient can look more like an RSD patient. These patients rarely, if ever, progress through the classical stages of RSD and almost universally retain some other typical fibromyalgia symptom such as interstitial cystitis or irritable bowel.

Although there can be considerable overlap between patients with sympathetic pain who do not develop full blown RSD and Fibromyalgia patients who are weather-sensitive pain, in the majority of cases a skilled clinician should be able to differentiate between the two conditions.

RSD Subsets

The Angry Backfiring "C" Syndrome

The Angry Backfiring C Syndrome (ABC) occurs when the sympathetic nerve fiber becomes angry, or backfires (like a car engine) in response to an underlying injury (usually ligament or other soft tissue).

The nerve itself spits out various vasodilating chemicals such as substance "p", kinins and histamine. These chemicals inflame the tissues and cause pain. In addition, the C-fiber itself becomes hypersensitive because of its own actions. The ABC syndrome is felt to be due to an aberrant firing of the calcium dependant potassium channel (voltage gate).

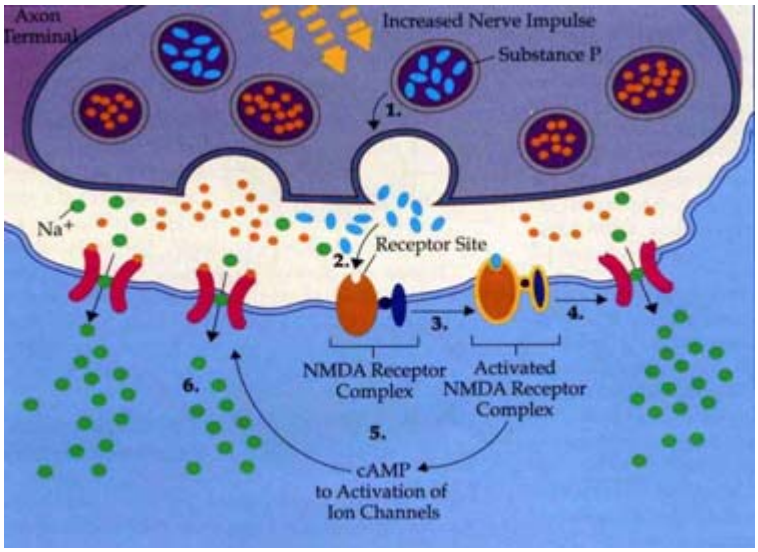
When someone sprains an ankle, it would not be surprising if he complained of continued burning pain afterwards. It is also easy to imagine the ankle becoming warm, swollen, discolored, and painful to light touch. It is the vasodilating chemicals that cause this to occur. This is entirely normal, however, if persistent sympathetic pain develops and localized vasodilatation is seen on sympathetic skin response testing such as medical infrared thermography then the physician should suspect, it is called the ABC syndrome.

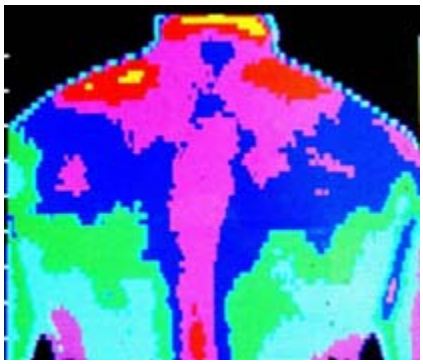
The ABC syndrome does not represent a subset of a true RSD pathology. Thermographic examination shows localized instead vasodilatation instead of widespread vasodilatation. P, and patients are often much more usually responsive to d quite local treatment (such as well to ligamentous injection, physical therapy, orthotics, etc) as compared to other RSD presentations. In addition, or the use of vasoconstricting medications (such as inderol) maybe paradoxically

effective (most RSD cases are felt to have excess vasoconstrictor tone).

Treatments such as capsaicin cream, which reduce neuro-immuno-inflammatory responses, can also be quite helpful. In the ABC syndrome, sympathetic blockade often does not work, and in fact only makes the problem worse (by vasodilating the area further).

The ABC syndrome should be thought of whenever someone fails to respond to sympathetic block or who say the block made them worse.





SYMPTOMS OF ABC SYNDROME

1. Erythralgia - redness of the skin.
2. Alodynia - light touch is painful.
3. Warm hyperalgesia - warm hurts.
4. Cold abolishes the pain.
5. Pain burns - patients feel as if they are burning when experiencing pain.

The Triple C Syndrome (Triple Cold Syndrome)

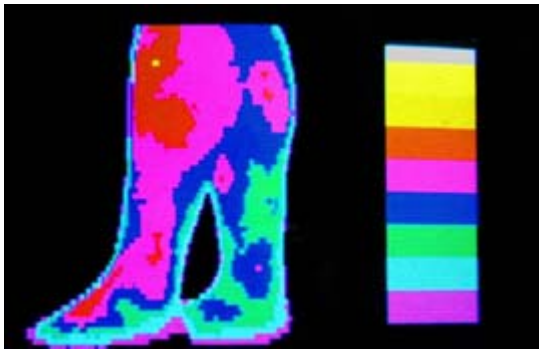
The term triple cold syndrome is used to describe the subset of RSD patients that present with cold hyperalgesia, cold hypoaesthesia, and cold skin. There is a mechanism of sensory disinhibition, where diminished cold-specific A delta input releases cold pain input carried by C nociceptors (patients do not feel cold but rather feel pain when exposed to something like ice). This is proposed to explain the hyperalgesia. In most patients, the symptomatic skin is abnormally cold. This is a likely consequence of vasospasm, due to sympathetic denervation supersensitivity, caused by dropout of sympathetic efferents as part of the small caliber nerve fibre insult [23]. A hyperexcitable, fast potassium voltage gate has also been implicated.

The Triple C (CCC) Syndrome occurs when the C fiber, by reflex becomes super sensitive to an underlying injury. Since “C” and "A delta" fibers share similar physiologic characteristics most patients with sympathetic pain are sensitive to vibration, and therefore complain that driving or

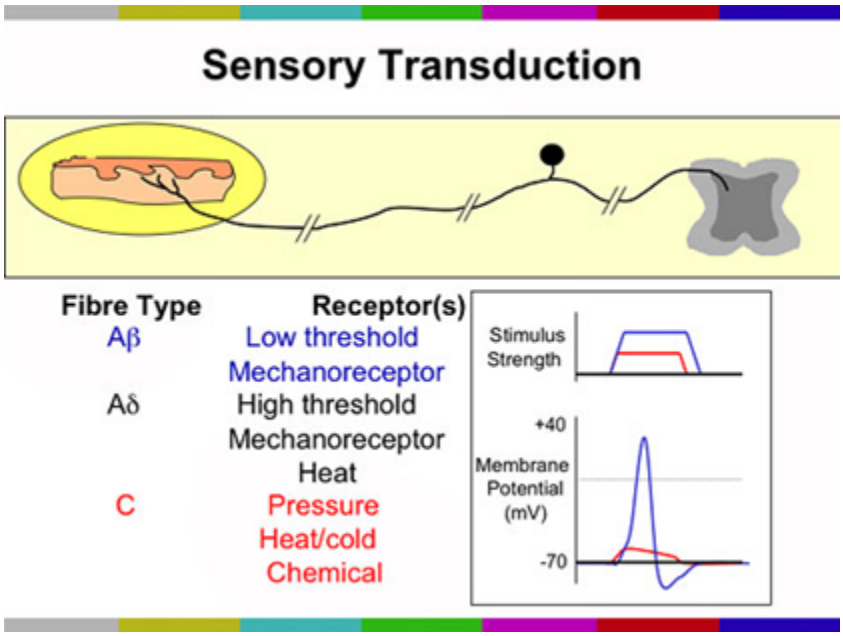
operating any machinery that vibrates makes them worse. When a CCC syndrome occurs this sensitivity is even further enhanced.

Patients with CCC syndrome in effect report that (1) cold is painful, (2) cold burns and (3) that they have cold skin. Since the C fiber is intensely overactive at the injury site there is marked, localized or regional vasoconstriction seen on infrared Thermographic examination.

Medical Thermology studies are read by looking for temperature asymmetry patterns. Each color in the palette represents a one degree centigrade change from its neighbor on the color tool bar. The top of the tool bar is warmest and the bottom is coldest. CCC syndrome patients demonstrate obvious, localized regions on relatively cold skin temperature.



Localized or regional vasoconstriction through thermographic exam



Sensory transduction sensitivity is based upon the fibre type.

Typical symptoms of patients afflicted with triple c syndrome include:

1. Cold hypoesthesia - patients don't feel the cold. They cannot distinguish cold from pain.
2. Cold hyperalgesia - cold hurts
3. Cold skin
4. Pain burns

Traditional Sympathetic blockade is less effective with CCC patients versus classical RSD patients as the vasoconstricted area is most often in the foot or hand (farther from the trunk). This means a more deeply penetrating and complete block must be performed to influence the dystrophic site. In addition, once the block wears off, the C fiber remains more intensely hyperactive as compared to classical cases of RSD so it is more resistant to remedy. As a result, in addition to sympathetic blockade treatment should be directed toward peripheral nerve block (that may still be “C” fiber selective) closer to (but still above) the injury site. Electroceutical applications of sympathetic block have been described that try to target the actual voltage gate or channel involved [24, 25].

To confound the treatment of RSD patients further it should be pointed out that not all patients present with simply classical RSD or one of its variants or subsets. Rather a combination of subsets or variants can exist in the same patient. As a result physicians should consider various nerve membrane stabilizing medications (such as lyrica or lidoderm patches) and make use of their training in voltage gated receptor pharmacology rather then simply prescribing analgesics that do not address the underlying problem.

RSD Variants

RSD variants represent one of the most recently recognized forms of reflex sympathetic dystrophy.

There is yet another special form for RSD referred to as Barre-Lieou as well. In this instance a traction injury of the posterior cervical sympathetic chain results in complaints of pain, dizziness, tinnitus, blurred vision and nausea. While traction injuries (as in whiplash) to the posterior cervical chain are the most common etiology for Barre-Lieou, other causes include local trauma, chronic infection or even coagulopathies. In some cases the sphenopalatine or the superior cervical sympathetic ganglia may be involved instead of the posterior cervical chain.

While other examples exist, cluster headache is commonly recognized form of autonomic pathology where both the internal organs and musculoskeletal system are involved. The literature is filled with references that implicated vasoactive peptides at the arteriole in multiple forms of headache. Due to its diffuse nature the humeral neuro-immuno-endocrine system has been offered as an explanation. Finally, Hoffman’s zones (regions of aberrantly behaving sympathetically innervated venous valves), have been implicated. In the end there is no unifying explanation for spread of RSD to visceral organs.

Treatment of an RSD variant is most difficult. It is usually best to focus intervention onto the portion of the sympathetic system cephalad to the initial injury site and to encourage mobility. Success in controlling internal organ system symptoms has also been accomplished through sympathetic block to the ganglion that impacts the organ affected, through the use of

medications that help stabilize autonomic function, correct neurotransmitter imbalance or assist hormonal regulation.

RSD & Visceral Involvement

It has been postulated that musculoskeletal RSD can affect the internal organs [26]. While it is generally accepted that internal organs can refer pain to the musculoskeletal system not everyone agrees that the internal organs can be impacted by the musculoskeletal system. None the less the occurrence of somato-visceral interaction is not a new concept. Furthermore it easily explains aberrant autonomic effects of internal organs that have been reported dystrophy patients. The most common viscera affected include the heart and eyes. Signs of autonomic involvement include heart failure, rapid heart rate, and blurred vision. Other reported visceral effects include change in bowel, bladder and sexual function.

Although the autonomic nervous system is ultimately ubiquitous and acts as a conduit between the, musculoskeletal system and viscera it does not necessarily provide a direct connection between them. Rather a distant form of feedback comes into play. Think of a cell phone tower that has a short or static emitting from within it such that any phone within range of the network is affected. Other indirect methods of communication between the two systems exist. These include hypothalamic biasing and body-wide hormone and neuro-transmitter responses to altered autonomic activity.

Ophthalmic, cardiac, hormonal, and dental system involvement should be carefully considered as a complication of Reflex Sympathetic Dystrophy (RSD), especially when a clinical presentation occurs where ophthalmic, cardiac, hormonal, or dental systems become involved, and the only discernable etiology for their involvement was the pre-existence or RSD.

Due to the autonomic innervation of the eye, patients with RSD not uncommonly complain of difficulty with dry eyes or blurred vision. In some instances accommodation, the eye’s ability to focus on images at varying distance is impaired. In others, the tearing mechanism is altered. Pupilary function can become sluggish as well. While these problems may wax and wane in concert with exacerbations and remission of pain, there does not need to be a direct correlation.

Cardiac abnormalities most commonly include arrhythmias (due to the dependency of the heart on the autonomic system for proper pacing and rhythm) and low ejection fraction related to heart failure. This should not be surprising as the sympathetic system modulates heart contractility, left ventricular wall tension, vascular tone, and impacts left ventricular remodeling or hypertrophy.

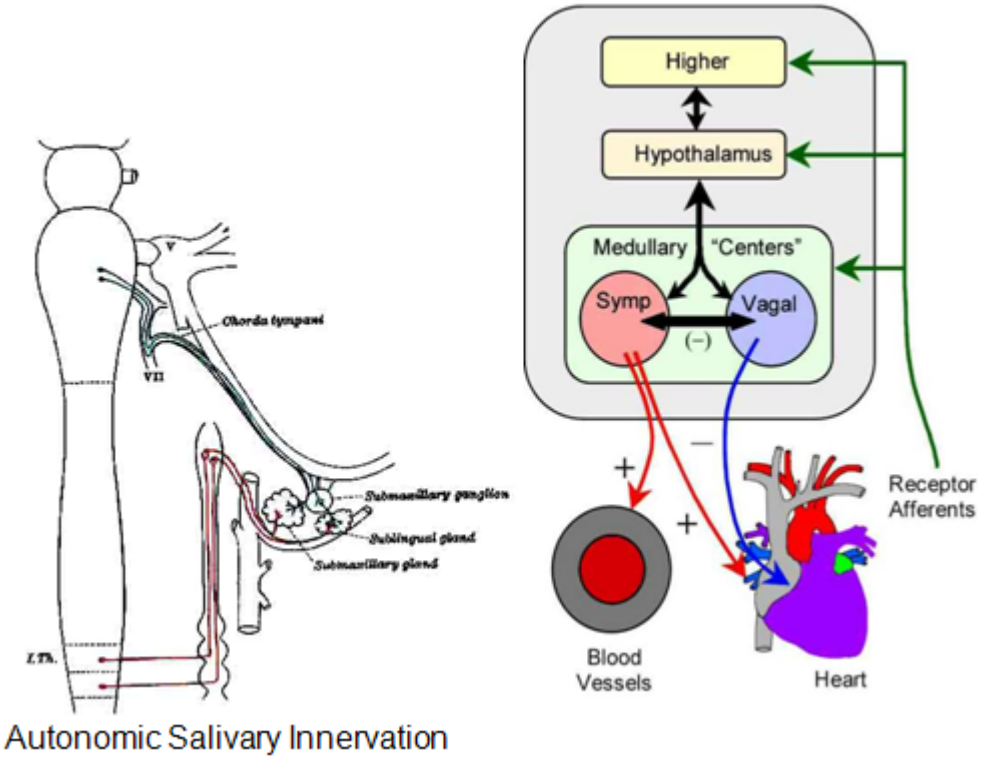
Heart failure is associated with reduced norepinephrine responsiveness. The body commonly reacts this way when prolonged or abnormal amounts of circulating neurotransmitter occur. Further more heart failure responds to treatment with Carvedilol, a medication that prevents the release of norepinephrine. The mechanism of action and response to therapeutic intervention are both quite consistent with a clinical condition generated by RSD.

The sympathetic nervous system is also known to be involved in feedback loops with the Renin-

Angiotensin system of the kidney, the androgen hormones, and the pituitary-hypothalamic axis. It stands to reason that complaints of fatigue, decreased libido, and diminished ability to deal with stress should be expected in the presence of RSD. Clinical practice in fact bears this out, often in patients who never had these symptoms prior to the onset of pain.

Many patients with RSD are worried about having dental procedures performed. Most dentists use epinephrine with local anesthetic, so the fear that their dystrophy may be worsened by the procedure has some justification. While sinus, gingival and tooth infection can all worsen RSD symptoms, the altered saliva content, viscosity and volume associated with aberrant sympathetic function probably play a grater role in creating these conditions to begin with. Medications used in the treatment of RSD may further worsen the situation.

Naturally, when any organ system becomes involved, a physician with expertise in the treatment of RSD and who has a longstanding relationship with that patient can help distinguish those cases that are due to RSD. When other causes are not evident, and the underlying condition is consistent with RSD as an etiology, ophthalmic, cardiac, hormonal, and dental system involvement should be carefully considered as a complication of Reflex Sympathetic Dystrophy (RSD).



Autonomic Salivary Innervation

In addition to any of the previously noted treatment approaches for RSD, when internal organ involvement occurs specific symptom intervention, such as cardiac enhancing medications or

pacing devices, artificial tears and duct correction procedures for dry eyes, and the use of epinephrine free xyolcaine for dental procedures are important.

Conclusion:

As with most medical conditions treatment directed toward the underlying pathology as opposed to symptom management portends a greater understanding of the patient's condition. With an increase awareness of the symptom source improved outcomes can be expected during treatment. Not all cases of CRPS have RSD and not all cases of RSD are the same. There are different stages, types, variants and subsets of sympathetic pain that have been identified. Rather then treating all cases from a symptom only point of view the physician should work toward identifying these differences and tailor care toward the individual needs of their patient. With this approach reversal of RSD, RSD in remission, improved functional outcome, or better quality of life can be achieved.

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