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CLINICAL REVIEW AND PATHOPHYSIOLOGY: CRPS

Complex regional pain syndrome—1: history, diagnostic criteria and etiology

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Abstract Physical therapists and other health care providers frequently evaluate and treat patients with complex regional pain syndrome (CRPS). The term CRPS replaces the previous terms reflex sympathetic dystrophy (now referred to as CRPS Type I) and causalgia (CRPS Type II). Part 1 of this paper describes the diagnostic criteria for CRPS and the clinical features and etiology of both CRPS Types I and II. CRPS is a multifactorial syndrome with overlapping symptoms. Although much progress has been made in the understanding of CRPS, many questions remain unanswered. CRPS is probably a disease of the central nervous system. Yet, peripheral inflammatory processes, abnormal sympathetic-afferent coupling, and adrenoreceptor pathology may also be part of the picture. It is likely that in the near future the current concepts of CRPS will be replaced by a new mechanism-based term or group of terms leading to improved clinical guidelines. Part 2 in this series reviews the physical therapy management of patients with CRPS.

Introduction

Complex regional pain syndrome (CRPS) is characterized by pain, abnormal regulation of blood flow and sweating, edema and trophic changes of skin and subcutaneous tissues, and active and passive movement disorders (Harden et al., 2001; Jänig and Stanton-Hicks, 1996). Patients with CRPS are frequently referred to physical therapy and physical therapy has been widely recommended as one of the most important components of the treatment plan (Harden, 2000; Kemler et al., 2001; Lee and Kirchner, 2002; Rho et al., 2002; Stanton-Hicks et al., 1998; Viel et al., 1999). Physical therapists need to be familiar with the current thinking about CRPS and the implications for physical therapy interventions. Part 1 includes an historical overview, describes the current diagnostic criteria, outlines the differences between CRPS I and CRPS II, and reviews different possible etiologies. Part 2 describes the current evidence for physical therapy management of patients with CRPS with suggestions for treatment interventions. Although the articles are written primarily from a physical therapy perspective, they are also of interest to other health care providers.

Historical overview

The first description of CRPS may date back to the 17th century when surgeon Ambroise Pare reported

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that King Charles IX suffered from persistent pain and contractures of his arm following a curative bloodletting procedure (Pare, 1634). During the Civil War, Mitchell described several cases of soldiers suffering from burning pain secondary to gunshot wounds, that he referred to as causalgia (Mitchell, 1872; Mitchell et al., 1864). In 1900, Sudeck described complications of trauma to the limbs, characterized by therapy-resistant pain, swelling, and limitations of motor function (Sudeck, 1900). For many years, the syndrome was referred to as Sudeck's atrophy especially in European countries. Other names that were used include minor causalgia, post-traumatic pain syndrome, post-traumatic painful arthrosis, Sudeck's dystrophy, post-traumatic edema, reflex dystrophy, shoulder-hand syndrome, chronic traumatic edema, algodystrophy, peripheral trophoneurosis and sympathalgia, among others.

In 1916, Lerich suggested that causalgia was caused by excessive activity of the sympathetic nervous system (Leriche, 1916). In 1946, Evans proposed the name reflex sympathetic dystrophy (RSD), based on Livingston's hypothesis of the presence of sympathosomatic coupling. (Evans, 1946; Livingston, 1976). Bonica adopted this term in the first edition of his classic textbook "The Management of Pain" and added that the syndrome appeared to develop through several stages, a concept that was later rejected (Bonica, 1953). In 1986, Roberts introduced the term sympathetically maintained pain (SMP) as a synonym of RSD, based on the observation that blocking the sympathetic nervous system often resulted in a significant improvement or even remission of symptoms (Roberts, 1986). Roberts suggested that in RSD the sympathetic nervous system was the primary driving force of the syndrome. To confirm the clinical diagnosis of RSD or SMP, a positive analgesic response to sympatholysis was considered necessary (Raja et al., 1992). Yet, there were many patients who did not respond favorably to sympathetic blocks, but had most of the symptoms of RSD. Campbell and colleagues used the term sympathetically independent pain (SIP) to describe pain states similar to RSD that did not respond well to sympatholysis (Campbell and Meyer, 1992). Increasingly, the role of the sympathetic nervous system in these pain states was questioned and became a controversial topic (Stanton-Hicks, 2000a, b).

In an effort to clarify the mechanisms, nature, diagnosis, and treatment of RSD and causalgia, the Special Interest Group "Pain and the Sympathetic Nervous System" of the International Association for the Study of Pain (IASP) developed a set of criteria during a 1993 consensus meeting in Florida. Participants of the conference agreed that each component of the term RSD was problematic. If reflex patterns were involved at all, they would have to be complex and multisynaptic. The role of the sympathetic component became increasingly less clear, as it became known that the sympathetic nervous system may or may not be causative or even perpetuate the problem. Furthermore, true dystrophy rarely occurred (van Hilten et al., 2001; Veldman et al., 1993). The international team of experts agreed to the term complex regional pain syndrome (Jänig and Stanton-Hicks, 1996). As Stanton-Hicks and Boas explained, the term CRPS was chosen for several reasons:

- *Complex* expresses the varied clinical features within a single person over time, as well as the features of inflammation, autonomic, cutaneous, motor, and dystrophic changes.
- *Regional* reflects that most cases involve a particular region of the body; pain can expand beyond the area of the initial lesion.
- *Pain* is essential to the diagnosis of CRPS; pain can be either spontaneous pain or evoked, such as allodynia or hyperalgesia.
- *Syndrome* indicates that the signs and symptoms of CRPS are a series of distinct correlated events (Boas, 1996; Stanton-Hicks et al., 1995).

In spite of the new criteria and taxonomy, the clinical approach to patients with CRPS remains difficult and largely empirical. Although Dr. Pare claimed to have cured King Charles IX in the 17th century, nearly four centuries later, and a decade after the new criteria were developed, the search for effective treatment remedies continues (Fox et al., 2001; Kingery, 1997; Schmid et al., 2002). This paper aims to review the criteria for CRPS, the common signs and symptoms of the syndrome, the potential mechanisms of CRPS, and the implications for the development of evidence-based physical therapy interventions.

The CRPS criteria

Participants of the 1993 consensus meeting agreed that the use of the term RSD was no longer useful and accepted the need for the development of new concepts and nomenclature. The new term—complex regional pain syndrome—encompasses both RSD and causalgia. RSD is now referred to as CRPS I. Causalgia has become CRPS II. SMP and SIP are no longer considered an essential component of any one condition, but may be a feature of several types of pain disorders.

The new guidelines were accepted with only marginal modifications by the IASP Task Force on Taxonomy (Merskey and Bogduk, 1994). Even though the IASP recommends adhering to the guidelines, Reinders and colleagues concluded that the IASP diagnostic criteria are not used uniformly in their analysis of 92 published studies and review articles on CRPS I. In fact, none of the 65 included original research articles satisfied the IASP criteria (Reinders et al., 2002). Van de Beek and colleagues came to a similar conclusion. Most studies of RSD and CRPS used vague sensory and autonomic criteria, and neglected the presence of motor features. There has been no noticeable difference since the introduction of the new criteria (van de Beek et al., 2002).

According to the new nomenclature, CRPS "describes a variety of painful conditions that usually follow injury, occur regionally, have a distal predominance of abnormal findings, exceed in both magnitude and duration the expected clinical course of the inciting event, often result in significant impairment of motor function, and show variable progression over time" (Boas, 1996). The subsets of CRPS are defined as follows:

- CRPS I (RSD) follows an initiating event; features spontaneous pain or allodynia/hyperalgesia beyond the territory of a single peripheral nerve(s), and is disproportionate to the inciting event. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity, in the region of the pain since the inciting event. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.
- CRPS II (causalgia) is similar to type I with the exception that CRPS II follows nerve injury. CRPS II is a more regionally confined presentation about a joint (e.g. ankle, knee, wrist) or area (e.g. face, eye, penis) associated with a noxious event. Spontaneous pain or allodynia/hyperalgesia is usually limited to the area involved, but may spread variably distal or proximal to the area, not in the territory of a dermatomal or peripheral nerve distribution. CRPS II features intermittent and variable edema, skin blood flow changes, temperature change, abnormal sudomotor activity, and motor dysfunction, disproportionate to the initiating event.
- CRPS III was created for "those difficult cases that contained pain and sensory changes, with either motor or tissue changes, but not comply fully with the more classical forms" (Boas, 1996).

Although CRPS I and II may overlap considerably, there are important differences. CRPS II is by definition a neuropathic pain syndrome; it is unlikely that CRPS I is a neuropathic pain syndrome (Jänig and Baron, 2002). CRPS II may develop after trauma with clearly detectable peripheral nerve or plexus injury. CRPS I patients rarely have a detectable peripheral nerve injury. The injury may be remote from the affected extremity and involve a lesion in the deep somatic tissues, visceral tissues, or the central nervous system (Jänig and Baron, 2002). Some researchers have suggested that myofascial pain syndrome may be a contributing factor in the development of CRPS I (Allen et al., 1999; Imamura et al., 1997; Mense and Simons, 2001; Rashiq and Galer, 1999).

Stages of CRPS

The consensus team rejected the notion that specific stages of progression of CRPS can be identified, even though some authors continue to include Bonica's stages of progression in their reviews of CRPS (Hendler, 2002). Bonica identified an acute, dystrophic and atrophic stage (Bonica, 1953). The acute stage was said to last 3–6 months, and was characterized by pain, tenderness, swelling, and vasomotor changes. The dystrophic stage, lasting another 3–6 months, had significantly more trophic and motor changes, more pain and sensory dysfunction, and continued evidence of vasomotor abnormalities. During the dystrophic stage the skin would shift from warm to cold. The atrophic stage was considered a permanent stage with marked skin and bone atrophy, severe muscle contractions, but with less pain and sensory disturbances. The consensus team concluded that there was insufficient data to support valid distinctions between stages, and therefore a universally acceptable standard of grading was rejected at that time (Boas, 1996).

Several research groups have since provided evidence against the presence of sequential stages. Veldman and colleagues failed to identify a three-stage progression in a prospective 8-year study of 829 subjects (Veldman et al., 1993). They did establish that persons with longstanding CRPS were more likely to have a cold limb. However, several early-stage patients also presented with cold limbs, while many late-stage patients had warm limbs. Veldman and colleagues did not find much evidence of tissue atrophy and osteopenia (Veldman et al., 1993). During a second IASP conference on CRPS in 2000 in Cardiff, Wales, new research, experiences,

and opinions were reviewed. The concept of staging was again rejected (Harden et al., 2001). Bruehl and colleagues used a cluster analysis technique to test the evidence of sequential stages of CRPS in 113 subjects and found no support for the staging concept either (Bruehl et al., 2002). Instead, three statistically distinct possible subtypes of CRPS were identified:

1. a relatively limited syndrome with vasomotor signs predominating;
2. a relatively limited syndrome with neuropathic pain/sensory abnormalities predominating; electromyographic and nerve conduction tests suggested that this group may in fact be CRPS II;
3. a CRPS syndrome similar to ''classic RSD'' descriptions. This group featured the highest levels of motor and trophic signs and possible disuse-related changes (osteopenia) on bone scan, despite having the briefest pain duration of the three groups (Bruehl et al., 2002).

Soon after the inception of the 1993 criteria, it became obvious that there continued to be a need for more specific criteria. Part of the objectives of the initial criteria was that they would evolve and be subjected to systematic empirical testing, validation, and improvement. The criteria are in a way a compromise between researchers and clinicians. They are consensus-based and not mechanism-based. Gifford and Thacker argued that mechanism-based approaches are not necessarily helpful in physical therapy as they perceive physical therapists to become too focused on altering the mechanism without consideration of other aspects of pain (Gifford and Thacker, 2002). Yet, it is important to determine what mechanisms are responsible for patients' individual pain and to target treatments specifically at those mechanisms without losing sight of the bigger picture (Lidbeck, 2002; Woolf et al., 1998; Woolf and Max, 2001). Although the 1993 criteria are highly sensitive and an important step in the right direction, they lack specificity, which makes it difficult to determine new treatment approaches targeted at particular pain mechanisms (Bruehl et al., 1999; Galer et al., 1998; Harden et al., 1999). The specificity of the criteria can be improved upon by objective data of the sensory, vasomotor, sudomotor/edema, and motor/trophic components that make up CRPS. This requires a better understanding of the underlying mechanisms of the syndrome. The previously used term ''reflex sympathetic dystrophy'' reflected a presumed underlying mechanism, that could however not be substantiated. The term complex regional pain syndrome does not necessarily mean that much either. In principle, the name could be applied to other complex and regional pain syndromes, such as myofascial pain syndrome or thoracic outlet syndrome. It is likely that with the advancement of insights in the underlying mechanisms, the name will be replaced by a new mechanism-based term or group of terms (Jänig and Baron, 2002).

Incidence and prevalence

The incidence and prevalence of CRPS are unknown. An older study estimated the incidence at 1 case in every 2000 accidents (Plewes, 1956). Stanton-Hicks and colleagues reported that in Sweden 27 cases of causalgia and 67 cases of RSD were reported in 1990, 40 and 44 cases in 1991, 38 and 40 cases in 1992, and 29 and 80 cases in 1993. The population of Sweden in 1990 was 8.6 million (Stanton-Hicks et al., 1998). Based on the total number of patients with a diagnosis of ''pain in an extremity'', the prevalence in extremity pain was estimated as 10% (Stanton-Hicks, 2000a). In the Netherlands, the incidence of RSD was about 8,000 new cases per year with a total population of 16 million (Oerlemans et al., 2000).

CRPS I

The term reflex sympathetic dystrophy was first used by Evans (1946). CRPS I is more common than CRPS II and may develop after trauma with little or no nerve lesion, such as minor bruising, bone fractures, surgical procedures, or other lesions. CRPS 1 affects adults and children (Parano et al., 1998; Petje and Aigner, 2000; Sherry et al., 1999; Tong and Nelson, 2000; Wesdock et al., 1991). The key features are spontaneous pain, allodynia, hyperalgesia, abnormal vasomotor activity, abnormal sudomotor activity, trophic changes, and movement disorders. A characteristic of CRPS is that the initiating events are disproportional to the resulting pain and dysfunction. Frequently CRPS has a devastating effect on sleep patterns, activities of daily living, and overall quality of life (Kemler and Furnee, 2002; Schasfoort et al., 2003).

Onset

The onset of symptoms is usually within hours or days following the initiating noxious event, but may be delayed for several weeks or even months. The symptoms show a distal and generalized distribution and are not limited to the innervation zone of

an individual nerve. Patients with CRPS I commonly localize their spontaneous pain into deep somatic structures with varying pain patterns (Jänig and Baron, 2002; Maleki et al., 2000). Many case reports link the onset of CRPS I to a wide variety of injuries and diseases. CRPS 1 may be triggered by remote injuries, including visceral lesions and central lesions. CRPS I has been described in conjunction with minor limb sprains, burn and electrical injuries, fractures, nerve entrapments, myofascial pain syndrome, herpes zoster, cocaine use, familial Mediterranean fever, cancer, hemophilia, stroke, and amyotrophic lateral sclerosis, among others (Bodur et al., 1999; Field and Atkins, 1997; Gay and Singh, 2000; Kim and Bryant, 2001; Mekhail and Kapural, 2000; Norris et al., 2001; Querol and Cisneros, 2001; Rashiq and Galer, 1999; Shibata et al., 2003; van der Laan and Goris, 1996). Okada and colleagues described the onset of CRPS I following implantation of a pacemaker, while several others linked the syndrome to other medical procedures, including mastectomies, knee arthroscopy, club foot surgery, cervical epidural steroid injections, and others (Graham et al., 2002; Leitha et al., 2000; Okada et al., 2002; Petje and Aigner, 2000; Siegfried, 1997). In a group of 145 patients with CRPS, 42% had previous fractures and 32% had carpal tunnel surgery. Seventy-three percent of the patients developed CRPS of the hand, compared to 22% of the foot, and 5% of the knee (Birklein et al., 2000). These conditions do not appear to have a homogeneous common etiology, but are multifactorial with individuals exhibiting their own cluster of factors.

Diagnostic tests

There are no specific diagnostic tests for CRPS. The diagnosis is based on history and clinical examination and is not determined by test results. The diagnosis is made by excluding other diagnoses that could account for the pain and other symptoms. Several tests can be used that may assist in the differential diagnostic process, such as X-rays, thermography, peripheral blood flow measurements, quantitative sweat testing, quantitative sensory testing, a sympathetic skin response test, 3-phase bone scintigraphy, muscle strength and joint testing, and psychological testing (Cepeda et al., 2002; Stanton-Hicks, 2000a). Driessens and colleagues recommended using 3-phase bone scintigraphy to differentiate CRPS from a pseudo-dystrophy conversion disorder based on the assumption that in CRPS the bone scan would show a typical increased tracer uptake, whereas in pseudo-dystrophy there would be a normal or decreased tracer uptake in the affected region (Driessens et al., 2002). However, extreme caution is warranted with diagnosing patients with psychiatric disorders based on bone scans, especially since several studies have seriously questioned the utility of this modality. A 30% false positive/false negative response rate has been reported (Allen et al., 1999). Harden confirmed that 3-phase bone scans are not reliable and actually can be confusing (Harden, 2000; Lee and Weeks, 1995; Werner et al., 1989).

The sympathetic nervous system

The role of the sympathetic nervous system in CRPS I continues to require further scientific inquiry. The study of SMP in CRPS I has been difficult as there are no animal models that represent SMP in CRPS I (Jänig and Baron, 2002). Under normal conditions, activity in the sympathetic nervous system does not produce pain. In a systematic Medline review of the literature from 1966 to 1999, Cepeda and colleagues found only three randomized controlled trials that evaluated the efficacy of local sympathetic blockades. Even after including 26 non-randomized studies, the efficacy of local anaesthetic sympathetic blockades could not be established (Cepeda et al., 2002). Figuerola and colleagues did not find any evidence of an abnormal sympathetic response in patients with CRPS I either, but suggested an adaptive supersensitivity instead. Because of an assumed decreased adrenergic outflow from the efferent sympathetic neurons, it is likely that the adrenergic receptors on the primary nociceptors are upregulated to accommodate the decreased outflow. This would lead to an increase in receptor function and synaptic efficacy, and excessive responses to normal neurotransmitter activity. Even though this may give the impression of an hyperactivity of the sympathetic nervous system, in fact, many patients may develop an adaptive supersensitivity rather than a sympathetic hyperactivity (Figuerola Mde et al., 2002).

On the other hand, several studies have confirmed that disturbances in the sympathetic nervous system in CRPS I patients are common. These discrepancies may be partially due to the lack of specificity and uniform application of the IASP criteria (Bruehl et al., 1999; Galer et al., 1998; Harden et al., 1999; Reinders et al., 2002; van de Beek et al., 2002). According to Schurmann and colleagues, the sympathetic disturbances are systemic and not limited to just the affected limb (Schurmann et al., 2000, 2001). Price and colleagues confirmed that blockade of sympathetic activity at the sympathetic paravertebral ganglia relieved pain beyond the duration of a

local anaesthetic (Price et al., 1998). A recent German study examined the nature of vasomotor disturbance in patients with CRPS I and found reduced venous concentrations of norepinephrine in the affected limbs, suggesting that pain and vasomotor disturbances were indeed due to a reduced sympathetic vasoconstrictor activity (Baron et al., 2002; Wasner et al., 2001b). In a subgroup of patients with CRPS and SMP, there was a pathological interaction between sympathetic activity and afferent neurons. Although the exact mechanism of a sympathetic–afferent coupling remains unknown, Baron and colleagues proposed that sympathetic activity can sensitize nociceptors via a sympathetic release of norepinephrine acting directly on adrenoreceptors expressed on afferent fibers, rather than supporting the concept of hypersensitivity due to a decreased adrenergic outflow from the efferent sympathetic neurons (Chen et al., 1996; Jänig et al., 1996; Shi et al., 2000), Jänig and Barron concluded that the observed adrenergic hypersensitivity is in fact part of SMP, and argued that excitation and sensitization of peripheral nociceptors may generate a state of central sensitization or hyperexcitability with spontaneous and secondary evoked pain (Baron et al., 2002; Jänig and Baron, 2002). In addition, the increased sympathetic activity was found to have an impact on the spatial distribution of mechanical hyperalgesia, suggesting that low threshold A β fibers may be implicated in sympathetic–afferent coupling (Baron et al., 2002).

Drummond and colleagues confirmed the finding of adrenergic supersensitivity, but speculated that the symptoms of CRPS are not necessarily due to excessive sympathetic adrenergic outflow, but could be the result of an impairment of supraspinal pain modulatory systems (Drummond, 2001; Drummond et al., 2001). Failure of normal pain inhibition in the spinal cord can unmask an excitatory adrenergic influence on nociceptive transmission in the thalamus and in the spinal cord itself. This would in turn also lead to sensitization and other symptoms of CRPS (Drummond, 2001).

In summary, the development of adrenergic supersensitivity can be due to several mechanisms. Depletion of sympathetic neurotransmitters may stimulate the expression of α-adrenergic receptors of nociceptive afferents. Adrenergic supersensitivity can also result in tissue inflammation (see below) and may interfere with the normal production and release of prostaglandins and nerve growth factor, which can also sensitize nociceptive afferents via prostaglandin release and increased growth of nociceptive afferents (Shu and Mendell, 1999). Whether any of these mechanisms are relevant for the development of CRPS needs to be seen (Wasner et al., 2001a).

CRPS II

Mitchell and colleagues coined the term ''causalgia'' during the American Civil War (Mitchell, 1872; Mitchell et al., 1864). One of the major differences between CRPS I and II is that CRPS II occurs after partial injury of a nerve or one of its branches, making it a true neuropathic syndrome. The majority of reported cases have been attributed to partial nerve injury due to high-velocity missile penetration as seen in gunshot wounds. Bryant and colleagues reported that only in 5% of cases CRPS II is the result of complete nerve injury (Bryant et al., 2002). The onset of symptoms is usually immediately following the injury, but occasionally may be delayed for several weeks or months. CRPS II affects both children and adults. Clinically, the patient presents with abnormal sensory perceptions involving the affected limb, including spontaneous pain, allodynia and hyperpathy. Usually, the distribution of pain is limited to the distribution of the involved nerve, but may sometimes extend beyond the nerve distribution. The intensity of pain may vary substantially. The pain may be SMP or SIP.

There is some evidence that sympathetically maintained changes are more common in CRPS II (Jänig and Baron, 2002). This may be related to the observation that the most commonly involved nerves carry the greatest proportion of sympathetic fibers, including the median, ulnar, sciatic, and tibial nerves. CRPS II rarely involves the radial nerve (Bryant et al., 2002). However, Schmid and colleagues presented a case of CRPS II as a complication of radial artery harvesting, in which a surgical titanium clip near the superficial radial nerve and a small neuroma were thought to have caused the syndrome. Unfortunately, removal of the clip and the neuroma did not reduce the symptoms (Schmid et al., 2002). Forouzanfar and colleagues reported that radiofrequency stellate ganglion blocks were more effective in CRPS II than in CRPS I (Forouzanfar et al., 2000).

Neurogenic inflammation and CRPS

As both CRPS I and II feature common signs of inflammation, namely pain, swelling, discoloration of the skin, altered skin temperature, and decreased function, several studies have focused on the role of local inflammation in the etiology of CRPS (Huygen et al., 2001; Oyen et al., 1993). Huygen and colleagues found significantly higher levels of interleukin-6 (IL-6) and tumor necrosing factor-alpha (TNF-α) in blister fluid in the involved

extremity compared to the uninvolved side (Huygen et al., 2002). This raises several important questions. Is CRPS a neurogenic inflammatory process? Is the inflammatory response due to adrenergic supersensitivity? What is the effect of locally applied anti-inflammatory medications? What is the role of the immune system? There is much evidence that CRPS is at least partially due to an exaggerated inflammatory response to tissue injury, mediated by an excessive production of toxic oxygen radicals (Oyen et al., 1993; van der Laan et al., 1998a). The positive effects of topical dimethylsulfoxide (DMSO), a free radical scavenger, sustain the hypothesis that there is an inflammatory component to the etiology of CRPS 1. A recent comparison of DMSO and the free radical scavenger *N*-acetylcysteine (NAC) demonstrated equal efficacy for both drugs. For warm CRPS I (warm limb), DMSO appeared more effective, while NAC appeared more effective for cold CRPS I (cold limb) (Perez et al., 2003).

The finding of pro-inflammatory cytokines IL-6 and TNF-α suggests a possible decreased activity of the immune system in patients with CRPS. However, a recent study did not show any evidence in support of a primary role of the immune system in CRPS, providing more support for the neurogenic inflammatory hypothesis (van de Beek et al., 2001). Tissue inflammation may be due to adrenergic supersensitivity through the release of prostaglandins and nerve growth factor (Wasner et al., 2001a). Another possibility that has not been explored adequately in the research of CRPS is spinal cord glia activation. There is much evidence that activation of spinal cord glia plays a major role in driving pathological pain states, including CRPS. Activated glia regulate not only excitatory amino acids, prostaglandins, nitric oxide, and substance P, they also release pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α. Watkins speculates that glia are a driving force in CRPS, particularly following inflammation or constriction or damage of peripheral nerves (personal communication, 2003). Glia activation may also underlie the spread of pain and other symptoms beyond the initial injury site (Watkins et al., 2001a, b).

CRPS and Myofascial Pain Syndrome (MPS)

There are many similarities between CRPS and MPS, including local and referred pain, muscle pain, autonomic changes, and limited range of motion. Of particular interest is the finding of tissue hypoxia in patients with CRPS and in patients with MPS (Allen et al., 1999; Harden, 2000; Koban et al., 2003; Simons et al., 1999; van der Laan and Goris, 1997). Brückle and colleagues have established that the local oxygen saturation at myofascial trigger points (MTrP) is severely impaired (Brückle et al., 1990). Hypoxia is known to result in the release of sensitizing substances, such as bradykinin, that activate and sensitize peripheral nerve endings and autonomic nerves, and release pain evoking substances including TNF-α and several pro-inflammatory interleukins (Poole et al., 1999). Sensitization of peripheral nerve endings can cause pain through the activation of amongst others, *N*-methyl-D-aspartate (NMDA) receptors and the release of neurokinin (Yaksh et al., 1999). Preliminary findings of a study by Shah at the National Institutes of Health suggest an increase of several pro-inflammatory cytokines at the site of MTrPs, when compared to muscle tissue away from MTrPs (Shah, 2003). Simons and colleagues proposed that the sensitizing substances may activate sympathetic fibers leading to the autonomic signs and symptoms of MPS (Simons et al., 1999). It is noteworthy that Baron and colleagues also suggested the presence of sympathetic–afferent coupling in deep somatic tissues, including muscles and joints, in patients with CRPS and SMP (Baron et al., 2002).

Although there are many overlapping characteristics in MPS and CRPS, there are no well-designed studies that investigate a shared etiology or possible correlation between the two syndromes. Fifty-six percent of patients with CRPS had clinically relevant MTrPs at the time of evaluation in a tertiary chronic pain center. The mean duration of CRPS symptoms prior to the pain center evaluation was 30 months (Allen et al., 1999). In a retrospective review, 61% of patients with CRPS were found to have myofascial dysfunction (Rashiq and Galer, 1999). Imamura and colleagues found that 80% of patients with CRPS I had MPS, using the criteria by Travell and Simons (Imamura et al., 1997; Travell and Simons, 1983). Treatment of the MPS ''expressively decreased the pain intensity and disability'' in 87% of those patients (Imamura et al., 1997). Unfortunately, these retrospective MPS studies were poorly controlled or lacked statistical analyses and adequate descriptions of the applied methodology. Rashiq and Galer suggest that in patients with CRPS, MPS must be treated first. Frequently, the symptoms of CRPS are reported to resolve as a result of the treatment of MPS (Rashiq and Galer, 1999). There are no studies of local muscle dysfunction in CRPS other than a study of 8 patients by van der Laan and colleagues, who found a decrease of type I fibers, an increase of lipofuscin

pigment, atrophic fibers, and severely thickened basal membrane layers of the capillaries in the gastrocnemius and soleus muscles (van der Laan et al., 1998b). Empirical and anecdotal evidence suggest that there are many correlations or co-morbidities between MPS and CRPS. Further prospective studies are needed.

Summary

The research on CRPS has made significant strides since Dr. Pare treated King Charles IX. The diagnosis of CRPS continues to raise many questions regarding the etiology, underlying mechanisms, contributing and perpetuating factors, and ultimately the management of patients. The current criteria have stimulated much focused research on underlying mechanisms, but not on therapeutic management and clinical outcome studies. Definitive conclusions are still lacking. It is likely that CRPS is a disease of the central nervous system, but at the same time, there are numerous indications that point to peripheral inflammatory processes, abnormal sympathetic–afferent coupling, and adrenoreceptor pathology. It is plausible that there are multiple simultaneous processes that contribute to the development of CRPS. Whether these are all the result of changes in central representations remains to be seen. Several areas of research remain, such as the role of glia activation, the overlap between MPS and CRPS, the clinical management of patients with CRPS, the differences in patient's susceptibility to develop CRPS, the criteria themselves, etc. As new evidence emerges, the current concepts of CRPS will likely be replaced by a new mechanism-based term or group of terms. Part 2 of this article focuses on the physical therapy management. As will become evident, there is a considerable lack of randomized controlled trials. Even thought the majority of reports are case-report-based or consensus-based, several treatment options are proposed to assist patients diagnosed with CRPS.

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