Psychologic Factors in the Development of Complex Regional Pain Syndrome: History, Myth, and Evidence

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Objective: The present paper examines the literature that addresses psychologic aspects involved in complex regional pain syndrome from a historic perspective to provide a rationale for the emergence of psychologic theories to explain its pathogenesis. The support of such perspective is then analyzed through the review of evidence-based studies.

Methods: A review of the literature from a historic perspective was presented since its first description to the present time, including the clinical presentation and associated symptoms. An evidence-based approach was used to review the literature on complex regional pain syndrome and psychologic factors associated with the etiology or as predictors in the development of the disorder.

Results: After reviewing the literature on the history and the myths associated with complex regional pain syndrome, a hypothesis is provided based on an analysis of the Zeitgeist in the development of the psychologic theory associated with the disorder. We also concluded there is no evidence to support a linear relationship that establishes a psychologic predisposition to develop the disorder.

Discussion: An analysis of the Zeitgeist when complex regional pain syndrome was first described helps to understand the long-standing theories associated with a psychological theory of its etiology. This understanding should help to undermine the perpetuation of such claims which may contribute to undertreatment and misdiagnosis. To be consistent with today s Zeitgeist we must incorporate psychologic aspects, which while not causal in nature or exclusive of complex regional pain syndrome, are strongly associated with a wide spectrum of chronic pain disorders.

Key Words: complex regional pain syndrome, sympathetically mediated pain, sympathetically independent pain, reflex sympathetic dystrophy

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Complex regional pain syndrome (CRPS) is a neuropathic disorder that can develop after a trauma. The legacy of CRPS encompasses a long and controversial history that has included multiple specialties with little agreement on its etiology, symptoms, labels, or existence. Premorbid emotional problems and psychologic disturbance have been frequently implicated in the pathogenesis of the disorder, but not consistently demonstrated. Attributions for CRPS have ranged from psychiatric factors such as an underlying personality pattern,[1] psychosomatic disposition,[2] pain proneness and psychosomatic disease,[3] secondary gain,[4] hysteria and conversion,[5–7] to somatoform disorder and malingering,[8] and pseudoneurologic presentation.[9]

On the basis of the psychogenic conceptualization of CRPS, Pawl[4] concluded that invasive therapy might not be appropriate and recommended behavior therapy as the treatment of choice. On the contrary, others propose that this pain disorder is so severe that pharmacologic management should be implemented early and in an aggressive manner.[10–12] Even given this great disparity in conceptualization, better understanding the influence of psychologic factors in the development and maintenance of the disorder may prove productive in the reliable diagnosis and treatment of patients with CRPS. At present, delays in diagnosis are associated with worsening and spread of the condition, with catastrophic impacts on quality of life and ultimately disability.[13,14]

Historically, the scientific community has lacked specific knowledge about the etiology and mechanisms of actions and acquisition of this disorder, thus, perpetuating the promulgation of unidimensional psychosomatic and factitious-related disorders as the sole explanation of symptom presentation. The purpose of the current paper is to present the history of CRPS, describe the myths associated with the disorder, and understand the evidence behind what have been purely psychologic explanations for this disorder.

HISTORY

The first documented description of CRPS may have been that of Ambroise Pare, a surgeon in France who during the 16th century reported that King Charles IX experienced persistent pain and contractures after a bloodletting procedure.[15,16] In 1766, Hunter described distant effects after a joint injury. The first description of this disorder in North America was made by Mitchell et al[17] in soldiers with penetrating wounds during the Civil War. They vividly described the severe presentation and the burning quality of pains in soldiers after traumatic tissue destruction.[18] In 1872, Mitchell coined the term causalgia from the Greek *kausis,* which means fire. He stressed the exaggerated nature of the presentation of pain in relation to the injury, a problem that was frequently found in veterans of the Civil War who were exposed to low velocity, high mass missiles used by the confederates.[11] Mitchell's description has seemingly passed the test of time and remains the best depiction of the clinical presentation of the current models of CRPS more than 100 years later, but it marked the beginning of a most ambiguous and controversial history.[19]

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In Germany around 1900, Sudeck described the clinical and radiologic features of a posttraumatic reflex atrophy of the bone, latter known as *morbus Sudeck* or *Sudeck's atrophy*. He described a posttraumatic pain syndrome that included edema and trophic changes. His publication inspired interest in the disorder and several scientific articles describing clinical variants and predisposing factors.[20]

In 1939, Leriche developed a vicious cycle hypothesis to describe the circular nature of the symptomatology associated with CRPS. In 1946, Evans introduced the label Reflex Sympathetic Dystrophy (RSD).[21] The term settled, the acronym became popular and historically has been the most widely used nomenclature for the disorder. In 1986, Roberts conceptualized the term sympathetically mediated pain (SMP) as one that could be used synonymously with RSD, whereas Campbell and colleagues used the term sympathetically independent pain (SIP) to refer to those patients with nerve injuries that did not respond to sympathetic blockage.[10] A useful category, as CRPS can present with and without obvious neurologic injury, SIP implies that a different mechanism could be responsible for similar presentations of pain, and potentially facilitating differing responses to treatment including sympathetic blocks. A caveat is that the description of SMP may be thought of as a tautologic definition or a circular approach to the disorder when described as a sympathetically mediated disorder triggered by sympathetic arousal. However, caution is recommended as SMP basically refers to the mechanism of pain; it is not exclusive of CRPS and it is not considered synonymous anymore.[10]

Historically, the pursuit of the elusive disorder has generated a wide spectrum of terms such as posttraumatic sympathalgia, traumatic vasospasm, posttraumatic dystrophy, algoneurodystrophy, shoulder-hand syndrome, posttraumatic osteoporosis, and postinfarctional sclerodactily, and others including several eponyms.[18] The disorder was also known as *algodystrophie* in France, *algodystropher reflex* in Germany, besides the well known suspects: causalgia and RSD in many other countries.[22] The multiple and diverse nomenclature of CRPS earlier in its history likely contributed to our lack of progress in identifying its etiology, progression, and resolution in the clinical setting.

Due to the history of terms associated with CRPS, and a vast array of suspected pathogenesis, there was a need to clarify terminology and standardize diagnostic criteria for chronic pain syndromes. Inaccurate terminology and imprecise classifications had led to confusion, misdiagnosis, and mistreatment of patients with this pathology.[23] Harden[19] described the rationale behind pursuing a new taxonomy for the obscure and often confounding term *Reflex Sympathetic Dystrophy*, stating that when a reflex is involved, it is complicated, multisynaptic, and not fully characterized, adding that the sympathetic changes may be epiphenomena and not causative, and that dystrophy rarely occurs.

In 1993, the International Association for the Study of Pain (IASP) designated a Task Force to review the nomenclature and develop criteria. In 1994, the Task Force reached consensus through a Dahlem-type workshop developing a new nomenclature, *Complex Regional Pain Syndrome*, noting that it is a complex disorder, which tends to begin in a region of the body, usually the distal aspect of an extremity, where pain is a necessary component with presentation of a variety of clinical symptoms.

The new classification was published by IASP in the second edition of *Classification of Chronic Pain* in 1994. Two types were described, Type I, formerly known as RSD refers to a neuropathic disorder that can develop from trauma to the extremities without an overt nerve injury. This syndrome is distinguished from CRPS Type II, formerly known as causalgia, where at least a partial lesion of a nerve needs to be present for the diagnosis.[24] The new taxonomy included the following criteria: (1) the presence of an initiating noxious event; (2) continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event; (3) 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; (4) this diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.[24]

More recently, a consensus group met in Budapest and proposed a revised taxonomy with a polythetic approach and the inclusion of a diagnostic subtype for patients that do not meet full criteria: CRPS, not otherwise specified.[25] They also proposed the need for early and more aggressive management of pain including pharmacologic management.[11]

CLINICAL PRESENTATION OF CRPS

The clinical presentation of CRPS can be sudden or insidious after a trauma or insult, usually to a limb or extremity.[26] The etiology of the trauma can range from distal fractures, nerve injury, postsurgical, damage to nerve, tight cast, nerve compression syndromes, myocardial infarction, stroke, infection, injections, and tumors.[22] The syndrome may include hyperalgesia, allodynia, edema, vasomotor activity with color changes, hyperhidrosis, dystonia, muscle atrophy, and osteopenia.[27] In the majority of patients, the initial regional distribution remains unchanged. However, the presentation of the disorder can extend usually from a region, typically a limb with a mirror-effect spread (opposite limb), or an ipsilateral pattern.[28] This progression may manifest spontaneously, but oftentimes is triggered by lack of or delayed treatment, or through an inciting event, such as insults to other parts of the body. The presentation of this progression to other areas of the body may vary in intensity from CRPS-like symptoms (similar but minimal) to full-blown CRPS.[29] When a spread of symptoms occurs it may fluctuate in time, with an immediate or delayed presentation.[29]

The incidence of CRPS is 1% to 2% after all fractures, 2% to 4% fractures with peripheral nerve injuries, and up to 35% after a Colles fracture.[22] Female incidence ranges from 60% to 80% in adults where upper extremities is more prevalent[30]; whereas it is rare in children, lower extremity presentation is more common and prognosis is better.[22] A higher incidence has been recently reported in a population-based study in the Netherlands as well as a higher risk for postmenopausal women.[31] The presentation of CRPS is usually distal to the original trauma, and the severity of pain remains well after the trauma has healed. Early diagnosis is relevant, as when this disorder goes untreated can lead to severe long-term disability.[14] More recent research points to earlier more invasive procedures to treat the disorder.[32]

Imaging of the limbs affected by CRPS often shows diffuse loss of bone density on conventional radiography, increased uptake on bone scintigraphy and hyperintensity on T2-weighted magnetic resonance images (personal

communication S. Martinez, MD). These changes are expected signs of osteoporosis, hyperemia, and bone marrow edema, respectively, usually after some time of the presentation of the disorder, especially when lack of mobility is involved due to the severity of pain. Imaging techniques show less conclusive results during the early stages.[33] However, these symptoms do not seem to be exclusive to the lack of mobility, as rat models have shown that sympathetic nervous system regulates hematopoietic stem cell egression from the bone marrow.[34] More recently, autopsy results of a patient with intractable pain with CRPS showed glial activation and neuronal loss throughout the posterior horn of the spinal cord.[35]

Van der Laan et al[36] posited 4 main categories of factors that explain pathophysiology, sources of variance in presentation, and etiology of CRPS across patient populations: (1) psychologic factors; (2) sympathetic factors; (3) causalgic factors (nerve damage involvement); and (4) inflammatory factors. Notably, inflammatory factors are only a recent focus in understanding CRPS.[11,37] A growing body of research suggests central nervous system involvement,[38-41] changes in structure of the brain,[42] and possible genetic predisposition[43] in the development of the disorder.

MYTHS

Historically, several concepts have been used to explain the pathogenesis, progression, and maintenance of CRPS. Early researchers and current experts struggle with the essence of the development, progression, and resolution of CRPS.[12] Sudeck's personality is a construct, which was premised on the concept that individuals with a specific psychiatric pathology are more prone to develop CRPS.[2,3] Of interest, this psychiatric perspective of CRPS has persisted even in the absence of overwhelming evidence to support such a conclusion, and may contribute to undertreatment and misdiagnosis.

A historical review can provide some insight into the impact that culture, societal norms, politics, and geography may exert on the development of theories, schools of thoughts, and research about CRPS. Given the early boom of CRPS cases described by Sudeck in Germany, with such influence that the disorder became known worldwide as Sudeck's atrophy, it is relevant to analyze the background and epistemology of the prevalent theories of psychiatry at the time.

Freudian psychoanalysis was the dominant psychologic theory when CRPS was first described. Freud's "Interpretation of Dreams" was published circa 1900 and marked the beginning of psychoanalytic thought. The psychodynamic theory stressed trauma from childhood through a pansexualist postulate, which was largely criticized and generated dissent in many followers such as Alfred Adler and Carl Jung. Still, a strong theory for the first half of the 20th century, it not only influenced the European Zeitgest, but American culture as well. The approach to psychologic issues was mainly the publication of case studies.

It is not difficult to understand that the first cases of CRPS were likely interpreted in a manner consistent with the zeitgeist of the time, mainly psychoanalytical theory. The physiologic nature and etiology were not understood but largely associated with emotional distress due to the severity of pain. Recent anecdotic reports and case studies after a psychoanalytical approach have continued this conceptualization[44] in particular involving the administration and interpretation of projective tests such as the Rorschack Inkblot Test[45] to uncover psychologic disturbances and maladaptive personality structures in patients with CRPS. But it has also been true of other disorders of unclear pathogenesis such as multiple sclerosis and fibromyalgia. For example, even though multiple sclerosis was described as a distinct nosologic entity by Charcot in 1868, in 1920 it was still considered a rare disease as compared with 1950[46] probably due to the diffuse presentation and overlapping symptoms with other disorders as well as the tendency to ascribe neurologic disorders to syphilis.[47] Initially it was considered to be more frequent in men, mainly due to the fact that the same symptoms in women would generate a diagnosis of hysteria; today it is reported that it affects women twice as often than men.[46] Furthermore, Butler et al[48] made an historical analysis of how a feud between the fields of psychiatry and neurology was an obstacle in the advancement of our knowledge about cognitive factors involved in the presentation of multiple sclerosis.

By the same token, historically fibromyalgia has been considered a psychosomatic disorder, as many psychologic findings have been associated with its presentation.[49–51] Further studies have expanded subtypes that impact different aspects including pressure-pain thresholds and psychologic/cognitive factors[52] that compare to subgroups in other chronic pain conditions[53] and more recently focus on habituation and sensitization,[54] pharmacologic management,[55] and brain changes observed through functional magnetic resonance imaging.[56]

The advent of psychosomatic medicine around the beginning of the 20th century brought a wider spectrum of the disease model into the table and opened a big road to explore psychologic issues that impacted bodily functions and morbidity.[57] It was a paradigm that allowed explanation of psychophysiologic aspects of disease and the influence of psychologic issues in the development of illnesses. The psychosomatic model was particularly relevant after the long reign of Cartesian dualism, which ruled for almost 300 years and postulated a separation of body and mind. The work of Selye[58] brought a more scientific approach by integrating the role of hormone secretion triggered by thoughts and the impact on visceral functions.

Finally, the biopsychosocial model emerged (consistent with Kuhn's elegant epistemologic analysis in 1970)[59] out of the need to explain new exemplars the former Cartesian model could not explain. A scientific revolution had occurred but it would take years to build a body of literature that would back its postulates.

The biopsychosocial model incorporated psychologic aspects, biologic issues, and environmental pressures as variables that influence on each other and make a qualitative difference.[60] A growing body of research is confirming the need to incorporate the biopsychosocial model to chronic pain disorders.[61–63] Development of advanced inquiry and clinical treatments have ultimately guided debates that have advanced our understanding of biopsychosocial principles concerning relevant constructs in pain management.[64,65] Consistent with the biopsychosocial model, a theoretical approach has emerged for understanding behavioral aspects such as self-report and observational measures in chronic pain patients.[66] This conceptualization has been applied to our understanding of CRPS. The zeitgeist of psychologic research related to pain has shifted during the last 50 years from a mainly theoretical case study psychodynamic to a behavioral-cognitive approach that follows the rules of science and central tendencies.[67]

THE EVIDENCE

With the advent of evidence-based medicine, which has not been free of philosophical debate, a more useful paradigm has emerged in contrast to a web of belief-based approach to scientific questions.[68] The Gate-Control Theory of Pain is the most widely researched theory of pain[69] and its major contribution to research and practice has been the ability to integrate psychologic, social and biologic phenomena into the conceptualization of pathology.[70,71] A more recent revision incorporates the construct of a neuromatrix, which addresses genetic and sensory influences[72] on clinical outcomes. One of the most salient characteristics of the paradigm was the inclusion of psychologic and environmental aspects added to the already known biologic aspects of pain.

Patients with chronic pain have been found to be more likely than the general population to develop psychiatric disorders[73,74] (Edwards et al, unpublished data; 2009), whereas physical function is better predicted by psychologic and social factors than by biomedical factors.[75] Moreover, at least 40% to 60% of women and 20% of men with chronic pain disorders report a history of abuse.[63] A high prevalence of sexual dysfunction has also been described.[76] By the same token, anxiety and depression have been found to be positive predictors of pain, number of medication, and disability.[77] Depression in chronic pain patients have also shown to impede recall of changes in pain levels[78] whereas altered perception of pain has been described in patients with major depressive disorder and with adjustment disorder with depressed mood.[79]

It is also accepted that there is significant comorbidity of CRPS patients associated with psychiatric disorders like depression[74] and kinesiophobia.[80] In contrast, in a prospective study, patients who developed CRPS Type I after radial forearm fracture did not show a unique psychologic pattern, neither more symptoms of depression than those who gained full recovery.[81]

DeGood et al[82] compared RSD patients to low back pain and headache patients and found elevations in pain, emotional distress, and behavioral disturbance in all groups; however, although RSD patients showed the highest level of pain, employment disruption, and financial compensation, paradoxically they were less emotionally distressed. Monti et al[74] compared personality patterns in CRPS patients with disc-related radiculopathy patients and found significant depression and personality disorders but no significant difference between the 2 groups. These findings are consistent with earlier studies.[83]

More recently with a methodology of randomized controlled trials, Apkarian et al[49] found presurgical depression in patients but no associated significance in patients who developed CRPS Type I from non-CRPS patients. Harden et al[29] also through a randomized controlled trial analyzed medical and psychologic predictors of CRPS after total knee arthroplasty (TKA). They found that preoperative anxiety mildly predicts initial CRPS symptomatology after TKA whereas elevated preoperative pain predicts longer-term post-TKA CRPS. Given the psychologic issues associated, Harden et al[84] measured epinephrine and norepinephrine levels in CRPS patients and controls and found them to be higher in CRPS patients but the question still remains: are they higher as a result of pain, affective distress, or both or whether they predispose the development of the syndrome. Consistent with these findings, Kaufmann et al[85] also found significant elevations in norepinephrine levels and stress-related scores in CRPS patients when compared with controls. These results suggest an interaction between immunity, stress, and pain levels. The relevance in the relationship between catecholamines, psychologic distress, and neurogenic inflammation cannot be denied and may be the clue for the strong association between psychiatric presentation and CRPS. Pain is multidimensional and deciphering the interaction should impact our knowledge and treatment of the disorder. Bruehl et al,[86] for example, reported a study for the treatment of acute pain that integrates both physiologic and psychologic aspects in acute pain.

Rommel et al[39] found no difference in pain perception between CRPS patients and patients with neuropathic pain but found that CRPS patients with allodynia showed significant distress levels. Reedjik et al[87] compared CRPS Type I with dystonia and found more somatoform dissociation, traumatic experiences, general psychopathology, and lower quality of life scores compared with psychiatric population. The elevations on clinical scales did not support a disturbed psychologic profile when compared with the general population. De Mos et al[88] found an association with medical history with onset of CRPS specifically asthma, migraine, osteoporosis, and a recent history of menstrual cycle problems and preexisting neuropathies. No association of onset to psychologic factors was found. A recent trial showed significant improvement in soldiers with Post Traumatic Stress Disorder and CRPS Types I and II treated with spinal cord stimulation.[32]

The significant comorbidity of CRPS patients and psychiatric symptoms is well known,[39,74,89] as well as the psychiatric comorbidity associated with chronic pain patients in general.[61,62,79,82] However, mostly in the case of CRPS the controversy continues as to whether it is a result or a cause of the disorder.

A controversial history of frequent misdiagnosis, overlapping taxonomy, psychiatric implications, and even denial of the entity have contributed to misguided research and a lack of clarity about the etiology, progression, and resolution of CRPS for more than a century. The recent development of a taxonomy with distinct nomenclature and classification has advanced a unified understanding of common and unique presentation of the disorder through clear criteria, standards of practice and guidelines for treatment.

As previously described, CRPS is a severe disorder, with variable and uncommon presentation. Early diagnosis is associated with better prognosis, as the disorder can be debilitating and disabling if mistreated or untreated. However, the pathophysiology of CRPS is perplexing and probably has fueled speculation about psychiatric etiologies of the disease.[74] But it has been also true of other disorders of unclear pathogenesis such as multiple sclerosis and fibromyalgia.

Historically, it has been our lack of knowledge about some disorders which has at times triggered psychiatric debates and hypotheses, while patients have carried the burden of stigmatized labels, which can exacerbate their already critical presentation. Caution is needed to appropriately include psychiatric factors in the development and maintenance of CRPS, but with balance given to the range of other contributing factors. We can no longer afford to have psychiatric explanations as the only conceptualization for the lack of physical findings for CRPS. Anecdotal review based on a psychoanalytical model traditionally has

implied a linear relationship of psychologic involvement specific to CRPS. However, a review of the literature does not provide evidence that psychologic factors are exclusive of this disorder or that they are predisposed or present a more complicated psychiatric history that is not common to other pain population. Some of the studies reviewed showed elevated psychologic factors but consistent with other chronic pain disorders and higher exacerbation when allodynia was present. The previous presentation of evidence points more to an interaction rather than to a causal relationship between psychologic variables and physiologic presentation of CRPS. We propose that a model of research that integrates that relationship[86] in the context of the biopsychosocial model is consistent with the current zeitgeist. For the purpose of treatment, the integrated approach, as proposed by Bruehl,[90] can be optimized through comprehensive pain programs.

The trend in the field of the management of chronic pain conditions demands a multidisciplinary approach as a way of addressing all the components that can influence not only the presentation of CRPS but of chronic pain disorders in general. The multidisciplinary approach incorporating the biopsychosocial model to the conceptualization of the disease should further lead to the development of advanced multifactorial interventions that take advantage of the resources associated with the multidisciplinary treatment team.

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