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Complex regional pain syndrome – Autoimmune or functional neurologic syndrome

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ABSTRACT

Complex regional pain syndrome (CRPS) purports to explain extremity pain accompanied by a variety of subjective complaints, including sensitivity to touch, fatigue, burning sensations, allodynia and signs consistent with voluntary immobilization, including skin changes, edema and trophic changes. By its own definition, CRPS pain is disproportionate to any inciting event or underlying pathology, which means that the syndrome describes non-anatomic and exaggerated symptoms. Although CRPS was coined in the early 1990s, physicians have described unexplained exaggerated pain for centuries. Before a small group of researchers assigned this historical phenomenon with the name CRPS, other physicians in various subspecialties investigated the existence of a common pathophysiologic mechanism but found none. The literature was searched for evidence of a reproducible pathologic mechanism for CRPS. Although some have suggested that CRPS is an autoimmune disease, there is a paucity of evidence to support this. While cytokines such as IL-1β, IL-6 and TNF-α have been detected during the early phases of CRPS, this cannot lead to the conclusion that CRPS is an autoimmune disease, nor that it is an autoinflammatory disorder. Moreover, intravenous immunoglobulin has showed inconsistent results in the treatment of CRPS. On the other hand, CRPS has been found to meet at least three out of four criteria of malingering, which was previously a DSM-IV diagnosis; and its diagnostic criteria are virtually identical to current DSM-5 Functional Neurological Disorder ("FND"), and proposed ICD-11 classification, which includes FND as a distinct neurological diagnosis apart from any psychiatric condition. Unfortunately, the creation of CPRS is not merely misguided brand marketing. It has serious social and health issues. At least in part, the existence of CRPS has led to the labeling of many patients with a diagnosis that allows the inappropriate use of invasive surgery, addictive opioids, and ketamine. The CRPS hypothesis also ignores the nature and purpose of pain, as a symptom of some organic or psychological process. Physicians have long encountered patients who voice symptoms that cannot be biologically explained. Terminology historically used to describe this phenomenon have been medically unexplained symptoms ("MUS"), hysterical, somatic, non-organic, psychogenic, conversion disorder, or dissociative symptoms. The more recent trend describes disorders where there is a functional, rather than structural cause of the symptoms, as "functional disorders." Physicians report high success treating functional neurological symptoms with reassurance, physiotherapy, and cognitive behavior therapy measured in terms of functional improvement. The CRPS label, however, neither leads to functional improvement in these patients nor resolution of symptoms. Under principles of evidence-based medicine, the CRPS label should be abandoned and the syndrome should simply be considered a subset of FNDs, specifically Functional Pain Disorder; and treated appropriately.

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1. Introduction

One of the great challenges of medicine is to effectively manage pain, a symptom that accompanies many illnesses or injuries. Patients who voice physical symptoms like pain for which no disease cause can be found are extraordinarily common across all medical disciplines. Pain is a symptom that exists to alert us to an injury or malady, such as an infection or a tumor. Pain is meant to be a protective mechanism, but once it has served that purpose, its root cause, physical or psychological, must be effectively treated for the benefit of the patient. In the absence of a physical or organic cause, pain traditionally alerted physicians to potential psychological or emotional causes. The modern trend is to describe nonorganic physical symptoms, including movement disorders and nonepileptic seizures, as functional neurological disorders ("FND"); and there is no reason why nonorganic pain, including CRPS, should not be similarly considered to be a functional pain disorder. Fortunately, there has been great progress recently in identifying and treating functional disorders, often with full resolution of the symptoms and without invasive treatment or addictive medication.

2. The original problem

According to the International Association for the Study of Pain ("IASP), "pain" is defined as: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [1]." Traditionally, physicians, including IASP pain physicians, recognized that pain in the absence of a physical cause was psychological:

Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain, and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus.

Therefore, for most of modern medical practice, physicians recognized that pain in the absence of a definable biological process is psychological, which is nonetheless still considered genuine pain.

The management of pain, regardless of its origin, is twofold. First, to identify the origin of the pain and secondly, to provide relief for patients suffering from pain. Pain can result from a variety of etiologies. It can be a product of acute injury or chronic inflammation, as in a broken bone or arthritis respectively. Pain can also be the result of medical procedures, as in surgery, which may be a necessary treatment to save a life or cure an illness but can be associated with pain. Pain is usually perceived to be a manifestation of some pathological entity, but pain can exist in the absence of any other illness, as in the case of certain categories of headache. In many cases, pain is physiologic, but it can also be psychologic, as in psychosomatic manifestations of pain. Pain can also be a manifestation of anxiety, depression and other psychiatric conditions; but one can have psychogenic pain in the absence of psychological or psychiatric illness. Characterizing pain as psychological neither suggests anything about whether the pain is genuine, nor suggests that it is feigned. It merely describes pain that is experienced subjectively by the patient in the absence of any recognized physical cause.

Since pain is such a subjective symptom, it is hard to know its severity and whether to treat. Not treating pain aggressively enough can be considered inhumane, while overaggressive treatment of pain may predispose the patient to complications from the treatment itself, such as side effects, including dependency, addiction, and masking of physical or psychological diseases.

The intentions of treating pain symptomatically were noble at first. Pain had always been and still is difficult to assess and treat. Patients had been dissatisfied with their practitioner's ability to manage their pain, particularly in the hospital setting. Physicians trained before or during the Vietnam War era opiate epidemic were understandably cautious in prescribing pain medication that could lead to addiction or dependency even where it was indicated following surgery. In many cases, physicians limited opiates for terminal cancer patients. In 1995, in his presidential address to the American Pain Society, James Campbell proposed that pain be considered the "5th vital sign", after pulse, respiratory rate, temperature and blood pressure, and that pain be assessed at the same time vital signs were taken [2,3] The problem is that while all the other vital signs can be measurable objectively, there was no way to objectively assess pain.

Nevertheless, the use of pain as a 5th vital sign was adopted rapidly; and physicians were evaluated on their ability to control their patient's pain. Acceptance was spurred on by the fact that high profile healthcare organizations including the Veterans Health Administration (VHA) and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), regulatory groups with considerable influence in health management, endorsed pain as the 5th vital sign. But pain is not quantifiable or measurable. It is a subjective symptom, not a disease. Because of this subjectivity, what followed was the impossible task of transforming pain from a subjective complaint into an objective measure. In an attempt to standardize the perception of pain, patients were asked to rank their pain on a visual analogue scale (VAS) of 0–10. Proponents of this VAS pain scale believed they could forcibly transform a subjective symptom into an objective one. But even the ranking itself is subjective in many ways. What one person perceives as a 1, another person may perceive as a 9. One could argue that it is what the patient perceives that is important, but this fails to consider other confounding issues the patient may harbor, such as psychological distress, personal gain, drug seeking behavior or self-validation. This practice went even further, and it was proposed that multiple pain VAS ratings were necessary to obtain reliable and valid assessments of a patient's pain [4], leading to an added level of unnecessary and confusing complexity to an already impossible task. Ultimately, pain began to be managed based almost exclusively in the reduction of a patient's subjective pain reports rather than any underlying pathology or functional changes, which led to the overaggressive use of opiates and interventional procedures.

3. The emergence of reflex sympathetic dystrophy and its de-evolution to complex regional pain syndrome

The earliest descriptions of a syndrome that could be related to the current condition of complex regional pain syndrome (CRPS) was reported by Ambroise Pare in the 17th century [5]. He described a patient who experienced severe and persistent pain following a limb phlebotomy. Ambroise Pare was also credited with describing the "Phantom Limb" syndrome [6]. The original syndrome described by Mitchell, Morehouse and Keen in the mid-19th century was one of burning pain, swelling, changes in skin color or temperature, joint stiffness or tenderness, sensitivity to touch that they original called causalgia [7]. Some of these cases followed gunshot wounds. Later, Sudeck proposed that there was an inflammatory pathology to these symptoms. Autonomic and sympathetic neurological signs or symptoms were later added to this syndrome by Mitchell and Sudeck in the late 19th century [8]. A report of treatment by surgical sympathectomy was published by the French surgeon Leriche in 1916 [9], at the time solidifying the notion that the sympathetic nervous system was involved in the pathophysiology of causalgia. Multiple terminology for this vague syndrome were proposed over the ensuing years [10], the most commonly encountered being Sudeck's atrophy, Sudeck's dystrophy, reflex neurovascular dystrophy, algodystrophy and algoneurodystrophy.

In 1946, the term reflex sympathetic dystrophy (RSD) was introduced by Evans as a possible unifying concept to consolidate patients with the conglomeration of all or some of these symptoms [11,12]. Because the cause of the symptoms appeared to implicate abnormal sympathetic nervous system function, the original investigators, usually neurologists, utilized various analgesic blocks to isolate the sympathetic nervous system. The treatment for RSD, blocking the sympathetic nervous system,

was thought to be both diagnostic and curative. If blocking the sympathetic nervous system eliminated the patient's symptoms, then the favorable response to the nerve blocks "proved" that the patient was suffering from sympathetically maintained pain. After several decades of research and false promises, including the fact that many of these patients did not report a favorable response to the nerve blocks, investigators gradually abandoned the theory that the sympathetic nervous system was primarily responsible for the symptoms and recognized that the term RSD was a misnomer.

4. Misguided and unscientific solutions to the problem

Around the same time that certain physicians aggressively promoted the idea that chronic pain itself was a disease separate from its organic cause; and that it should be treated even if the diagnosis was unknown, various symptom-based pain syndromes, including the simple label, chronic pain, were invented and promoted directly to the public. This campaign also advocated the use of opiates for the outpatient treatment of chronic non-cancer pain ("CNCP") without regard to the underlying diagnosis [13]. Concurrent with recommendations that pain be considered the 5th vital sign, pain researchers, including the International Association for the Study of Pain (IASP), coined the term Complex Regional Pain Syndrome (CRPS) at a 1993 Orlando conference to replace RSD. This diagnosis was intended to describe a pain syndrome that is either spontaneous or triggered by an injury, but is disproportionate to the injury or inciting event, and which is accompanied by a wide variety of vague autonomic and motor abnormalities in an unlimited number of permutations [14].

The researchers described two types of CRPS, Type 1 and Type 2 [15]. Type 1 purportedly occurs following an injury, usually a minor injury and usually involving an extremity [16,17], or surgery [18], although cases of spontaneous CRPS have been described [19]. There are no associated and demonstrable nerve lesions. The extent of the pain is out of proportion with the initial cause. Other symptoms such as movement disorders in the form of tremors, jerking movements or tics, as well as signs such as edema, diminished range of motion and changes in perfusion have been described to accompany CRPS Type 1. Type 2 CRPS is similar to type 1 CRPS, but there is an identifiable nerve lesion [20]. The same research group met at subsequent conferences, including a 2003 Budapest conference, to try and address the limitations of their original 1993 Orlando criteria, and proposed new changes to the diagnostic criteria in an effort to improve specificity [21].

In this paper, we discuss CRPS 1, in which there is no discernible nerve lesion. The natural course of CRPS has been described to progress in stages, in which sensory symptoms decrease over time whereas motor or trophic abnormalities increase over time [22]. In one study, about a third of patients were still incapable of working after 5.8 years [23].

Attempts to establish an objective, measurable parameter or mechanism to explain the variable signs and symptoms of CRPS1 has yielded limited results. Neuroimaging studies have attempted to prove that minor injury can lead to changes in subcortical and cortical organization within the brain, but these studies have not been convincing and generally fail to establish a causal link [24]. In fact, a study to determine if the brain of patients with CRPS is truly abnormal failed to duplicate any of the previous literature, concluding that previous MRI evidence of aberrant neuroplasticity in patients with CRPS was inconsistent from the standpoint of quantity, localization and directionality [25].

CRPS has also been described in children [26]. The description of CRPS in children exhibit different characteristics from those in adults from the standpoint of triggers, psychopathology and clinical manifestations. There is a predominance of females in CRPS in children. The mean age of onset is usually in the early second decade of life. Pain is predominantly in the lower extremities. There may be elicited a history of minor preceding injury but not always, and there is often the presence of psychological disorders. The role of the central nervous system in CRPS in children is, similarly to adults, controversial, with autonomic dysfunction, functional MRI changes and microcirculatory changes reported but unsubstantiated. While inflammatory markers may be elevated, the role of these changes in the pathophysiology of CRPS in children is not known. Treatments normally used in adult CRPS have not been shown to be effective in children. Conversely, aggressive physical and cognitive behavioral therapy produces very favorable rates of resolution in children. For example, Sherry et al. achieved a 92% success rate with an intensive exercise program of up to 6 h daily, without the use of medication or more intensive procedures [27]. Despite the remarkable success of this protocol in children, no similar program has been tested or evaluated for adults.

5. Establishing diagnostic criteria

When a small group of researchers met at the 2003 Budapest conference to address limitations in the diagnostic criteria for CRPS, including the fact that the original Orlando criteria were nonspecific and could lead to over diagnosis, the incidence of CRPS in the United States were 5.46 and 0.82 per 100,000 person years for CRPS 1 and CRPS 2 respectively [28]. Within the US population Sandroni et al. studied at the Mayo Clinic, 74% recovered fully within a year, which suggested that CRPS symptoms were largely transient and related to immobility. More recent studies conducted in 2006 in the Netherlands purportedly found an incidence of 26.2 new cases per 100,000 population each year, a significant higher rate than previously reported, and lower rates of resolution [29]. This number was adjusted to 16.8 per 100,000 person years when using more stringent criteria, but still significantly higher than the incidence Sandroni reported. Whether this increase reflects an increased awareness or recognition of the term CRPS, different diagnostic criteria, or differences in population, is unknown. What is clear is that there is no epidemiological explanation, based upon science, as to why the problem of chronic regional pain persisting for a year or more should be increasing.

In addition to the original Orlando conference criteria, there have been numerous criteria which have been published to help make the diagnosis of CRPS. Under the original Orlando IASP criteria, a diagnosis can be made largely upon a patient's subjective report of nonspecific symptoms. Nonetheless, one of the four criteria of CRPS1 is exclusion of other conditions that would account for the pain or dysfunction, and this exclusionary criterion has been maintained through subsequent revisions. The original criteria suggested that any person with disproportionate pain and one other sign or symptom could potentially meet the criteria. Subsequent modifications of the proposed criteria occurred in 2003 and then in 2010 requiring the specific identification of particular signs, but no set of criteria has been universally accepted.

The Budapest conference criteria are allegedly more specific but essentially similar. The IASP has claimed that the Budapest criteria have been validated. Harden et al. discussed the validation methodology of the Budapest criteria and found that sensitivity was high at 99% but specificity, while higher than the original IASP criteria (41%) was still low (68%), meaning in a study where researchers had a 50% chance of diagnosing CRPS correctly, they misdiagnosed nearly 1/3 of the controls as having CRPS [21]. The sample sizes in all the validation groups were extremely small; and the control groups were variable. In many cases, physicians applying the proposed criteria could not distinguish between the control group, which included diabetic and other common neuropathies, and CRPS.

Rather than address this diagnostic inaccuracy, the researchers simply substituted more easily distinguishable conditions in subsequent control groups to improve specificity. Challenges remain regarding the inherent possibility of validating a condition which not only has no gold standard, but also is has such high degree of heterogeneity in its definition (even using the Budapest criteria). Since there is no objective test for CRPS, what is it being validated against? In many cases such as CRPS, criteria are actually validated against itself, which creates a type of circular logic. In other words, A may be validated by B, but B is actually

validated by A. Harden and Bruehl, themselves creators of a set of diagnostic criteria for CRPS, state "*In the absence of a definitive pathophysiology of CRPS and thus the absence of a definitive objective test to serve as a "gold standard", providing evidence for external validity of a diagnostic criteria is challenging*" [30,31]. Interestingly, after the validation studies showed poor or equivocal specificity, there have been no additional independent studies that corroborated or duplicated the Harden-Bruehl research, or other validation studies conducted using homogeneous controls. For example, it is unclear whether physicians applying the current Budapest criteria can distinguish diabetic neuropathy from purported CRPS.

Another point to make is that research criteria for CRPS is more stringent than clinical criteria. The question is why that should be at all the case. Why should the clinical diagnosis of CRPS be less precise than that in research? This variability in the criteria needed to make a diagnosis itself raises questions as to the existence of this condition.

Other criteria that have been used, and which are basically similar or synonymous, include the Veldman [32], Harden-Bruehl [31] and Adkins [33] criteria. The Budapest criteria and others are shown in Table 1, along with an analysis of each criteria.

6. A search for the pathogenesis of CRPS

After the term CRPS was introduced, many investigators began to search for the pathogenesis of CRPS. This seems backwards, since the invention of the diagnosis of CRPS preceded any pathophysiologic evidence for its existence. Dystonia, the primary movement disorder associated with CRPS, is reported in nearly 90% of cases. Neurophysiologic studies in CRPS patients have shown mixed results, with one studies showing a reduced inhibition of motor and sensory processing in the brainstem and spinal cord [34], and another later study by the same group showing normal somatosensory processing in 33 patients with CRPS [35]. Like much CRPS research, the studies involve small sample sizes and the same small group of researchers.

It appears that CRPS is a case in which the condition was created first, then attempts were subsequently made to justify its existence by searching for a mechanism. Because there were symptoms of pain, edema, increased sensitivity to touch and temperature, it was thought that neuropeptides may be playing a role [36]. In one study, it was determined that transcutaneous electrical stimulation provoked plasma protein extravasation (PPE) in the affected limb, whereas substance P applied intradermally would induce PPE in both limbs. It was thought that depolarization of afferent C-fibers could cause neurogenic inflammation, which leads to the release of neuropeptides Substance P and calcitonin-gene-related peptide (CGRP) [37–40]. The plasma protein extravasation occurs as a result of Substance P activation of CGRP. How this process leads to the various symptoms of CRPS is unclear. The hypothesis is that Substance P acts through the neurokinin 1 receptor to induce the release of inflammatory mediators [41]. The various known mechanisms for pain are shown in Table 2.

The original mechanism for CRPS was thought to be an abnormal activation of the autonomic nervous system. This was the reason for the earlier terminology of RSD. The theory was that sympathetic nervous system activation leads to upregulation of alpha-adrenergic receptors in the skin of CRPS patients leads to inflammation, and that the link between postganglionic sympathetic neurons and afferent neurons is dependent on this activation [42]. An autoimmune etiology has also been proposed, after autoantibodies to β2-adrenergic receptors and m2-acetylcholine receptors were detectable in patients with CRPS [43]. However, the clinical relevance of these autoantibodies has not been demonstrated. The other issue with this proposed mechanism is that sympathetic nervous system blockade has not been demonstrated to be particularly effective in the treatment of CRPS. It has also been noted in one study that more CRPS patients had a positive IgG serology to parvovirus B19 than controls (71% versus 40%), but this finding did not reflect an increase in anti-endothelial antibodies in patients with CRPS [44].

Table 1
Criteria for the diagnosis of CRPS.

1 A. Original 1994 criteria (Orlando criteria)
1. The presence of an initiating noxious event, or a cause of mobilization
2. Continuing pain, allodynia, or hyperalgesia in which the pain is disproportionate to any known inciting event
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain (can be sign or symptom)
4. This diagnosis is excluded by the existence of other conditions that would otherwise account for the degree of pain and dysfunction

1 B. Harden-Bruehl criteria/Budapest criteria
General definition of the syndrome:
CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time
To establish the clinical diagnosis, the following criteria must be met
1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in three of the four following categories:
   a. Sensory: Reports of hyperesthesia and/or allodynia
   b. Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   c. Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   d. Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign at time of evaluation in two or more of the following categories:
   a. Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch) and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   b. Vasomotor: Evidence of temperature asymmetry (>1 °C) and/or skin color changes and/or symmetry
   c. Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   d. Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms.

For research purposes: diagnostic decision rule should be at least one symptom in all four symptom categories and at least one sign (observed at evaluation) in two or more sign categories.

1C. The Veldman criteria
1. The presence of 4 of 5 of the following:
a. Unexplained diffuse pain
b. Difference in skin color relative to the other limb
c. Diffuse edema
d. Difference in skin temperature relative to the other limb
e. Limited range of motion
2. Occurrence or increase of above signs and symptoms after use
3. The above signs and symptoms are present in an area larger than the area of primary injury or operation and include the area distal to the primary injury

1D. The Atkins criteria
The diagnosis is made clinically by the finding of the following abnormalities
1. Neuropathic pain
   a. Non dermatomal, without cause, burning, with associated allodynia and hyperpathia
2. Vasomotor instability and abnormalities of sweating
   a. Warm red and dry, cool blue and clammy or an increase in temperature sensitivity
   b. Associated with an abnormal temperature difference between the limbs
3. Swelling
4. Loss of joint mobility
   a. Joint and soft tissue contracture

Clinical findings supported by a) radiographic evidence of osteoporosis after 3 months, b) increased uptake on bone scintigraphy early in CRPS

Abnormal cortical reorganization has been another mechanism that has been proposed. This has also been referred to as a form of maladaptive plasticity. This cortical reorganization has been described in studies using magnetoencephalography and functional MRI. The movement disorders in CRPS include tremors, dystonia, myoclonus and muscle weakness, which are controlled by the primary motor cortex, the posterior parietal cortex and the supplementary motor area. Unfortunately, studies attempting to demonstrate a correlation between cortical

Table 2
Types and mechanisms of pain [98].

Type of pain	Cause	Proposed mechanisms	Examples
Centralized pain	Damage to central nervous system	Central sensitization inducing hyperexcitability in the CNS, glutamate/NMDA receptor mediated sensitization	Fibromyalgia, irritable bowel syndrome, chronic arthritis, temporal mandibular joint pain
Inflammatory pain	Damage to local tissues	Cytokine release	Rheumatoid arthritis, systemic lupus erythematosus, other rheumatologic conditions
Mechanical pain	Damage to joints	Stimulation of type I (high-threshold mechanical nociceptors), a form of nociceptive pain	Osteoarthritis, tendinitis
Neuropathic pain	Pressure on nerves or nerve damage	Activation of peripheral terminal receptors of primary afferent neurons, a form of nociceptive pain	Sciatica (the pain is often described more as a burning, stinging or "pins and needles" sensation)
Nociceptive	Stimulation of nociceptors on tissue surfaces	Type I (high-threshold mechanical nociceptors, C-fibers) or Type II Aδ nociceptor stimulation, Activation of mechanotranducers (e.g. TRPV2, TRPA1, KCNK channels)	
Psychogenic pain	Psychosomatic	Poorly understood, pain memory hypothesis	Some cases of headache, muscle pain, achiness, depression, phantom-limb pain

reorganization of these regions and the movement disorders seen in CRPS failed to consistently establish a connection [45,46]. Moreover, a study of patients with CRPS and fixed posture of the hand demonstrated normal sensorimotor plasticity [47]. Contrary to earlier studies, a magnetic resonance imaging (MRI) study found no differences in brain structure between patients with a diagnosis of CRPS and age- and sex-matched healthy controls [25].

A genetic predisposition to developing CRPS has also been proposed because HLA-DR13 has been associated with fixed dystonia syndromes, and HLA-DR15 and DQ1 have been shown to be associated with CRPS without motor symptoms. However, the validity of these associations has come into question due to the subjective nature of the symptoms of CRPS, and the difficulty in confirming an injury causing CRPS and making the correct diagnosis of CRPS.

Sometimes, response to therapy can provide clues to pathogenesis. However, major multicenter randomized controlled trials have yet to be done in CRPS and agreeing on common endpoints for the conduct of such studies is a significant hurdle. Previously used non-medical therapies for CRPS including mirror therapy, graded motor imagery, psychotherapy, medical therapies including glucocorticoids, intravenous immunoglobulins (IVIG), bisphosphonates, topical dimethyl sulfoxide (DMSO), and pain medications such as gabapentin and opioids, have been inconsistent. The dissociative pain medication ketamine, which exerts its action by inhibiting the *N*-methyl-D-aspartate (NMDA) receptor and by its muscarinic and opioid effects has not been shown to be effective in a systematic review of 45 papers [48]. Even invasive pain treatment such as sympathetic blockade and spinal cord stimulation have not been particularly effective, especially in the management of non-pain related symptoms of CRPS [49]. An outcome specific review showed that spinal cord stimulation reduced pain but was inconsistent in relieving sleep anomalies and reducing the use of analgesics [50]. Two papers, both published in 2010, reviewed the level of evidence for the treatment modalities for CRPS. It was interesting to note that those studies of the highest evidence scores (e.g. random controlled trials) are few and far between and tended to show a negative benefit to the respective treatment [51,52].

6.1. Is CRPS an autoimmune or autoinflammatory disorder?

Although there have been suggestions that CRPS may have an immune pathogenesis or that it is an autoimmune disease, the evidence for this claim is weak to this point. Autoantibodies directed against the autonomic nervous system and its components, including the β2-adrenergic receptor and the muscarinic-2 receptor, have been reported in studies on subsets of patients with CRPS, but these have not been substantiated [43,53]. Unfortunately, this has led to the use of IVIG as a treatment for CRPS. This is consistent with the potentially excessive use of IVIG to treat disease when the mechanism is unclear, simply based on the fact that IVIG may function as an immunomodulator or an immunosuppressant. The results of trials of IVIG in CRPS, as mentioned earlier, is inconsistent [54,55].

Another proposal was that the tissue damage sustained from an injury leads to a systemic increase in pro-inflammatory cytokines, including IL-1β, TNFα and IL-6. It has been reported that there is an elevated level of these cytokines in the plasma and cerebrospinal fluid of patients suffering from CRPS [56–58]. The involvement of supraspinal glial and glial-derived proinflammatory cytokines has been proposed to explain the spread of CRPS to ipsilateral and then contralateral limbs [59].

It has indeed been observed that any injury, be it mechanical trauma or fractures, burns or other insults to the musculoskeletal system or skin can lead to inflammation, accompanied by elevations in proinflammatory cytokines such as TNF-α, IL-1β and IL-6 [60]. Similar observations have been made in CRPS, in which keratinocytes expressed elevated levels of proinflammatory cytokines. Serum IL-10 levels have been shown to be lower in patients with CRPS [61]. TNF-α levels have been shown to be elevated in joints of patients with CRPS. The trigger for the upregulation of these proinflammatory cytokines in CRPS appears to be mitogen-activated protein kinase (MAPK) in keratinocytes. However, it is often observed that these elevations of proinflammatory cytokines generally resolve by 6 months [62]. Other hypotheses suggest that Substance P and calcitonin gene-related peptide (CGRP) is responsible for the rise in proinflammatory cytokines [63]. It should, however, be noted that the observation of aberrant levels of cytokines in no way establishes the role of autoimmunity or even autoinflammatory mechanisms in CRPS.

There is also the suggestion that mast cells play a role in CRPS. While it is currently popular to blame mast cells for a wide variety of vague symptomatologies, a theme encouraged by the creation of a syndrome known as mast cell activation syndrome. Although patients with mastocytosis frequently complain of pain, there is no evidence that mast cells play any role in the type of pain attributed to a diagnosis of CRPS [64,65].

7. Denial of psychological component to symptoms

Despite the IASP's recognition that medically unexplained pain is generally psychological, CRPS researchers have taken great pains to "prove" that CRPS pain is not psychogenic and that psychological factors are not contributive. Throughout the academic discussion of CRPS, there has been ongoing controversy over whether the pain is the result of a genuine medical disorder or the experience of psychological distress as physical pain. In some studies, psychological factors have not been found to be associated with CRPS [66]. Yet, an anxious personality has been found to be a risk factor for the development of CRPS [67]. These studies miss the point and rely upon the fallacy that patients suffering confirmed FNDs or psychogenic disorders must also have an underlying psychological or psychiatric condition. Patients diagnosed with FNDs and other psychogenic movement disorders often have no diagnosable

psychological or mental illness; and FNDs are associated with normal scores in psychological questionnaires [68].

In their efforts to find a physical cause of the pain, wide-ranging and completely unrelated mechanisms have been proposed. An inherent difficulty in the pursuit of a common biological mechanism has been the huge heterogeneity in signs and symptoms which cannot be objectively measured, along with the poorly defined criteria and variable responses to a wide range of treatment modalities [69]. In the end, the dystonia seen in CRPS is likely a psychogenic movement disorder, or a FND [70]. Despite the similarities between FND/psychogenic movement disorders and CRPS, no studies have included known cases of FND as controls to determine whether CRPS is a different clinical entity than FND, or simply a variant with pain as its hallmark. Indeed, there have been no validation studies purporting to demonstrate that researchers are capable of differentiating CRPS from any somatic or psychiatric condition. Although CRPS is a diagnosis of exclusion with a wide differential diagnosis, there also have been no studies demonstrating that researchers are capable of excluding medical or psychological conditions that produce similar symptoms.

Other studies have suggested that the hyperalgesia symptoms seen in CRPS are a result of limb immobilization [71]. The pathophysiology of how this occurs is unknown, but it does not appear to occur through changes in sympathetically mediated vascular tone [72]. Associations with other preceding medical history has been performed to help decipher the pathogenesis of CRPS, and in one study, osteoporosis, migraines, asthma and menstrual cycle abnormalities were found to be associated with CRPS. However, this study, like others, was hampered by the significant limitation of misdiagnosis of CRPS [73].

8. Amplification and extension of the problem

It is more than the objective determination of pain that is a problem. A bigger problem is the association of multiple subjective complaints in association with the pain. It is unclear if this is an exaggeration of symptoms by patients with pain who find their pain inadequately treated, malingering, or part of a separate psychological issue. Moreover, given the stigma of psychological and mental illness, some patients may be more willing to voice physical complaints and symptoms without providing the emotional context in which they arise. Nevertheless, combining the symptom of pain with other unsubstantiated symptoms has made the problem more complex and less amenable to a physiologic etiology. Symptoms such as memory loss, fatigue, lack of concentration, difficulty focusing, foggy brain and learning difficulties [74] are simply too subjective to quantify, nor do they lend themselves well to a pathophysiologic mechanism. Studies have postulated that although CRSP and fibromyalgia and repetitive strain injury are separate entities, they share some common characteristics [75]. It is noteworthy that fibromyalgia is also a condition where there is no clear pathophysiology, and which many neurologists and rheumatologists consider to be a FND. Lumping CRSP with fibromyalgia [76], another syndrome of unknown pathophysiology and dubious existence itself, certainly does not help to simplify the issue [76]. Interestingly, anti-depressants such as: tricyclics, SSRIs, Venlafaxine, Bupropion, Duloxetine, are also widely prescribed for both these conditions, which means that, for these patients, expressing psychological distress as chronic physical pain may lead to being prescribed medications that improves their psychological distress [77].

An additional issue with CRPS is the *a priori* acceptance of this syndrome as a real entity, and the use of this term or syndrome as an endpoint in pain studies. An example can be found in a paper entitled "Complex Regional Pain Syndrome following Spine Surgery: Clinical and Prognostic Implication" [18]. This assumes that CRPS is a validated entity. There is an inherent problem in conducting a study on a false condition or one that does not exist. It is almost as farcical as a study of diabetes in unicorns. And yet, one can find thousands of papers on CRPS, as if it is indeed a well-established disease.

9. CRPS is just pain, and the complexity is in the psychology – functional neurologic disorders

The syndrome of CRPS has not only contributed to the confusion regarding the treatment of pain but has also created phantom associations between pain and other symptoms. An interesting observation is that treatment of CRPS with spinal cord (and Dorsal Root) stimulation reduces patient's pain complaints according to a VAS pain scale, but not any of the other subjective and functional symptoms associated with CRPS [50], suggesting than pain is just pain, and there is no real syndrome combining pain and these other subjective maladies. It is not to say that these patients are not experiencing these symptoms. They may be indeed suffering for various reasons, but the creation of an encumbering syndrome such as CRPS has only hindered and not helped to develop scientific research into these other symptoms and signs. Unfortunately, even to this date, there is no specific diagnostic test for CRPS [52], and the diagnosis relies on medical history and physical alone, and the exclusion of other disorders.

9.1. CRPS and FND

Neurologists frequently encounter Functional Neurological Disorders ("FND") in their daily practice with a reported incidence of nearly 30–50% [78]. According to a UK review, the incidence is between 4 and 12 per 100,000, and it is the second most common diagnosis in neurology clinics [79]. According to a review authored by Stone and Carson, "Functional disorders describe bodily symptoms and disorders, such as functional movement disorders, or nonepileptic seizures, which are genuine but not related to a defined disease." Among conditions considered to be functional are "chronic widespread pain (fibromyalgia), chronic fatigue syndrome, and irritable bowel syndrome." In the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the requirement that a patient have a primary psychological stressor or condition has been eliminated. DSM-5 lists these criteria for conversion disorder (functional neurological symptom disorder):

A. One or more symptoms of altered voluntary motor or sensory function.
B. Clinical findings provide evidence of incompatibility between the symptom and recognized neurological or medical conditions.
C. The symptom or deficit is not better explained by another medical or mental disorder.

The symptom or deficit causes clinically significant distress or impairment in social, occupational, or other important areas of functioning or warrants medical evaluation [80].

Based upon these DSM-5 criteria, it is clear that CRPS constitutes an FND unless it is recognized as a separate disorder. Indeed, the CRPS "Budapest" diagnostic criteria are now circular with the DSM-5 FND criteria. In that respect, the Budapest CRPS criteria requires that "no other disease or condition better explains the signs and symptoms." However, but for the invention of CRPS, the diagnosis of FND would explain disproportionate pain and symptoms that do not occur in a neurological pathway and which cannot be explained by another neurological or medical condition. Moreover, a diagnosis of FND does not require that the patient also be diagnosed with another psychological condition, or even a known psychological stressor. A recognized precipitating factor for the development of a FND includes "acute physical pain or limb injury" [81]. Perpetuating physical factors include such issues as "chronic pain, abnormal motor habit formation, deconditioning, " which are similar to the factors that cause the signs and symptoms associated with CRPS. Significantly, one of the purported reasons for excluding CRPS as a FND or conversion disorder, research suggesting that CRPS patients do not demonstrate unusual psychological pathology (or that the pathology is related to chronic pain), is (are) no longer valid.

FND patients do not necessarily demonstrate abnormal psychological profiles or carry a psychiatric diagnosis.

Although the exact mechanism by which patients develop functional disorders is unknown, some have proposed that it can be explained in the context of the placebo effect, which is the result of a combination of classical conditioning and explicit expectancies [82]. Essentially, FNDs can be viewed as the converse to the placebo effect commonly seen in medical practice where a sham treatment "cures" physical symptom. In addition to a reverse placebo effect, there is neurobiological evidence for the production and maintenance of FNDs, which is similar to the subtle reported findings purportedly associated with CRPS.

What can be seen clearly from the literature are two divergent trends. While CRPS specialists are advocating a pain syndrome model, often with financial incentives in the form of very expensive invasive palliative treatments to address symptoms; neurologists and psychiatrists are successfully treating virtually identical patients by addressing the underlying functional mechanisms for the symptoms, often in a cost-effective manner. Although the traditional CRPS approach is largely symptom based; the FND model currently utilizes evidence-based medicine to address the underlying functional causes of the symptoms, which include voluntary immobility and an exaggerated pain response. Interestingly, where CRPS researchers have utilized a functional approach to the symptoms, for example, physical therapy under hypnosis, or aggressive physical therapy to treat children, the outcomes have been overwhelmingly positive. Symptom based approaches to CRPS, including spinal cord (and dorsal root) stimulation and ketamine, have failed to produce significant functional improvement, and their only measure of success is reported improvement in VAS pain scales.

Numerous case reports have also described patients with movement disorders similar to CRPS who ultimately are diagnosed with a psychogenic etiology or a psychiatric illness. A case of clenched fist syndrome mimicking reflex sympathetic dystrophy was presented in 1995 in a 45-year-old with post-traumatic stress disorder who sustained a hand injury [83]. In 1997, another case of a movement disorder was proven to be psychogenic by video surveillance monitoring [84]. Further evidence of a psychogenic component to CRPS is evidenced by the positive response to physical therapy in conjunction with hypnosis among 20 patients with the diagnosis of CRPS-1 [85].

10. CRPS and MPRD

The management of pain disorders is a very delicate subject. This is because of the lack of an objective measure of pain, which leads to it being a symptom that can be manipulated, whether intentionally or unintentionally. DSM-IV defines pain disorders as a "behavioral signaling of physical distress in excess of medical findings." The evaluation of such disorders, in order to determine if psychological or cognitive factors are influencing the reporting of pain by patients, is difficult to impossible, even by trained clinical psychologists, neuropsychologists or psychiatrists. The question of secondary gain, especially financial, cannot be ignored in the evaluation of pain [86,87], and pain can also be weaponized and used as a means of social control [88]. In a study of 73 participants who meet CRPS-1 criteria as defined by the IASP, all of them met at least 3 of 4 criteria for Malingered Pain-Related Disability [89], as defined by Bianchini et al. [90]. Self-induced injury has also been reported to be associated with CRPS in a small study of 175 referrals for neuropathic pain to a comprehensive pain clinic in 2001–2002. Of 15 women with a diagnosis of CRPS, 4 had evidence of self-induced disorder. Moreover, in that study, 42% of female and 27% of the male subjects who carried a diagnosis of CRPS presented with factors inconsistent with a neuropathic pain syndrome [91].

11. Social consequences of CRPS

Although CRPS, and its predecessor RSD, have not been scientifically validated as a distinct scientific entity, and its causation has not been established, this has not prevented its use in issues of disability. The contention that literally anything or nothing causes CRPS, permanent disability, and the need for lifetime catastrophic medical care obviously has significant social and financial consequences [92,93]. The AMA Impairment Guidelines used in most state's workmen's compensation courts also emphasize the lack of scientific reliability and the need to exclude other medical and psychiatric conditions [94]. As discussed above, a diagnosis of FND, or conversion disorder, can be made under the current diagnostic guidelines without the need to diagnose or find another underlying psychological ailment or stressor. Because the hallmark of CRPS is disproportionate pain that does not follow a recognized biological pathway, such patients also meet the diagnostic criteria for FND, which under the current CRPS criteria, is a diagnosis that could better (or equally) explain the patient's symptoms.

In a study of 50 consecutive CRPS patients who were involved in litigation in the United Kingdom, the investigators found that somatoform disorders, as defined by DSM-V, were found in 42 patients. Twenty-one demonstrated three or more pain-related functional somatic syndromes, and twenty-one also showed functional neurological symptoms such as claw hand. Again, in 19, the diagnosis of CRPS was even questioned. Depression and panic attacks were common (30/50 and 10/50 respectively). But what was perhaps the most disturbing was that 32 (64%) were on opiates, perhaps illustrating the contribution of CRPS toward the opioid epidemic of the 21st century [95].

The prominent role of litigation and compensation seeking in a large proportion of CRPS patients means that their symptoms are often reinforced and prolonged by the legal system. Involvement in litigation and disability cases reinforces the idea that CRPS is a permanent disabling condition that is unlikely to improve.

12. Conclusions

It is somewhat of a paradox that in this day and age of modern medicine, some 400 years after the introduction of the scientific method, with all the technical tools available to us, that we continue to find non-scientific ways to categorize certain human maladies. In most cases, diseases are defined by stringent objective criteria. So why does the medical community accept blindly the existence of CRPS, a condition in which there are no objective tests, variable and vague presentation and no consistently effective therapy [96]. There is nothing scientific about the diagnostic criteria for CRPS. It is vague and inconsistent and is completely unable to be validated due to the heterogeneity of the patients that could fall under the criteria, as well as the lack of any objective testing. Factor analysis, an artificial statistical tool, has been used to justify the creation of these criteria [97], but again, this is not a valid scientific method.

Although CRPS is a diagnosis of exclusion, the same symptoms would also require a physician to consider FND, which means that there is always a better (or equally as likely) explanation for the symptoms than CRPS. Attempts to determine etiology of CRPS have led to several proposed theories involving immune, vascular and neurological anomalies, including abnormal cytokine production, autoimmunity, sympathetic nervous system abnormalities, central cortical reorganization, altered blood flow and sensory disorders. None of the studies attempting to attribute CRPS to any of these pathogenic mechanisms have had appropriate controls or enough patients to conduct statistical calculations with sufficient power [56]. As mentioned earlier, pharmacological and surgical management of CRPS has also been found to be ineffective, with the only consistently effective treatment being reduction of the period of immobilization through early physical rehabilitation. Coincidentally, aggressive physical therapy also effectively restores function in FND patients.

We are not doubting that in some patients, pain can occur that is disproportionate to the injury, or that other sensations or symptoms can occur in conjunction with the pain. If this is the case, however, there should be a discernible pathogenesis for the symptoms and signs. If a

pathophysiologic etiology for these symptoms or collections symptoms is not found, and there is no evidence of secondary gain or psychological contributions to these symptoms, then FND can be diagnosed under the current diagnostic guidelines with an excellent prognosis for return to function with reassurance, physical therapy, and cognitive behavior therapy. There is, of course the possibility that we do not have enough knowledge of the human body, including full knowledge of the psychiatry underlying chronic pain, to discover the reasons why patients are suffering these maladies. However, to create a disease or syndrome to corral patients with varying symptoms into one category and provide a label for this group of patients can be counterproductive and dangerous, and in this case, has contributed to wasted resources. The effectiveness of CRPS treatments is currently measured not in functional outcomes but instead in improvement in VAS pain scales, which is quintessential symptom-based medicine. Symptom based medicine, with its heavy reliance on subjective pain scales, significantly contributed to the misuse of opioid analgesics, which in turn, compounded the opioid epidemic.

CRSP is thus included in a collection of syndromes with no discernible pathogenic mechanism, a group of syndromes which have been created based on subjective symptoms to provide a label for patients seeking desperately for a diagnosis. These creations illustrate the proverbial “driving ditch to ditch,” or overreacting to certain minor problems and ending up in bigger ones. In response to valid complaints that pain was being undertreated in the hospital setting, the medical community began overtreating even minor pain complaints with powerful addictive opioids for prolonged outpatient periods with catastrophic consequences. In response to physicians glibly dismissing valid complaints as “hysteria” or being “all in one’s head,” the medical community began classifying vague non-anatomic symptoms as various syndromes that should be treated medically and/or invasively. These syndromes include CRPS, Ehler-Danlos type 3, postural orthostatic tachycardia syndrome, mast cell activation syndrome, mycotoxicosis and pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS).

Respect for both the patient (and science) requires physicians to acknowledge a biopsychosocial connection to subjective pain complaints; and decline to label every symptom complex with a purely descriptive diagnosis. The new DSM-5 FND Diagnosis provides an appropriate framework to treat a patient’s subjective complaints with respect, provide appropriate reassurance, and enable a patient to return to function. Neither the CRPS label nor its invasive and ineffective treatment accomplishes these goals. Instead, it imposes a heavy social and financial cost without achieving any functional improvement to the patient.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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