

A brief review of complex regional pain syndrome and current management

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ABSTRACT

Complex regional pain syndrome (CRPS) is a debilitating chronic pain condition that, although exceedingly rare, carries a significant burden for the affected patient population. The complex and ambiguous pathophysiology of this condition further complicates clinical management and therapeutic interventions. Furthermore, being a diagnosis of exclusion requires a diligent workup to ensure an accurate diagnosis and subsequent targeted management. The development of the Budapest diagnostic criteria helped to consolidate existing definitions of CRPS but extensive work remains in identifying the underlying pathways. Currently, two distinct types are identified by the presence (CRPS type 1) or absence (CRPS type 2) of neuronal injury. Current management directed at this disease is broad and growing, ranging from non-invasive modalities such as physical and psychological therapy to more invasive techniques such as dorsal root ganglion stimulation and potentially amputation. Ideal therapeutic interventions are multimodal in nature to address the likely multifactorial pathological development of CRPS. Regardless, a significant need remains for continued studies to elucidate the pathways involved in developing CRPS as well as more robust clinical trials for various treatment modalities.

SUMMARY

- Complex regional pain syndrome (CRPS) is a debilitating and complex condition that places a significant physical, psychological and emotional burden upon afflicted patients necessitating multi-modal approaches to treatment.
- The development of the Budapest criteria provided a robust and well-tested set of diagnostic criteria to aid clinicians in the diagnosis of CRPS.
- The pathophysiology of CRPS has been challenging to elucidate with numerous proposed mechanisms, altogether suggesting a multi-factorial process is involved in the development of this condition.
- Non-invasive treatments for CRPS are essential in addressing the physical limitations this disease can cause as well as addressing the significant psychological burden that involves increased incidence of depression and suicidal ideation.
- Invasive treatments offer promising results, especially when considering dorsal root ganglion stimulation; however, the need for more robust clinical trials remains, especially when considering a small portion of patients who have refractory CRPS resort to amputation to control their pain symptoms.

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Introduction

Complex regional pain syndrome (CRPS) is a debilitating chronic pain condition that has been known by several names, including reflex sympathetic dystrophy or causalgia. First described in the sixteenth century, it was not recently that the Budapest criteria for

diagnosis were developed to better enhance the specificity of diagnosing. Consisting of two general types delineated by the presence (CRPS type 1) or absence (CRPS type 2) of neuronal injury, further delineation of CRPS has been proposed although debate remains regarding these additional descriptors. An exceedingly

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rare condition affecting 6.28–26.2 per 100,000 person-years, CRPS is characterized by continuing pain, allodynia or hyperalgesia that is disproportionate to the inciting event with evidence of edema, skin or blood flow changes or abnormal sudomotor activity in the region of pain with a predominance for the distal extremities [1]. Despite the development of the Budapest criteria, the challenge with diagnosing CRPS remains due to a lack of understanding regarding the underlying pathophysiology. Multiple etiologies have been proposed and its mechanism of onset is likely multifactorial in nature given the complexity of symptoms. Most often, patients will develop CRPS after fractures or blunt traumatic injuries. In a retrospective review, a rare subset of patients developed CRPS spontaneously without any memorable underlying event [2]. The predominance for preceding fracture or blunt traumatic injuries suggests a higher prevalence in athletes, a consideration that should be given to that particular population since earlier diagnosis allows for a greater likelihood of response to treatment modalities [3]. Given the currently elusive nature of CRPS pathophysiology, it behooves a multimodal approach to treatment with modalities therefore remaining broad, ranging from a variety of non-invasive and invasive modalities [4–6].

Classifications

CRPS has previously been known by other names, usually reflex sympathetic dystrophy or causalgia. It first entered the medical lexicon in 1994 at a meeting in Orlando where the International Association for the Study of Pain convened and defined CRPS. This led to the categorization of Type 1 and Type 2 CRPS being separated by the presence of a defined nerve lesion (Type 2) [7]. A number of society consensus meetings, most recently in 2007, have resulted in a more standardized common methodology for the diagnosis of CRPS [8]. This resulted in what is now known as the Budapest Criteria, a more widely accepted set of diagnostic criteria for CRPS. This requires continuing pain disproportionate to any inciting event; one symptom in three of the following four categories: Sensory, Vasomotor, Sudomotor/Edema, Motor/Trophic; one sign at the time of evaluation from the same categories; and there must be no other diagnosis which better explains these signs and symptoms. At the same Budapest conference, the decision was made to keep the distinction of CRPS Type 1 and Type 2, again delineated by the absence or presence

(respectively) of known nerve lesion, though of possibly limited clinical utility.

Looking at the role of the autonomic nervous system in CRPS however may help us make a more useful clinical distinction however. When tissue injury occurs, regardless of whether direct peripheral nerve injury occurs as well, there is an upregulation of proinflammatory factors and sympathetic nervous system nor-adrenaline receptors [9]. Additionally, in the milieu of recently damaged tissue, there is evidence of dysfunction in the autoinflammatory and autoimmune responses [10]. This leads to an exaggerated response to endogenous catecholamines in the post-injury period, again regardless of direct peripheral nerve injury. This may explain the periods of sweating, warmth, swelling and inflammation, alternating with periods of coolness (as the catecholamine/autonomic response waxes and wanes) that is not consistent with the normal expected course of tissue healing after trauma. As the post-trauma period continues, patients with CRPS tend to develop into either a Warm or Cold type of CRPS. This classification of Warm versus Cold CRPS was recently explored in a larger multisite study which sought to better define these subtypes and their prognostic implications. They found that there is a Warm subtype that is predominantly patients with acute CRPS which resolves within 6 months, while the Cold subtype is associated with a chronic type of CRPS [11]. These classifications of Warm or Cold CRPS thus are independent of classification as Type 1 or Type 2 CRPS as they are not explicitly related to the evidence of direct peripheral nerve injury. Furthermore, it must be emphasized that these stages are not necessarily progressive, but related to time intervals from initial insult or onset [12].

Pathophysiology

As previously noted, CRPS can be classified into two main categories: type 1 and type 2. Type 1 is also known as sympathetic dystrophy and is notable for there being no neural injury involved in the pathogenesis. In contrast, type 2 is a result of nerve damage [13]. Pathogenesis is still unknown, yet there have been several studies conducted which have revealed some important mechanisms that are involved with it.

Type 1 CRPS has two agreed upon clinical stages, with the first stage being the acute 'warm' phase and the second stage referred to as the chronic phase, also known as the 'cold' phase. In the acute 'warm' phase patients show clinical signs of inflammation, edema, pain and change in skin temperature in the affected limb [13,14]. Studies show that the inflammation could

be caused by an amplification of the innate immune response that leads to the proliferation of skin cells such as keratinocytes that are responsible for releasing pro-inflammatory cytokines TNF-alpha, IL-1B and IL-6, thus triggering an inflammatory response [6,15]. The release of cytokines results in the symptoms seen in the effected limb during the warm phase of CRPS such as vasodilation, swelling, warmth, and pain [16]. More evidence to this comes from a meta-analysis of studies that investigated the classic mediators of inflammation in CRPS. These studies found that IL-8 levels, a biomarker for the inflammatory response, were elevated significantly during the acute 'warm' phase of CRPS [13,17,18]. In multiple studies it was found that CD4+ and CD8+ lymphocyte population were increased suggesting a response from antigen-mediated T lymphocytes [6,19,20]. Analysis of serum levels of pro-inflammatory and anti-inflammatory cytokines showed IL-37 as a biomarker for the immune response. It was found that there was decreased serum levels of IL-37 as well as an increase of GM-CSF showing pro and anti-inflammatory cytokine response in CRPS with pro-inflammatory dominating the pathogenesis [16,20]. Several studies posit that exaggerated inflammatory response in the setting of impaired healing can help define or establish a CRPS course. Inflammatory cytokines may also be implicated as there is some evidence from elevated levels of IL-1B and IL-6 in cerebrospinal fluids from chronic CRPS patients while other studies by do not agree [21–23]. Interestingly, several studies have noted the observed inflammatory-mediated changes in both peripheral and central sensitization are not due to cell-mediated immune responses as they have reported normal levels of cell markers such as lymphocyte counts, sedimentation rates, antibody levels, activated T-cells and blood cell counts [24–26]. The exact role of cell upregulation or activation therefore remains unclear.

The chronic phase is associated with a reduction in the inflammatory component but persistence of pain [13]. Despite the decrease in inflammation seen in the chronic 'cold' phase of CRPS, pro-inflammatory mediators such as IL-6, MCP-1, and MIP-1B remain elevated [13,27]. In fact, some of the changes and symptoms seen in the chronic phase are the result of elevated inflammatory markers noted in the acute phase. The pro-inflammatory cytokines in the acute phase, including TNF-alpha, IL1B, and IL-17, activate osteoblasts and osteoclasts which result in osteoporotic changes due to rapid bone turnover [14,28–30].

Neurogenic inflammation plays a key role in the development of CRPS symptoms such as allodynia and hyperalgesia. The peripheral nociceptive C-fibers are

stimulated, resulting in the conduction of the stimulus both afferently to the dorsal ganglia as well as efferently to the affected tissue. This retrograde transmission causes the release of pro-inflammatory neuropeptides substance P, calcitonin gene-related peptic (CGRP), as well as adrenomedullin, neurokinin B, vasoactive intestinal peptide, neuropeptide Y and gastrin-releasing peptide [13,31]. Neuropeptide substance P and CGRP would bind to their respective receptors on keratinocytes leading to proliferation and neurogenic inflammation [6,32]. Substance P and CGRP also activate mast and dendritic cells which release histamine, serotonin and TNF alpha resulting in the attraction of inflammatory cells to the area in which they were released, resulting in further inflammation [33].

Multiple studies have shown evidence of an autoimmune component to CRPS. It was found that 35-40% of CRPS patients show surface binding autoantibodies targeting their sympathetic neurons, mesenteric plexus neurons, and cholinergic type cell lines [34,35]. Additionally, collected samples of serum, skin, and tissue from CRPS patients were found to have an elevated level of autoantibodies [6,36]. In an experiment conducted using mice injected with the IgG serum from a CRPS patient, findings were notable for those mice subsequently experiencing hypersensitivity to painful mechanical stimuli but not to tactile stimulation [37]. Additionally, the increased IgM levels that were found in the skin of CRPS patients as well as in the spinal tissue of rats, is thought to be responsible for the increased nociceptive sensitization.

Specifically, the elevated deposits of IgM in the skin could be caused by the release of neuropeptides during the retrograde transmission seen in the C-fibers during neurogenic inflammation [33]. Further evidence to support the autoimmune component involves dendritic cells which are stimulated by IgG complexes resulting in the migration of the dendritic cells to draining lymph nodes from peripheral tissue [14,38]. Furthermore, there may be genetic dispositions as noted by polymorphisms in tumor necrosis factor-alpha (TNF-alpha) and human leukocyte antigen (HLA) which may contribute to an earlier age of onset [39].

Increased Langerhans cell numbers were also found in affected skin samples of patients with CRPS, yet patients with chronic CRPS showed fewer Langerhans cells [40]. However, studies performed comparing wild-type and Langerhans cell knockout animals sensitization found no difference between the two groups when testing sensitization [33]. Notably, Russo et al. argues that the significance of the difference in the numbers of Langerhans cells found in the Osbourne

study is important. Citing Langerhans cells migrating to the dermis and draining the lymph node results in the priming of T-Cells to initiate an immune response [41,42]. Regardless of the role of Langerhans cells, there is a clear need for additional research to better understand the role Langerhans cells potentially play in the immunological response in CRPS pathogenesis.

Sensitization in CRPS

As previously noted, the typical classification of CRPS into type 1 and 2 can be ambiguous. The former is associated with noxious stimulus while the later with aberrant nerve. In CRPS, the constant noxious stimuli can result in peripheral and central sensitization. The sensitization is demonstrated by an enhanced level of sensation either from heightened pain (hyperalgesia) and unprovoked pain (allodynia). The states of hyperalgesia and allodynia is further explained by the aberrant interpretation by somatosensory units of the central nervous system (CNS) of benign stimuli such as light touch as pain. The skin over, and even beyond the initial area of insult, can become affected by the aberrant pain perception reflecting the characteristic regional presentation of this chronic pain syndrome in addition to other changes that reflect sensory, peripheral and sympathetic nervous system dysregulation [43].

The pathophysiology of peripheral and central sensitization underscores changes in the sympathetic nervous system (SNS) with resultant localized heightened sympathetic activity. Activated peripheral nociceptors that convey pain from either chemical, mechanical or thermal stimuli *via* unmyelinated C fibers and partially myelinated A-delta fibers that project to the Rexed layers I, II, and V in the spinal cord activate the release of excitatory amino acids glutamine and asparagine. These amino acids serve as ligands on *N* -methyl- *D* -aspartic acid (NMDA) receptors, further resulting in the release of substance P [44].

Peripheral sensitization

In peripheral sensitization, repetitive noxious stimulation of C fibers results in heightened sensitivity, coupled with reduced stimulus thresholds and prolonged activation of dorsal horn cells, particularly those with excitatory glutamine receptors. The resultant excitation is largely due to a myriad of inflammatory mediated processes that includes actions by substance P (SP), calcitonin gene-related peptide (CRGP), leukotrienes, prostaglandins, histamine, bradykinin, and serotonin,

all of which have versatile ligand properties that further compound the inflammatory process and algogenic states [45].

It is known that tissue trauma can cause the release of cytokines and nerve growth factor (NGF) which further activate nociceptors by stimulating the release of inflammatory or excitatory amino acids and neuropeptides in primary afferent neurons as previously noted thus contributing to *long-term* peripheral sensitization [46].

Central sensitization

In the pathological spectrum of CRPS, several mechanisms underlying central sensitization have been posited to include not only the state of enhanced excitability of neurons in the spinal cord but also inclusive of neuroplastic alterations in the somatosensory cortex and endogenous pain modulations [45].

The role of the central nervous system (CNS) cannot be overemphasized as it is thought to undergo structural and functional changes in CRPS patients. In particular, there are plastic changes such as the excitability of thalamocortical nociceptive pathways due to loss of peripheral inhibition and upregulation of glutamate receptors domicile in the CNS [47,48]. In addition, other neuronal plastic changes confer motor dysfunction in CRPS patients as evidenced by increased dystonia in the population [49]. The exact mechanism underlying dystonia in these patients is still unclear as several studies have only suggested an association.

Furthermore, an inherent characteristic of central sensitization is *mechanical hyperalgesia*. It has been posited that this phenomenon is due to the activity of second-order nociceptor specific neurons and particularly wide-dynamic-range (WDR) neurons in the spinal cord contribute to an expansion of pain sensation beyond the initial loci of injury. There is a compounding of effects due to contributions from peripheral inputs (sensitization) that creates a crescendo-like amplification of pain patterns [50].

One of many classic representations of peripheral contribution to CNS amplification is seen with excitatory neurons mediated-disinhibition of both trigeminal and spinal mechanical neurons and or excitatory neurons mediated-facilitation of nociceptive activity which project from the rostroventral medulla [51].

Autonomic

The old dogma on the etiology of CRPS was the role of sympathetic nervous system (SNS) hyperactivity and

the unique pattern of pain observed in patients was thought to be sympathetically mediated. While current literature highlights numerous addenda to this founding posit, it nevertheless reflects a more complex etiology that has been recently explained as an unusual pathological synergy between nociceptive afferent neurons and sympathetic efferent neurons.

Some physiologic changes have been observed particularly in the acute and subacute phase of CRPS, including aberrant skin color, temperature, sweating from vasodilatation, edema, hypertrichosis, hyperhidrosis, hypohidrosis, accelerated or decelerated nail [49]. Furthermore, the vasodilatory signs observed in acute settings suggests an inhibition/denervation of sympathetic action in the short-term that eventually results in hypersensitivity and upregulation of adrenergic receptors such that in subacute and chronic phase of CRPS, the presence of circulating catecholamine results in vasoconstriction as manifested as coolness. The psychological distress of the pervasive pain and autonomic symptoms further enhances catecholamine release and potentially exacerbates the aforementioned pathophysiologic mechanisms. In one study, a significant positive correlation between Beck Depression Inventory scores and catecholamine concentration was identified, further supporting the potential augmentation of CRPS pathways and subsequent symptoms [52,53].

The unusual synchrony or coupling between the nociceptive afferent and sympathetic efferent neurons have been described as likely to be a norepinephrine-mediated interaction between the afferent somata within the dorsal root ganglion (DRG) and sympathetic vasoconstrictor neurons, or between regenerating or intact peripheral nociceptive C-fiber and sympathetic efferent neurons [54]. mRNA activity for α -2-adrenergic receptors have been described in DRG neurons of injured nerves as contributing to vasodilatation [55].

Presentation and diagnosis

Historic considerations

Presentations consistent with CRPS have been described as early as the sixteenth century. Amroise Paré is often credited with the first account of CRPS when he described persistent extremity pain experienced by King Charles IX after bloodletting [56]. In the early 1800s, Denmark reported a case of unrelenting burning pain after a gunshot wound necessitating upper extremity amputation [57]. During the civil war era, Mitchell and colleagues described multiple

accounts of trauma-induced intractable burning pain [58]. Mitchell, aware of the afore mentioned, coined the term *causalgia* to describe such presentations. However, it was not until the early 1900s that the first diagnostic criterion was described. This criterion highlighted the spontaneous and burning characteristics of the pain while noting the tendency for painful exacerbations and mental status changes [59]. As early as 1916, there were speculations that the underlying mechanism of such presentations involved over excitation of the sympathetic nervous system [60]. Sudek and Evans described associated edema and motor limitations with or without the presence of an identified nerve lesion, naming such syndromes *reflex sympathetic dystrophy* (RSD) and *Sudek dystrophy/atrophy*, respectively [61,62].

It was not until 1979 that the International Association for the Study of Pain (IASP) formally defined these syndromes as sustained burning pain after a traumatic injury involving vasomotor, sudomotor and trophic changes with similar presentations but different causes [63]. In 1994 the IASP accepted and published the descriptor 'complex regional pain syndrome' to describe a condition clinically defined by: (1) The presence of an initiating noxious event, (2) continuing pain, allodynia or hyperalgesia, which is disproportionate to the inciting event, (3) evidence of edema, skin or blood flow changes or abnormal sudomotor activity in the region of pain, (4) the diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction [64]. These criteria, known as the Orlando criteria, were found to have high sensitivity but poor specificity on internal and external validation testing, leading to inadvertent over diagnosis of CRPS [59].

The Budapest criteria

At the consensus meeting of the IASP in Budapest in 2004, new criteria for the diagnosis of CRPS were developed [8]. In an effort to enhance specificity, these criteria included both symptoms and signs of the disease. These criteria, known as the Budapest criteria, are listed in Table 1. Concordant with their objective, validation testing revealed a sensitivity of 0.76 (formerly 0.98 with the Orlando criteria) and a specificity of 0.81 (formerly 0.36 with the Orlando criteria) when utilizing 3 of 4 symptom and 2 of 4 sign decision rules for diagnosis [65]. The Budapest criteria were formally accepted by the IASP in 2012 after more robust validation testing [66]. It should be noted that a 4 of 4 symptom decision rule is

Table 1. Budapest criteria.

Procedure Standards*	I. All symptoms criteria should be asked at each formal evaluation II. For unilateral CRPS, assess asymmetry via comparison with the contralateral extremity III. For bilateral CRPS, assess for changes relative to an unaffected extremity or assess for asymmetry relative to a typical, healthy individual IV. The full criteria must be applied to each individual extremity v. In the event an examiner observes a sign that the patient does not express as a symptom, a “signs over-rides symptoms” approach cannot automatically apply[#]
The Budapest Criteria	For the clinical diagnosis of CRPS, all of the following must be true: I. Patient describes continuing pain, disproportionate to the inciting event II. Patient reports at least one symptom in all four categories 1. Sensory a. Allodynia b. Hyperalgesia 2. Vasomotor a. Temperature asymmetry b. Skin color changes c. Skin color asymmetry 3. Sudomotor a. Change in or asymmetrical edema b. Change in or asymmetrical sweating 4. Trophic a. Decreased range of motion b. Weakness, tremor, dystonia c. Changes of hair, nail, skin III. Physician observes at least one sign in at least two categories 1. Sensory a. Allodynia to light touch (light manual touch or brush*), temperature, somatic pressure (application of pressure until the examiner's nail bed turns white, roughly 100g/cm²*) or vibration (assessed with a graded tuning fork over a bony prominence*) b. Hyperalgesia to pinprick (applied centrally in most affected extremity and compared to the same location in the unaffected extremity*) 2. Vasomotor a. Temperature asymmetry of >1 °C (If quantitative metric is not obtainable, temperature change should be obvious to examiners when touching the area with the dorsum of their hands*) b. Skin color changes c. Skin color asymmetry 3. Sudomotor a. Change in or asymmetrical edema b. Change in or asymmetrical sweating 4. Trophic a. Decreased range of motion b. Weakness, tremor, dystonia c. Changes of hair, nail, skin IV. No other diagnosis better explains the described symptoms and observed signs
Corresponding Diagnosis	CRPS Type I If the criteria are met at the time of evaluation and there is no known nerve lesion in the affected area CRPS Type II If the criteria are met at the time of evaluation in an anatomic region extending beyond the territory of any identified nerve injury* CRPS with Remission of Some Features* If the medical record confirms the criteria have been met at some historical point. However, the criteria are not met at the time of evaluation CRPS Not Otherwise Specified If the medical record confirms the criteria have never been met.* However, there is no alternative diagnosis that better explains the presentation

Adapted from Harden et al.

*Indicates taxonomic or procedural clarification described by Goebel et al.

[#]See Goebel et al for examples of such situations and recommended action.

recommended when applying the criteria for research purposes [65].

In 2019, the IASP CRPS special interest group convened for a discussion of perceived ambiguities in the Budapest criteria for CRPS diagnosis. This resulted in a consensus-based adaptation of diagnostic taxonomy, which represents a clarification of CRPS assessment instructions without changing the diagnostic criteria, itself [67]. Notable areas of clarification include: (1) recognition that CRPS 1 and 2 have identical diagnostic signs.

For correct diagnosis of CRPS 2, the diagnostic signs must extend beyond the territory of any identified injured nerve (2) the diagnosis ‘CRPS Not Otherwise Specified’ should only be applied to patients who have never fulfilled the Budapest criteria for CRPS diagnosis but whose condition is not better explained by another disease process (3) definitions for asymmetry, hyperalgesia, and allodynia, as they relate specifically to CRPS diagnostic assessment. While this expert group acknowledged the importance of distinguishing warm and cold variations of

CRPS, they did not feel there was sufficient data to support a consensus adoption of these variations to formal CRPS subtypes. They did, however, introduce a new CRPS subtype, CRPS with Remission of Some Features, which represents a patient population not currently meeting the Budapest criteria but who have a documented history of meeting the criteria in the past. The group acknowledged that future work would focus on further defining the diagnostic transition to this subtype.

The Budapest criteria remain the gold standard for the clinical diagnosis of CRPS. The criteria are endorsed by the IASP and all its affiliate federations and chapters. Multiple researchers and physicians have proposed other criteria for the diagnosis of CRPS, but none of these have undergone and withstood robust validation testing as successfully as the Budapest criteria [24,68–73].

Utility of diagnostic testing

No singular objective test is specific for CRPS. Diagnostic standards for many pain organizations, including the European Pain Federation, support the use of diagnostic testing as a means to exclude differential diagnoses [74]. A majority of those ultimately diagnosed with CRPS have undergone extensive diagnostic testing including but not limited to the following: bone scintigraphy and other bone densitometry studies have been reported to show increased uptake in CRPS affected joints [75]. It is generally recognized that earlier use of tri-phase bone scintigraphy correlates with increased specificity of the study for CRPS. Compared to other utilized objective tools, these studies are relatively easy to obtain in clinical practice. Multiple meta-analyses have concluded scintigraphy should not be used to rule in disease; however, it could have utility as a confirmatory test [76,77].

Doppler flow studies have been suggested to assess vascular reflexes, especially in patients with symptom duration of four months or less [65]. It can also be used for exclusion of contributing vascular pathologies, particularly venous thrombosis.

Infrared thermometry/thermography has the highest specificity of any objective test for CRPS [65]. In earlier phases of the disease, the affected limb typically shows higher temperatures compared to the contralateral control [78]. This observation has been shown to reverse with disease progression. Sensitivity for CRPS has been reported as low as 45% [63]. Thermography requires specialized equipment and accuracy depends on the ability to maintain thermoregulation during measurements [65,79]. The utility of other autonomic function tests including, quantitative

sudomotor axon reflex testing and thermoregulatory sweat testing, have similar limitations in that they require specialized equipment, knowledgeable operators, and they have a lower specificity for CRPS [63,65].

Magnetic resonance imaging (MRI) is especially useful in the exclusion of musculoskeletal disorders, particularly osteonecrosis [63]. MRI has been shown to be less sensitive for CRPS diagnosis than bone scintigraphy in comparative studies [80].

Plain radiography is one of the most affordable and easiest objective tests to obtain. Films often show a heterogeneous demineralization of bone in endorsed painful regions. However, x-ray has low reported sensitivity and specificity for CRPS [61,63]. Its greatest utility is arguably exclusion of other musculoskeletal injuries, particularly in early diagnosis of a unilateral extremity presentation of the disease.

Limitations of current diagnostic standards

As previously discussed, CRPS remains a clinical diagnosis of exclusion. Accurate diagnosis relies on standardized assessment and application of diagnostic criteria across physicians, which has historically been limited. Further taxonomic clarifications and standardization of assessment techniques, like those described by the CRPS task force in Valencia, represent necessary strides forward towards more uniform and generalizable diagnostic criteria. Specifically, clarification of prior definitions such that CRPS type 2 must include diagnostic signs that extend beyond the identified injured nerve territory. Additionally, the development of a third category, CRPS Not Otherwise Specified (NOS) allows for the inclusion of patients who had previously met diagnostic criteria but do not meet the updated diagnostic criteria put forth by the Valencia task force. Furthermore, the updated diagnostic criteria require patients to report at least one symptom in three or more of the four categories whereas previously they were required to have symptoms in all four categories outlined in the Budapest criteria. The task force also highlights a need to clarify if CRPS type 1 and 2 are truly unique diagnoses, as well as the need for sub-group identification (warm vs cold, for example) is critical to management [67].

Treatment

Non-invasive interventions

Physical, occupational and psychological therapy

The role of physical and occupational therapy (PT and OT, respectively) is part of a multi-modal approach to the management of CRPS and is often a keystone in a

patient's treatment regimen [4]. The challenge with implementing PT and OT is the broad range of interventions available to therapists and the persistent lack of understanding regarding the underlying pathophysiology of CRPS. Regardless, a number of case reports have been published showing efficacy in a wide range of interventions, ranging from strain-counterstrain (SCS), neural mobilization techniques, and thrust manipulation, to name a few [81–83]. These techniques often rely on some form of neuromodulation, either through decrease in proprioceptive hyperactivity as seen in SCS or activation of descending pain pathways and inhibitory mechanisms in spinal manual therapy. Additionally, there is evidence of analgesic effects achieved through the release of neurotensin and oxytocin, providing patients with short-term analgesia that may subsequently enhance their ability to participate in other therapeutic modalities they may previously not have tolerated [84,85]. Additionally, as previously noted, there is likely a role involving catecholamines in the pathophysiological pathway of CRPS. Although the evidence is lacking in clinical trial evidence, case series have shown promise in the benefits of various forms of psychotherapy intervention, especially when combined with other non-invasive modalities. Additionally, adaptation of the treatment regimen to the evolution of a patient's symptoms is critical [12]. Of particular interest is the study conducted by Fialka et al. who found a decrease in limb temperature in the psychotherapy arm compared to the physical therapy only group. Although the study was limited by its lack of power, it lends further support to the role psychological stress can play in the progression of CRPS [86,87]. Furthermore, this particular patient population carries significant risk factors for suicidal ideation, including: severe pain, depressive symptoms and functional impairment. The link between chronic pain and suicidal ideation has been well established, and given the additional autonomic dysfunction associated with CRPS, these patients carry a significant risk for suicidality [88–91]. The range of benefits is variable and there remains a paucity of evidence regarding these modalities; however, given the current understanding and proposed pathophysiological mechanisms, these interventions are logical in their employment.

Medical management

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are cyclooxygenase (COX)-2 inhibitors, preventing the synthesis of prostaglandins. Prostaglandins are inflammatory mediators and induce hyperalgesia; therefore, downregulating these molecules may disrupt the

process of spinal transmission of nociceptive signals and reduce the acute-pain stage of CRPS [92]. However, the evidence remains poor regarding the efficacy of this drug class although there are case reports showing potential benefits [6,93].

Steroids

Steroids are used to target the inflammatory component of the proposed CRPS pathophysiology mechanism. There have been several studies assessing the efficacy of steroids, at various doses, various time-intervals and in patients with varying degrees of CRPS duration (acute vs chronic) [94–96]. Given the noteworthy and potentially significant adverse effects associated with prolonged steroid use, care needs to be exercised by the clinician when considering these medications. One trial in particular was notable for the significant benefits of a tapered prednisone regimen in patients with an average duration of 1.9 months since onset of CRPS in reducing VAS pain scores [97].

Gabapentin

Gabapentin, originally used as a muscle relaxer and anti-spasmodic medication, has been found to be an effective adjunct anticonvulsant with neural pain control potential [98]. Van de Vusse et al. performed a randomized double blind placebo controlled crossover study and found that while gabapentin only had a mild effect on pain in CRPS I, it had a significant impact on reducing the sensory deficit in the affected limb [99]. These results were similar in the pediatric population, as Brown et al. found that gabapentin significantly reduced pain intensity scores while improving sleep [100]. This study found that both the antidepressant amitriptyline and the anticonvulsant gabapentin were analogous in their effectiveness in reducing pain in CRPS I. A limitation of these trials was the low number of participants in the trials. While commonly utilized in the treatment of CRPS, there are ultimately few randomized control trials with solid evidence to prove the efficacy of gabapentin, suggesting that there needs to be further research into gabapentin with respect to CRPS [4].

Bisphosphonates

Bisphosphonates inhibit osteoclastic bone resorption by to hydroxyapatite sites, especially at sites undergoing active bone resorption. The exact mechanism for how bisphosphonates provide analgesia in CRPS remains unclear, although there are a number of potential mechanisms that have been proposed and the true mechanism is likely multifactorial in nature

given the limited degree of bone turnover noted in CRPS [101]. Regardless, there appears to be a degree of evidence indicating the benefit of bisphosphonates in reducing pain scores in comparison to placebo; however, many of the early trials were often lacking in power. In addition, a lack of true understanding behind the mechanism of action for therapeutic benefit with bisphosphonates limits the ability to identify ideal drug and dosing regimens [4,102]. However, a randomized, double-blind, placebo-controlled study comparing four doses of IV neridronate to placebo found statistically significant decreases in VAS scores in the study of 82 patients. The authors posit that these results may be linked to bisphosphonate reduction of the increased bone turnover and subsequent marrow edema seen in CRPS that may contribute to chronic pain. Additionally, locally accumulated drug may interfere with the inflammatory pathways and subsequent pain generation by decreasing lactate concentration and acidosis. Interestingly, some patients also experienced permanent remission of their disease; however, it should be noted that these patients were identified early in their clinical course, an important caveat to the efficacy of bisphosphonates in treating CRPS. Regardless, the significant efficacy and limited adverse effects of the medications suggest an importance in incorporation of bisphosphonates as standard of care when initiating treatment for CRPS patients [103].

Ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist with a notable role in the modulation of the wind-up response to noxious stimuli that results in central sensitization classically seen in chronic pain conditions. There is also evidence of a role in immunomodulation resulting in the down-regulation of neuroinflammatory markers; therefore, it remains unclear if the potential role of ketamine in CRPS treatment is relegated solely to the effects of NMDA antagonism resulting in down-regulation of central sensitization or if there are additional factors involved [104,105]. Regardless, the current body of evidence is lacking in supporting the efficacy of ketamine in the treatment of CRPS with the majority of studies lacking in power or utilizing different modes of administration, making it difficult to determine the level of evidence supporting ketamine [5,105,106].

Botulinum Toxin A

The use of Botulinum Toxins A and B have been an emerging adjunct to local anesthetics for sympathectomies and treatment of dystonia/spasticity in the

treatment of CRPS, with most studies published starting in 2008. The mechanism of this therapy was hypothesized to be slightly different depending on the use for treating dystonia and spasticity or for a sympathectomy. In dystonia, the role of botulinum toxin in therapy is due to its function in disrupting the SNARE complex and inhibition of exocytosis. It prevents the release of acetylcholine and causes flaccid paralysis, effectively relieving the pain from muscle dystonia and spastic contractility [107,108]. A retrospective case review of the use of Botulinum Toxin A (BTA) in patients with neck or upper limb girdle muscles with dystonia and spasm showed that there was significant pain relief in 97% of the patients over the first 4 weeks after treatment. Given the efficacy of botulinum toxin in inhibition of cholinergic circuitry, several studies have expanded its use to blocking cholinergic signaling at the sympathetic ganglia in CRPS patients. The majority of studies have been small case-control or retrospective studies regarding the efficacy of Botulinum Toxin A (BTA) and Botulinum Toxin B (BTB), either by themselves or in conjunction with local anesthetic. While these studies range from retrospective studies to prospective randomized controlled trials, they all show moderate improvements in pain scores over the short term with either botulinum toxin alone or with local anesthetic. They also reliably show that the use of botulinum toxin has a greater duration of efficacy than the use of local anesthetic alone [109]. A meta-analysis performed in 2020 which evaluated randomized controlled trials provided good evidence for the efficacy of BTA for pain relief across neuropathic and muscle based pain syndromes [110]. There are numerous other studies that suggest the use of BTA or BTB depending on the location of the sympathectomy, but there is not yet strong evidence for the use of one or the other purely based on the site of CRPS being treated [111,112]. There is currently a study underway with very similar parameters looking at the impact to quality of life and disability scores in CRPS patients [113]. While BTA has significant therapeutic potential, there are concerns about possible extravasation into surrounding ganglia which could lead to neurologic complications as well as discrepancies between industry and non-industry-sponsored studies [114].

Antioxidants

In the search for improved pharmacological treatments for CRPS, the use of antioxidants has been increasingly studied over the past ten years, spanning the fields of rheumatology, anesthesiology and orthopedics. This is

primarily regarding CRPS Type 1, with an established injury or trauma, in many cases from surgery. In fact, Eisenberg et al. in 2008 demonstrated that when comparing CRPS 1 and control patients, the patients with CRPS had significantly elevated salivary peroxidase, superoxide dismutase activity, uric acid and total antioxidant status compared to controls [115]. In 2014 Baykal et al. had similar findings, showing that superoxide dismutase, glutathione peroxidase and glutathione s-transferase activity were all significantly elevated in patients who developed CRPS I when compared to patients who did not [116]. Several studies have been done regarding the prophylactic treatment of surgical patients with Vitamin C post-operatively. These have found that prophylaxis with 500mg to 1g of Vitamin C daily post operatively from total knee arthroplasty, foot and ankle surgery, and subacromial shoulder surgery had a statistically significant effect on the development of CRPS 1 [117–119]. Patients who received Vitamin C were less likely to develop CRPS, considered to be through the role of Vitamin C in stabilizing reactive oxygen species and in turn reducing inflammation. Beyond this, a meta-analysis of randomized controlled trials using vitamin C for CRPS prophylaxis found a similar reduction in the risk of CRPS development [120]. In all, it is safe to say that Vitamin C perioperatively could be a valuable tool in the prevention of CRPS Type 1, especially in the elective surgical setting, ultimately reducing the incidence of this often-debilitating disease.

Invasive interventions

Sympathetic blocks

A sympathetic block is a commonly used minimally invasive treatment for CRPS. Although frequently used, sympathetic blocks' short- and long-term analgesic effects are not well supported by evidence. It is thought that one of the underlying pathophysiologic mechanisms of CRPS is sympathetic hyperactivity. The most common sympathetic blocks for CRPS are the stellate ganglion sympathetic blocks used to treat upper extremity symptoms while lumbar sympathetic nerve blocks are used to treat lower extremity symptoms [13]. Although the quality of the evidence was low, a 2013 Cochrane review found that sympathetic blocks combined with local anesthetic were ineffective at reducing CRPS-related pain [121]. A more recent Cochrane review in 2016 was unable to make any firm judgments regarding the effectiveness of this type of treatment for CRPS [121]. In 2019 a study looked at the relationship between sympathetic blocks and spinal cord stimulation and found that the effects of a

sympathetic block did not predict the success of a spinal cord stimulator [122].

Spinal cord stimulation

With spinal cord stimulation (SCS), electrodes are positioned in the epidural space to deliver electric stimulation to the spinal cord's dorsal column. Some devices use an external pulse generator, but typically the electrodes are connected to an implanted pulse generator. Several mechanisms of action for SCS have been proposed, including vasodilation, reversal of cortical maladaptive neuroplastic changes, adrenergic inhibition, and inhibition of nociceptive neural conduction in the spinal cord. A comprehensive outcome specific review of the use of spinal cord stimulation specifically for CRPS was published in 2016. High-level evidence (1B+) continues to support spinal cord stimulation's beneficial and successful role in the treatment of CRPS patients' perceived pain relief, pain score, and quality of life. Functional improvements were noted with less evidence for CRPS resolution, sleep hygiene improvement, positive psychological impact, and analgesic sparing effects [123]. A different study looking at the long-term outcome of SCS in CRPS did not find statistical functional improvement or a reduction in opioid or neuropathic pain medication use. However, they did note that 70% of the patients continued to use their SCS devices at the eight-year follow-up [124].

Dorsal root ganglion stimulation

An innovative neuromodulation technique for the treatment of chronic pain targets the dorsal root ganglion (DRG) rather than the spinal cord. The DRG serves as an ideal target given its role in processing and transmitting sensory information from the periphery to the central nervous system. In animal models of chronic pain, pathophysiologic changes in the DRG have been noted, including altered expression of various genes that may play a role in the hyperexcitability of neurons involved in the nociceptive pathway. The exact mechanism of how DRG stimulation exerts its beneficial effects remains unknown, although it may be related to the modulation of a variety of cells housed within the DRG [125–128].

As opposed to conventional SCS, DRG stimulation enables a more targeted application of neurostimulation due to the DRG's more peripheral location and ease of access. For the treatment of lower extremity pain in CRPS, DRG stimulation received approval from the US Food and Drug Administration in 2016. According to a recent pooled analysis study, DRG

stimulation was safe and effective for CRPS, resulting in a 4.9-point mean decrease in CRPS-I pain intensity [129]. In 2017 the ACCURATE study compared SCS and DRG stimulation in 152 patients with CRPS. DRG stimulation was found to be more efficient than conventional SCS in this multicenter randomized trial for reducing pain and enhancing quality of life in CRPS patients [127].

Amputation

The role of amputation in chronic CRPS type 1 is a potentially viable one, specifically for those patients who suffer from intractable and refractory symptoms despite numerous multi-modal therapeutic interventions. Although not without their own risks as well as the potential for recurrence of CRPS in the remaining limb or other limbs, several studies have noted patient satisfaction with the benefits of amputation. These retrospective reviews are relatively limited in power; however, they suggest a potential intervention for those patients who have exhausted alternative options [130–132]. There may be additional benefit in selecting potential amputation candidates for their resilience, as a study conducted by Bodde et al. found that patients with higher resilience scores correlated with higher quality of life and lower psychological distress status post limb amputation [90]. Regardless of the potential benefits, the decision to pursue amputation should be taken in the context of the patient overall, recognizing and acknowledging the associated complications of amputation as well as the risk for minimal relief to recurrence of CRPS.

Conclusion

CRPS is a debilitating, life-altering condition that remains ambiguous regarding its underlying pathophysiology although notable progress has been made. Treatment modalities are therefore directed at symptomatic management and targeting potential pathways with initial modalities comprised of non-invasive options such as PT, OT and psychological therapies in addition to neuropathic medications. For patients with persistent or refractory symptoms, more invasive and alternative therapies can be considered; however, consideration must be given to the inherent risks associated with more invasive techniques and the lack of robust, high-quality evidence to support their use. Therefore, although DRG has shown to be especially promising in recent studies, more research directed at both invasive and alternative therapies is necessary given the scarcity of clinical trials with significant patient populations being involved to ensure patient

safety. As newer knowledge and advancements in the understanding of this condition expand, clinicians will be better equipped to target treatment modalities and manage these complex patients with an emphasis on early treatment initiation and adaptation of the rehabilitation program to ensure continued optimization for patients.

Authors contributions

Dr. Abd-Elseyed was involved with the conception and design of the article. Drs. Stark, Topoluk, Isaamullah, Uzodinma, Gyorfi and Schlidt as well as Mr. Fattouh were responsible for drafting of the manuscript. Drs. Abd-Elseyed, Stark, Viswanath and Dyara were responsible for critical revision of intellectual content. All authors approved the final version to be submitted and agree to be accountable for all aspects of the work.

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