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Commentary

Unravelling the Complex Regional Pain Syndrome Enigma

Sir Winston Churchill coined the phrase "a riddle, wrapped in a mystery, inside an enigma" to describe the unpredictable nature of Russia's tactics in the Second World War. It would seem that we have reached a similar level of ambivalence in a climate of changing diagnostic criteria, uncertain etiology, and unproven treatments in regards to complex regional pain syndrome type 1 (CRPS-1). By nature, such entities evoke fear and unease in one's mind. The question of how to manage these patients is a current conundrum. For this reason, the diagnosis and management of CRPS-1 deserves much greater care and scrutiny by the wider medical community. In recent times, it would seem that the overwhelming suffering and limb pain in injured workers and poorly chosen surgical patients have taken on almost epidemic proportions. Best estimates indicate a rate of 26.2 per 100,000 person-years, with particular risk to orthopedic surgery patients [1].

Part of this enigmatic issue is due to our failure to correctly define the clinical characteristics of the condition since its inception as a diagnostic entity. Over the past 60 years, criteria have been changing like pictures at an exhibition. The nomenclature of reflex sympathetic dystrophy has been discarded in favor of CRPS-1, along with changing clinical criteria that serve only to confuse the general practitioner and the growing number of subspecialized ("one organ") doctors, whose knowledge may be residual from medical school study. Wider education on CRPS-1 is required. As the goal posts for clinical diagnosis keep moving, so do the physicians' perceptions of what constitutes a CRPS-1 diagnosis. In modern times, Veldman's criteria have been discarded in favor of the 1998 International Association for the Study of Pain (IASP) criteria, which have since been discarded in favor of the 2004 Budapest criteria. When examining interobserver reliability between the aforementioned criteria, the claim that the presentation of CRPS-1 patients who reach the diagnostic threshold has changed with time is supported. Perez and colleagues reported percentages of agreement between Veldman's criteria and IASP of 74%, 63% between the Budapest criteria and Veldman's criteria, and 61% between IASP and Budapest criteria, corresponding to k values of 0.42, 0.31, and 0.29, respectively [2]. Moreover, different clinical symptoms and sign profiles between patient subsets diagnosed under different criteria have also been reported [2]. This has left us with no stereotypy to constitute a concrete diagnosis of CRPS-1. Hence, the historically poor clinical definition and confusion regarding symptom and sign profiles may be why this condition is overdiagnosed in modern times. However, there is method to this madness. The incremental improvements made to diagnostic criteria with empirical statistical derivation of larger study populations, akin to that of the Diagnostic and Statistical Manual of Mental Disorders, have improved diagnostic sensitivity and specificity significantly [3–5]. The Budapest criteria, our most sensitive and specific criteria to date, must be the clinical standard; otherwise the diagnosis of CRPS-1 can be used as a catchall for those with a constellation of nonspecific signs and symptoms and unexplainable chronic pain.

The Budapest criteria outline the set of requirements for diagnosis (Figure 1) [6]. Too often the fourth requirement—"there should be no better diagnosis that better explains the condition"—is conveniently avoided. Much of the research on CRPS-1 fails to specify how other conditions were excluded, and consequently its validity can be questioned. For this same reason, the condition is commonly overdiagnosed. In one study that examined referrals by general practitioners and specialists to a tertiary pain clinic for queried CRPS, 39 out of 54 referrals did not meet Budapest diagnostic criteria. Thirty-two had other musculoskeletal or neuropathic pain conditions, and seven had psychogenic pain disorders [7]. Similarly, 77% of those referred to a multidisciplinary pain clinic in the Netherlands did not actually have CRPS-1 [8]. The patient who has continuing disproportionate pain presents a diagnostic dilemma, as unexplained chronic pain with associated symptoms of deconditioning is not enough to diagnose CRPS-1. CRPS-1 shares characteristics with other persistent pain syndromes such as chronic postsurgical pain, which may occur in 10% to 30% of patients and should be considered as a differential in this group [9,10]. Interestingly, symptoms and signs of disuse may also masquerade in a CRPS-like syndrome, as was demonstrated in multiple studies that examined the effects of immobilization via cast in both postoperative and healthy subjects. These individuals began to show signs of CRPS-1 after approximately six weeks of immobilization [11,12]. A number of tools are available to

IASP Clinical Budapest Criteria in diagnosing CRPS	
1. Continuing pain that is disproportionate to any inciting event	
2. At least one symptom reported in at least three of the following categories:	
Sensory	Hyperesthesia or allodynia
Vasomotor	Temperature asymmetry, skin color changes, skin color asymmetry
Sudomotor	Edema, sweating changes, sweating asymmetry
Motor/trophic	Decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin)
3. At least one sign at time of evaluation in at least two of the following categories:	
Sensory	Evidence of hyperalgesia (to pinprick), allodynia (to light touch, temperature sensation, deep somatic pressure or joint movement)
Vasomotor	Evidence of temperature asymmetry (>1 C°), skin color changes or asymmetry
Sudomotor	Evidence of edema, sweating changes or sweating asymmetry
Motor/trophic	Evidence of decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin)
4. No other diagnosis can better explain the symptoms and signs	

Figure 1 Budapest Criteria[3]

assist the physician in the differential diagnosis, including three-phase bone scintigraphy, long-term skin temperature measurements, and joint and muscle pressure-pain thresholds, and should be used where appropriate [13–15]. The line between CRPS-1 and normal responses to immobilization, inflammation, and other persistent pain conditions appears blurred, and therefore diagnosis should be left to those experienced in the field.

Correct case definition is important, as it informs prognosis. Not surprisingly, despite 40+ years since the foundation of multidisciplinary pain clinics by Bonica and >200 years of descriptions of CPS-1, we still have no reliable data on the natural history of this elusive clinical disorder. Anecdotally, the senior author of the present Commentary, who has practiced in neurology, pain medicine, and rehabilitation, was only able to recall a small number of cases of definitive CRPS-1 without long-term improvement, as is the case with head injuries, cerebral palsy, and cerebrovascular accidents, which after a short period of limited recovery remain largely permanent. Yet, "Dr. Google" suggests a completely different picture of long-term disability and suffering, littered with websites for compensation lawyers. The most recent review of this topic, conducted by Bean and colleagues, favors the view of gradual recovery, with most cases resolving in six to 13 months and only a minority going on to experience a lack of improvement in pain and limb dysfunction [16]. Moreover, Bean and colleagues also conducted a prospective study of CRPS-1 patients qualifying for diagnosis under the Budapest criteria. They found that only 66% of the original patient cohort qualified for diagnosis at 12 months, and signs generally trended toward resolution, as was particularly the case with sudomotor and vasomotor symptoms. This would suggest that the majority of true cases of CRPS-1 improve with time. However, commonly mild pain, sensory symptoms, and motor dysfunction have been found to persist [17]. There is still no evidence-based consensus on how to manage these troubling residual symptoms. This should be a future imperative.

In those with symptoms that do not resolve, the pattern of CRPS-1 suggests a biopsychosocial basis for the disability

and pain in this condition. Yet, so often the confirmed "organic" diagnosis of CRPS-1 leaves the late entry of a psychiatrist little clinical leverage, as pain behavior and perceived disability become engrained [18]. So often these patients have a well-camouflaged background of childhood abuse and family dysfunction that is ignored as a significant contributing factor [19]. In these times of identity politics and taxing complaints, challenging diagnoses such as conversion syndrome, somatoform pain disorders, malingering, disuse syndromes, abnormal illness behavior, and functional neurological disorders are best left to psychiatrists who are well equipped to handle the multiple psychiatric comorbidities that can accompany these patients. The psychosocial profile of patients with CRPS-1 has been an area of significant debate, though to dismiss it as an etiological factor would seem counterintuitive, given the biopsychosocial etiology of many other chronic pain conditions. Anxiety, pain-related fears, and perceived disability are negative predictors of treatment success after one year [18]. Anxiety and kinesophobia are predictors of pain intensity, and depression is a predictor of perceived disability [20]. These studies emphasize the importance of psychiatric input as part of multidisciplinary care. Importantly, early psychiatric assessment is desirable, before the notions of abnormal illness behavior and secondary gains take hold.

Complex regional pain syndrome type 1 remains a condition crying out for an organic etiology. The current reviews remain more theoretical than concrete. Because of this, we have no gold standard investigation for diagnosis. Therefore, it is impossible to accurately calculate sensitivity and specificity, as index cases are still "best guesses." This is problematic when conducting trials on possible interventions, as there is no way of determining if the patients in the trial have CRPS-1 with 100% certainty. This may explain why there is such heterogenicity among study findings and would be rectified with further research into diagnostic tests of organic pathology. The use of weighted criteria, similar to the American College of Rheumatology criteria for rheumatoid arthritis, has already shown some promise in defining and grouping patients with this syndrome, with improved sensitivity and specificity in comparison with the current Budapest criteria [21]. In the absence of this identifiable organic etiology to target, a long list of medical treatments, including but not limited to ketamine infusions, guanethidine injections, vitamin C tablets, sympathetic nerve blocks, and neuromodulation, has been tried. Such therapies have been reviewed by Harden, with very little evidence found for their efficacy [3]. Bean and colleagues also were unable to demonstrate any beneficial effect of any treatment received on outcomes [22]. It would seem that treatment is more about medical income and physician hope to relieve the burden of suffering than any rational scientific basis justified by patient-centered and disease-modifying outcome indicators. Our current approach is ineffective and far from the modern desires of evidence-based practice. Aside from physical therapy and occupational therapy, which have demonstrated efficacy in randomized controlled trials, other effective therapies such as bisphosphonates and corticosteroids and possibly graded motor imagery, have yet to become common practice. Moreover, as pathogenic mechanisms become better elucidated, randomized controlled trials should be conducted on potential therapies. The cornerstones of chronic pain management, including Opioids, psychotherapy, and anticonvulsant and antidepressant use, also require further investigation [23–25].

In conclusion, the historical inconsistencies within literature and a lack of unifying testable organic pathology have made the diagnosis of CRPS-1 difficult. The large constellation of signs and symptoms that make up the condition has meant that the diagnosis has become a catchall for patients with unexplained chronic limb pain and is often labeled without consideration of alternative diagnosis. The Budapest criteria represent the current standard for diagnosis, though specialist input is probably desirable. Fortunately, for true CRPS-1, emerging evidence would suggest an improvement in most patients; however, the influence of psychosocial comorbidities cannot be ignored. Multidisciplinary care with psychiatric assessment is the standard. A renewed focus on further randomized controlled trials using the most specific and sensitive diagnostic criteria, investigating both new therapies as pathogenic mechanisms become elucidated and the current cornerstones of chronic pain management, is what is required.

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References

1 de Mos M, de Bruijn AGJ, Huygen FJPM, et al. The incidence of complex regional pain syndrome: A population-based study. Pain 2007;129(1–2):12–20.

2 Perez RSGM, Collins S, Marinus J, et al. Diagnostic criteria for CRPS I: Differences between patient profiles using three different diagnostic sets. Eur J Pain 2007;11(8):895–902.

3 Harden RN, Oaklander AL, Burton AW, et al. Complex regional pain syndrome: Practical diagnostic and treatment guidelines, 4th edition. Pain Med 2013;14(2):180–229.

4 Harden NR, Bruehl S, Galer BS, et al. Complex regional pain syndrome: Are the IASP diagnostic criteria valid and sufficiently comprehensive? Pain 1999;83(2):211–9.

5 Harden NR, Bruehl S, Perez RSGM, et al. Validation of proposed diagnostic criteria (the "Budapest criteria") for complex regional pain syndrome. Pain 2010;150(2):268–74.

6 Harden RN, Bruehl S, Stanton-Hicks M, et al. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8(4):326–31.

7 Mailis-Gagnon A, Lakha SF, Allen MD, et al. Characteristics of complex regional pain syndrome in patients referred to a tertiary pain clinic by community physicians, assessed by the Budapest clinical diagnostic criteria. Pain Med 2014;15(11):1965–74.

8 Frölke JP, van Rumund A, de Waardt D, et al. Complex regional pain-syndrome type 1: A different diagnosis for 77% of patients [in Dutch]. Nederlands Tijdschrift Voor Geneeskunde 2009;153(12):550–3.

9 Johansen A, Romundstad L, Nielsen CS, et al. Persistent postsurgical pain in a general population: Prevalence and predictors in the Tromso study. Pain 2012;153(7):1390–6.

10 Gierthmühlen J, Maier C, Baron R, et al. Sensory signs in complex regional pain syndrome and peripheral nerve injury. Pain 2012;153(4):765–74.

11 Terkelsen AJ, Bach FW, Jensen TS. Experimental forearm immobilization in humans induces cold and mechanical hyperalgesia. Anesthesiology 2008;109(2):297–307.

12 Pepper A, Li W, Kingery WS, et al. Changes resembling complex regional pain syndrome following surgery and immobilization. J Pain 2013;14(5):516–24.

13 Mainka T, Bischoff FS, Baron R, et al. Comparison of muscle and joint pressure-pain thresholds in patients with complex regional pain syndrome and upper limb pain of other origin. Pain 2014;155(3):591–7.

14 Krumova EK, Frettlöh J, Klauenberg S, et al. Long-term skin temperature measurements - a practical diagnostic tool in complex regional pain syndrome. Pain 2008;140 (1):8–22.

15 Wüppenhorst N, Maier C, Frettlöh J, et al. Sensitivity and specificity of 3-phase bone scintigraphy in the diagnosis of complex regional pain syndrome of the upper extremity. Clin J Pain 2010;26(3):182–9.

16 Bean DJ, Johnson MH, Kydd RR. The outcome of complex regional pain syndrome type 1: A systematic review. J Pain 2014;15(7):677–90.

17 Reimer M, Rempe T, Diedrichs C, et al. Sensitization of the nociceptive system in complex regional pain syndrome. PLoS One 2016;11(5):e0154553.

18 Bean DJ, Johnson MH, Heiss-Dunlop W, et al. Do psychological factors influence recovery from complex regional pain syndrome type 1? A prospective study. Pain 2015;156(11):2310–8.

19 Beerthuizen A, van't Spijker A, Huygen FJPM, et al. Is there an association between psychological factors and the complex regional pain syndrome type 1 (CRPS1) in adults? A systematic review. Pain 2009;145(1):52–9.

20 Bean DJ, Johnson MH, Kydd RR. Relationships between psychological factors, pain, and disability in complex regional pain syndrome and low back pain. Clin J Pain 2014;30(8):647–53.

21 Ott S, Maihöfner C. Signs and symptoms in 1,043 patients with complex regional pain syndrome. J Pain 2018;19(6):599–611.

22 Bean DJ, Johnson MH, Heiss-Dunlop W, et al. Extent of recovery in the first 12 months of complex regional pain syndrome type-1: A prospective study. Eur J Pain 2016;20(6):884–94.

23 Bruehl S. Complex regional pain syndrome. BMJ 2015; 351:h2730.

24 Perez RS, Zollinger PE, Dijkstra PU, et al. Evidence based guidelines for complex regional pain syndrome type 1. BMC Neurol 2010;10:20.

25 Cossins L, Okell RW, Cameron H, et al. Treatment of complex regional pain syndrome in adults: A systematic review of randomized controlled trials published from June 2000 to February 2012. Eur J Pain 2013;17 (2):158–73.