The Budapest criteria for complex regional pain syndrome: The diagnostic challenge.

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Abstract

Chronic regional pain syndrome (CRPS) is a neuropathic pain syndrome that involves both peripheral and central sensitization. Described in the literature as early as 1872, CRPS has been described using different names and different symptoms over the years. Since many neuropathic pain syndromes are rare, complex, and exhibit overlapping signs and symptoms, diagnosing CRPS has been challenging. Recently the Orlando Criteria in 1993, the subsequent Budapest Criteria in 2003 have attempted to provide a more helpful and robust diagnostic framework. However, the multiplicity of signs and symptoms and allowable variations have resulted in a diagnostic template that accommodates what may actually be a wide variety of conditions and obscures a better understanding of CRPS. The Budapest Criteria make CRPS ultimately a diagnosis of exclusion, leaving clinicians with patients who may be CRPS Type I, CRPS Type II or the new CRPS-NOS. CRPS can be challenging to treat and many treatments are ineffective, possibly owing to the fact that the syndrome is currently defined in such a diffuse way. The current diagnostic criteria of CRPS have even called the entire syndrome into question. There is an urgent need to better define and describe CRPS so that it can be appropriately diagnosed and its mechanisms elucidated. That step will lead to better treatment.

Keywords: Budapest criteria, Orlando criteria, Neuropathic pain syndromes, Complex Regional Pain Syndrome (CRPS).

Introduction

Pain specialists, neurologists, and many other clinicians must frequently confront the challenging and maladaptive condition of chronic neuropathic pain. Chronic pain of any type involves central sensitization and can be challenging to treat. Neuropathic pain involves aberrant neural signal processing which can amplify pain signals and result in pain that appears unrelated to the original nerve injury. Among the most difficult neuropathic pain syndromes to treat is complex regional pain syndrome (CRPS), a condition so diffuse and poorly defined that its very existence has recently been called into question [1]. CRPS, although not under that name, was described as early as the 19th century when it was termed “causalgia” [2]. By World War II, what clinicians today might recognize as CRPS was called “reflex sympathetic dystrophy” [3]. With the emergence of pain medicine as a specialty and a growing understanding of pain mechanisms, this amorphous condition was the subject of greater scrutiny and several notable attempts were made to better define it and establish diagnostic criteria. The great problem with CRPS is that although patients suffer from it or at least something that fits under the umbrella of what is being defined as CRPS, its pathophysiology and mechanisms are poorly understood. Without a clear understanding of what is involved, CRPS has become a catchall label for a variety of signs and symptoms and has emerged as a diagnosis of exclusion. Furthermore, the diagnostic criteria for CRPS may have emerged from clinical frustration about defining an extremely troublesome condition or from certain pressures to allow for specific patients to get treatment or damages [4].

The purpose of our article is to review in short narrative form the nature of CRPS, current diagnostic criteria and how they are used, and implications for pain specialists with regard to diagnosis and treatment of CRPS.

Literature Review

Diagnosing CRPS

Historically, the condition today known as CRPS was diagnosed by a variety of diagnostic criteria set forth by individuals and based largely or entirely on their own experiences. These diagnostic criteria never achieved any form of standardization, were not generally accepted by the medical community, and might most charitably be described as “idiosyncratic” [5-7]. It was not until 1994 that a consensus meeting of experts adopted the term “complex regional pain syndrome” to encompass both “causalgia” and “reflex sympathetic dystrophy,” which were difficult conditions to differentiate anyway [8,9]. The great issue was that patients were presenting with chronic neuropathic pain that appeared to involve both peripheral and central sensitization; the painful symptoms were also sometimes accompanied by edema, asymmetrical skin temperature and coloration differences, and trophic or motor symptoms.

These patients were often in moderate to severe or very severe pain, may have suffered from allodynia or hyperalgesia, and defied standard treatment. In many cases, it was difficult to ascertain how or why the condition began. The epidemiology of CRPS is unclear. In a retrospective cohort study conducted in Europe from 1996 to 2005, 600,000 patient records were searched and found an overall incidence of CRPS to be 26.2
per 100,000 person-years (95% confidence interval [CI], 23.0 to 29.7) [10]. Females were vastly more affected than males (ratio 3.4) with the highest incidence occurring in postmenopausal women between the ages of 61 and 70. The mean age at diagnosis in this study was 52.7 years. In 44% of cases, a fracture was identified as the precipitating event and the upper extremities were more likely to be involved than lower extremities [10]. As this is a highly distressing condition associated with reduced function and moderate to severe pain, there was a sense of urgency to create a solid diagnostic foundation and advance toward effective therapy.

In a meeting in Orlando in 1994, the International Association for the Study of Pain (IASP) entered the condition into its taxonomy as a diagnostic entity [7,9,11]. The IASP definition of CRPS was descriptive and led to a generally accepted set of standardized criteria by which to make a diagnosis [8]. The IASP was the first organization to enter CRPS into its taxonomy as a diagnostic entity and arrived at four conditions on which to base a diagnosis: (1) an initiating event or cause of immobilization; (2) continuing pain, allodynia, or hyperalgesia disproportionate to the inciting event; (3) evidence at some time(s) of edema, changes in skin blood flow, or abnormal sudomotor activity in the painful region; and (4) the diagnosis is excluded by the existence of other conditions that might account for the pain and dysfunction. The IASP then subdivided CRPS into Type I (without major nerve damage) and Type II (with major nerve damage) [11]. These initial criteria introduced a fair amount of confusion.

While an inciting event (typically a distal radius fracture or fracture of the ankle) was required by the so-called Orlando Criteria, the IASP itself noted that 5% to 10% of all patients will not have an inciting event or cause of immobilization and stated this criterion was not absolutely essential to make a diagnosis [11]. It has also been postulated that perhaps some patients experienced a triggering event but simply did not remember it or did not consider it meaningful. Since the type and nature of the inciting event can vary—indeed it may not even have occurred—it has opened up the question as to how such trauma might precipitate CRPS and, more importantly perhaps to understanding its mechanisms, why only a fraction of patients with such injuries progress to CRPS while most do not.

The IASP diagnostic criteria also specified that the patient experience continuous pain disproportionate to the inciting event. This relied on the patient’s own self-reports both of pain and a subjective assessment that this pain is out of proportion to the inciting event. Furthermore, other signs and symptoms relied on self-reports and subjective assessments. The diagnosis could be made based on historical experiences as recollected by the patient. Such subjective patient-centric criteria might be unreliable and could lead to over-reporting. Moreover, another difficulty with these diagnostic criteria emerged in that they were based on expert consensus rather than clinical findings or rigorous analysis of the literature [12].

The Orlando criteria for CRPS were sensitive (that is, they accurately identified most cases of CRPS) but lacked specificity (meaning they inappropriately labeled other neuropathic painful conditions as CRPS) [13,14]. A lack of specificity can result in false-positive diagnosis and possibly inappropriate treatment. In a study of 160 patients (113 CRPS and 47 neuropathic pain patients who did not have CRPS), IASP criteria were diagnostically sensitive (1.00) but not very specific (0.41) while the new Budapest criteria in this same group retained the high sensitivity (0.99) but offered improved specificity (0.68) [15-17]. Early studies of the IASP criteria found them to be highly sensitive but a lack of specificity resulted in false positives [13,15,18]. For example, the IASP mentioned in its criteria that the patient should have signs and symptoms relating to vasomotor changes, sudomotor changes, or edema, but allows that fulfilling any one of these conditions fulfills the criterion [14,19]. Thus, it is possible that the Orlando criteria led to overestimating the prevalence of the condition. The IASP criteria omitted references to motor/trophic signs and symptoms, which can play an important role in differential diagnoses [14,18,20].

CRPS is a relatively rare condition treated by a handful of experts who had generalized their observations to try to meet an urgent need—to better identify a potentially devastating condition—but one that proved over time to be suboptimal in real-world clinical practice. In 2003, a group of clinicians met in Budapest to review what had been learned about CRPS since the IASP diagnostic criteria were in use and to make recommendations in a think-tank type of forum that would lead to specific research efforts [13,14]. This resulted in the publication of a definitive book about CRPS21 and recommendations to IASP as to the incorporation of the so-called “Budapest criteria.”

In a study of 117 CRPS patients and 43 neuropathic pain patients without CRPS, a validation study found that the IASP criteria had high sensitivity in diagnosing CRPS (0.98, meaning it almost always diagnosed CRPS when it was present) but low specificity (0.36, meaning there were a lot of false-positives). Taken together, this translates into a very poor score in that CRPS diagnoses are only likely to be correct in less than half of all cases (about 40%) [13]. A factor analysis was conducted (n=123 CRPS patients) determining four distinct subgroups among CRPS signs and symptoms: pain processing (allodynia, hyperalgesia), vasomotor dysfunction (skin color and/or temperature changes), edema/sudomotor dysfunction, and motor/trophic signs and symptoms. The reorganization of these signs and symptoms into four subgroups differentiated the Budapest criteria from the IASP, which previously had treated vasomotor/sudomotor dysfunction and edema as one subgroup [4]. The addition of the fourth criterion (motor/trophic effects) allows clinicians to consider such conditions as dystonia or tremor in the diagnosis (omitted in the IASP criteria). These modified criteria allowed for better discrimination between CRPS and neuropathic painful conditions (Table 1).

**The face of CRPS in clinical practice**

CRPS as currently understood may be described as a type of persistent neuropathic pain syndrome. As such, it shares many features of neuropathic painful conditions: peripheral pain, hyperalgesia, allodynia, edema, and paresthesia. The pain of CRPS often described as deep or burning, is often moderate to severe. This pain is typically linked to an inciting event such as, but not limited to, a fracture of the wrist or ankle, but the pain intensity is disproportionate to that triggering injury.
Furthermore, the pain of CRPS may not be associated with the root or nerve territory that was originally affected that is a wrist injury may lead to pain sites in other parts of the body. The presence or absence of peripheral nerve damage has been used to differentiate so-called Type I from Type II CRPS, although the clinical utility of these two types of CRPS4 and indeed veracity of this categorization is disputed [21].

Swelling, asymmetrical temperature changes, atrophy, dystrophy, and movement disorders may (or may not) be present and may occur at varying degrees [22]. The painful condition may persist, and over time may progress and spread to new regions of the body in a subset of patients this chronic pain may become generalized [23].

The clinical presentation among CRPS patients can be extremely diverse. Skin temperature can be a telling symptom, but in a “typical” CRPS patient, skin temperature increases in the first six months of the disease and then decreases even to the point that the patient’s extremities grow cold over time—except that many patients suffer low skin temperature from the outset [24]. Thus, paradoxically, both increased and decreased skin temperature of the extremities might be considered indicative of CRPS. Yet some CRPS patients may have no skin temperature anomalies at all.

Edema, a prominent sign of early CRPS in some patients may decrease over time, but it is not clear if this is owing to the natural course of the inflammatory response or the nature of CRPS [25]. Trophic changes can be considered as signs of CRPS, but they occur in only about half of patients and may be mild or pronounced [25]. It is not clear why this occurs and why it occurs only in some patients.

CRPS is a syndrome not a disease and as such there is no definitive test, laboratory evaluation, or imaging that can objectively diagnose the condition. That in itself is not remarkable, many conditions rely on clinical diagnoses and patient self-reports (for example, headaches). But in the case of CRPS, attempts to define this syndrome have created considerable confusion.

**Who is the CRPS patient?**

The introduction of the Budapest criteria, which were more stringent than the preceding Orlando criteria, resulted in about 15% of previously diagnosed CRPS patients losing their diagnosis [19]. This resulted in the creation of a new category called CRPS-NOS (Not Otherwise Specified) which included those patients who did not fulfill the Budapest criteria but whose signs and symptoms could not be better explained by any other diagnosis. Rather than limit the scope of CRPS to two types, a third and non-specific new type was added.

The Budapest and Orlando criteria make CRPS a diagnosis of exclusion, but it may be that CRPS patients are those patients with pronounced neuropathic pain syndromes of a variety of etiologies. A systematic literature review evaluated cases of CRPS Type I occurring only in the knees [26]. A total of 31 articles encompassing 368 patients were found and it was determined the most common inciting event of knee CRPS Type I was knee surgery. This type of knee-only CRPS Type I condition is relatively rare although the 368 patients in this study technically fulfilled the Budapest criteria.

However, patients who undergo knee surgery might experience chronic postsurgical pain, a well described condition associated with many types of surgeries, including orthopedic surgery [27]. CRPS Type I of the hand (typically involving one to three fingers) is a rare clinical condition but a retrospective study retrieved reports in the literature involving a total of 16 such patients (11 men, five women) [28]. In this group, 88% of patients fulfilled the Budapest criteria for a diagnosis of CRPS Type I while the remainder were diagnosed using a three-phase bone scintigraphy test.

CRPS patients may have mild to severe or very severe symptoms. In some patients, so-called “warm CRPS” (with elevated asymmetrical skin temperatures) may progress to “cold CRPS” by Bruehl. This transition remains to be further elucidated but may represent the transition from acute to chronic phases. Older notions described three sequential stages of CRPS which have since been refuted but may represent a subtype of CRPS. These sequential stages include: a relatively limited form of CRPS in which vasomotor signs and symptoms predominate, a somewhat limited syndrome in which neuropathic pain and sensory symptoms predominate, and a more florid form of CRPS which aligns best with the “classic” descriptions of the syndrome and was most associated with motor/trophic signs [29].

CRPS is perhaps most robustly characterized as a chronic painful condition with periods of remission and relapse. In a study of

### Table 1. The Budapest Criteria: In order to make a clinical diagnosis of CRPS, the following four criteria must be met.

<table>
<thead>
<tr>
<th>S. No</th>
<th>Criteria</th>
<th>Sensory</th>
<th>Vasomotor</th>
<th>Sudomotor/Edema</th>
<th>Motor/Trophic</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Continuing pain, disproportionate to any inciting event</td>
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</tr>
<tr>
<td>2</td>
<td>Symptoms: Must report at least one symptom in three of the four categories shown to the right</td>
<td>Hyperesthesia; Allosodynia</td>
<td>Temperature asymmetry; Changes in skin color; Skin color asymmetry</td>
<td>Edema; Sweating changes; Sweating asymmetry</td>
<td>Decreased range of motion; Motor dysfunction; Trophic changes (hair, nails, skin)</td>
</tr>
<tr>
<td>3</td>
<td>Signs: At the time of evaluation, must have at least one sign in two or more of the categories shown to the right</td>
<td>Hyperalgiesia (pinprick); Allosodynia (light touch or temperature); Deep somatic pressure; Joint movement</td>
<td>Skin temperature asymmetry (&gt;1°C); Changes in skin color; Skin color asymmetry</td>
<td>Edema; Sweating changes; Sweating asymmetry</td>
<td>Decreased range of motion; Motor dysfunction (weakness, tremor, dystonia); Trophic changes (Hair, nails, sin)</td>
</tr>
<tr>
<td>4</td>
<td>No other diagnosis can better explain the patient’s signs and symptoms</td>
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596 patients with a single fracture of wrist, scaphoid, ankle, or metatarsal V in the Netherlands, none of the patients diagnosed with CRPS Type 1 were free of symptoms at 12 months and all patients with CRPS Type 1 had significantly more pain at baseline than those without CRPS Type 1 (p<0.001) [30]. CRPS typically—but not exclusively—occurs after an inciting event. In most cases (55% to 60%) the inciting event is traumatic, most commonly distal radius fracture [31-33]. CRPS Type 1, formerly called reflex sympathetic dystrophy syndrome, is cause by a noxious event or immobilization leading to persistent pain, allodynia, and hyperalgesia out of proportion to the noxious stimuli. Type 1 CRPS typically involves edema, changes in skin blood flood, and abnormal sudomotor activity. Type 2 CRPS, formerly called causalgia, describes persistent pain, allodynia, or hyperalgesia specifically after a nerve injury, although not necessarily in the distribution of that nerve and may include the features of Type 1 [34]. The pathophysiology does seem to differ between types [35]. In a 10-year population-based study, it was found women were four times more likely than men to develop CRPS and the average age at onset of CRPS was 46 years, the vast majority of cases (96.9%) appear to be CRPS Type 1 [36,37].

CRPS has been particularly associated with a fracture of an upper extremity although it may occur following the fracture of the foot or ankle as well as without a preceding fracture [10,36]. In a study of 390 foot/ankle surgery patients from 2009, in which the incidence of CRPS based on IASP criteria was 4.36%, nearly half of those who developed CRPS (47.06%) had a medical history of anxiety or depression and 29.41% were smokers [35]. In a study of 477 patients who underwent surgery to treat a distal radius fracture, 8.8% fulfilled the Budapest criteria for CRPS Type 1 at six months [38]. Females and older patients were more likely to develop CRPS Type 1. In fact, female patients and those with high-energy trauma or severe fracture were significantly more likely to develop CRPS Type 1 (p-values are 0.02, 0.01, and 0.01, respectively) [38]. A prospective study of 90 consecutive patients treated at a single center for a distal radius fracture diagnosed CRPS Type 1 in 32.2% of patients using earlier Veldman criteria and found it occurred most frequently in the third and fourth week after cast removal and was more likely to occur in females who reported severe pain and reduced physical quality of life [39]. Moreover, patients with musculoskeletal comorbidities and rheumatoid arthritis appeared more likely to develop CRPS Type 1 than those without these conditions [30]. Furthermore, there may be a genetic predisposition to CRPS Type 1 but further work is needed in this area [40-42].

**Diagnostic challenges**

Clinical diagnoses are inherently challenging, but the challenges with the Budapest and Orlando criteria are perhaps more pointed than most. The diagnostic scheme for the Budapest criteria relies primarily on dichotomous responses to conditions and fails to take into account subtle variations among patients. In the case of skin temperature asymmetry, it is possible to take an objective measure and to compare various degrees of temperature asymmetry. However, many of the other criteria are subjective. Clearly, the most important of these criteria is continuing pain. In a retrospective study of 190 patients diagnosed with CRPS according to the Budapest criteria and 26 patients with neuropathic pain not identified as CRPS, patients were mainly female, mean age 44 years, and median disease duration was 18 months. Among the CRPS patients, about a third had experienced pain in the affected limb prior to the inciting event. In this cohort of CRPS patients, clinically important and widespread pain affected more than 10% of patients [43].

The diagnostic sensitivity and specificity of the Budapest criteria may be affected in part by how the algorithm is employed [44]. High specificity/low specificity occurs when diagnosis requires at least one each of at least two of the sign categories, and at least one each of two of the symptom categories (0.94 and 0.36, respectively) [4]. High specificity/low sensitivity occurs when diagnosis depends on one each in at least two of the sign categories, and one each in all four of the symptom categories (0.70 and 0.94, respectively). The highest combination scores for sensitivity and specificity are 0.86 and 0.75, respectively, which can be achieved when diagnosis depends on at least one each of three of the sign categories, and one each of all four of the symptom categories [4].

The challenges of the various diagnostic criteria set forth for CRPS are evident in their results. In a study published in 2016 of 306 consecutive patients with foot or ankle fractures, the incidence of CRPS diagnosed according to the Budapest criteria was less than 1% [44]. Yet in a retrospective study of 390 foot/ankle surgery patients in 2009, 4.36% could be classified as having CRPS based on the IASP criteria [35]. In a study of 596 patients with a single fracture of wrist, scaphoid, ankle, or metatarsal V, the incidence of CRPS Type 1 varied depending on which diagnostic criteria were used: the incidences were 7.05%, 48.5%, and 21.3% based on the Harden and Bruhl criteria, the IASP criteria, and the Veldman criteria, respectively [30]. In that latter study, the data were collected around the time that the Budapest criteria were first published and so the Budapest criteria were not evaluated.

In 2010, a severity scale was proposed for CRPS diagnostics which allowed for clinicians to better capture the nuances in various metrics, such as the degree of skin coloration asymmetry or severity of dystonia [17]. In a study of 114 CRPS patients and 41 non-CRPS patients with neuropathic painful condition, 17 clinically assessed signs and symptoms were evaluated leading to a CRPS Severity Score (CSS). This CSS was able to differentiate between CRPS and non-CRPS patients (p<0.001) and exhibited strong associations with the dichotomous CRPS diagnoses in terms of both the earlier IASP diagnostic criteria and the newer Budapest criteria. Patients with higher CSS scores had significantly greater pain intensity, distress, and dysfunction compared to those with lower CSS scores. 

Attempts to correlate certain diagnostic criteria, such as overall CRPS severity score (CSS) and temperature asymmetry have not been successful [45].

While diagnosis of CRPS is primarily based on clinical signs, laboratory, neurophysiological, and radiologic testing may be helpful to support or refute a potential determination [46]. Indeed, the role of laboratory testing and radiology may be primarily to exclude other diagnostic possibilities. The Budapest
Criteria were specifically intended to be readily accessible and deployable by any clinician in the clinical setting, in that they did not require special training, elaborate equipment, or complicated testing. Such “bedside-ready” criteria serve a practical need. However, such criteria rely on the subjective impressions of both the patient (in terms of pain) and clinician (signs). This extensive (and in this case sole) use of subjective criteria for diagnosis is, of course, somewhat problematic [15]. For example, the pain required to fulfill Budapest criteria must be “disproportionate” with respect to the inciting event. This is problematic for two reasons. First, not all patients have or can remember the inciting event. Second, pain disproportionate to the injury is a highly subjective term. What is “disproportionate” to one patient may be reasonable to another.

Possible mechanisms of CRPS

CRPS remains a diffuse and vaguely described syndrome and it has been difficult to elucidate the mechanisms behind it. One particular characteristic of CRPS is that the pain is not confined to the innervation zone of an individual nerve [47]. Focal small-fiber axonal degeneration and alteration of the cutaneous innervation by small-diameter fibers (afferent and efferent) have been implicated in CRPS [48]. Patients with CRPS may have changes in the neural microenvironment at the peripheral site of injury that result in peripheral afferent sensitization along with neurogenic inflammation and sympathetic afferent coupling [49]. This functionally reorganizes somatosensory, motor, and autonomic circuits in the central nervous system (CNS) [22,50].

Because CRPS is a neuropathic pain disorder with autonomic features whose pathophysiology has not been well understood or elucidated, effective treatments have been elusive. The pathophysiology of CRPS is complex and multifactorial, involving both peripheral and central nervous systems.

CRPS is further characterized by inflammation, altered sympathetic and catecholaminergic function, and changes in the somatosensory representation in the brain. There are likely genetic factors at play, which remain to be elucidated, and psychophysiological interactions contribute as well. It may be that CRPS manifests in different ways depending on which factors are involved and to what degree they interact with each other [51].

Three-phase bone scintigraphy (TPBS) has given evidence that CRPS patients experience enhanced periarticular bone metabolism. Thus, hyperalgesia around the joints in response to blunt pressure may be a finding more specific to CRPS than hyperalgesia associated with muscle. Pressure-pain thresholds on the joints have been described in the literature as a type of noninvasive diagnostic test for CRPS [52].

Treatment of CRPS

CRPS treatment can be very challenging and a subset of all CRPS patients may be described as refractory to all standardized treatments. Indeed, treatment of CRPS may be described overall as generally ineffective. There is growing support for multidisciplinary approaches to CRPS treatment and certain promising new approaches [53].

Nonpharmacological treatment in the form of physiotherapy and occupational therapy may be helpful. In particular, occupational therapy may help improve functionality and the ability of the patient to carry on everyday activities [54]. Pharmacological treatment is individualized and may include steroids, free-radical scavengers, neuropathic pain treatments, and drugs that interfere with bone metabolism such as calcitonin and bisphosphonates [46].

Ketamine, an N-methyl-D-aspartate (NMDA) antagonist, has been evaluated in various acute and chronic pain syndromes. It is believed that systemic ketamine can modulate central sensitization over the long term [55]. Ketamine inhibits pro-inflammatory cytokines which may play a role in peripheral and central sensitization [56]. In the early stages of localized CRPS, low-dose ketamine can be effective, but this agent does not appear as effective in the treatment of more advanced CRPS. In a study of 20 CRPS patients (mean age 30.4±10.4 years, range 14 to 48 years) with severe and/or spreading CRPS, they were treated with anesthetic doses of ketamine over five days and followed for six months [57]. Significant pain relief was observed at one, three and six months after treatment (93.5 ± 11.1%, 89.4 ± 17.0%, and 79.3 ± 25.3%, p<0.001) and complete remission was observed in all patients at one month, in 17/20 at three months, and in 16/20 in six months. Even when relapse occurred, significant pain relief was still noted at three and six months (59.0 ± 14.7%, p<0.004 and 50.2 ± 10.6% p<0.002). In addition, most patients reported improvements in quality of life.

A case report in the literature describes complete recovery from intractable CRPS Type 1 following anesthetic ketamine and midazolam [58]. The patient had severe and rapidly progressing CRPS refractory to standard treatment and with unmanageable and severe pain levels. The patient entered the intensive care unit (ICU) and was administered anesthetics doses of ketamine (3-5 mg/kg/h) along with midazolam over five days. Improvement was visible at two days and all symptoms resolved completely by the sixth day. The patient was tapered off the drugs and emerged from anesthesia completely free of pain and related CRPS symptoms. The recovery was durable in that the patient has enjoyed this remission for eight years.

Steroids are conventionally used to help treat CRPS. In an open-label, uncontrolled study of CRPS outpatients evaluated in the period from 2009 to 2012, 31 patients (diagnosed with Budapest criteria) who had CRPS for at least three months refractory to standard treatment were treated in two centers. At Center 1 (C1), patients were administered 100 mg of oral prednisone tapered by 25 mg every four days to zero while patients at Center 2 (C2) were treated with oral prednisone 60 mg for two weeks, lowered by 20 mg every 4 days to zero. Patients were assessed for pain intensity levels at the outset of the study and six weeks after treatment commenced. No significant pain reduction was observed against baseline (p=0.059) but two patients had a consistently reduced pain intensity with return to baseline levels nine weeks after study onset; one patient reported ongoing stable pain relief >50% [59].

A single-center study (n=56 with painful peripheral neuropathy including but not exclusively CRPS) found 75% of patients could achieve a ≥50% reduction in pain at six months using...
A diagnosis of exclusion

The new Budapest criteria, like the Orlando criteria that preceded them, make CRPS of any type a diagnosis of exclusion, that is, that the clinician cannot find any better diagnosis that explains the patient’s signs and symptoms. While diagnoses of exclusion are hardly rare in medicine, in the case of CRPS with its wide constellation of varying signs and symptoms, it allows any number of other inexplicable neuropathic pain syndromes to be relegated to CRPS. This means that CRPS has become a catch-all diagnosis, and if there is any genuine CRPS sharing common pathophysiologic mechanisms, it will be difficult to define and elucidate as it is lumped together with a wide range of other neuropathic conditions.

The field of neuropathy includes a wide range of relatively rare and poorly understood conditions. These range from the fairly obscure, such as (but not limited to) Morvan’s syndrome [61,62], neuromyotonia [63], Charcot-Marie-Tooth neuropathy [64], demyelinating neuropathy [65], Parsonage-Turner syndrome [66], deQuervain’s stenosing tenosynovitis [67], and meralgia paresthetica [68]. Neuropathic pain may also occur with an injury to the central nervous system, such as stroke [69]. It is beyond the scope of this article to discuss the many possible neuropathic conditions that might factor into a diagnosis of exclusion. The diagnosis of neuropathic syndromes can be extremely challenging.

Chronic postsurgical pain (CPSP), on the other hand, is known to affect about 10% to 30% of surgical patients and thus neuropathic pain following surgery should be considered [70]. CPSP often has a significant and pronounced neuropathic component [71]. For example, when an inciting injury was treated surgically, it may be that the resulting constellation of symptoms owes to CPSP rather than CRPS.

Neuropathic pain is a typical feature not just in CPSP, but also in many forms of chronic noncancerous pain (such as chronic low back pain), and cancer pain, such as lymphoma or iatrogenic neuropathic pain associated with chemotherapy [72,73]. New conditions are emerging which at least overlap to some degree with CRPS: for example POEMS syndrome which involves demyelinating neuropathy manifesting initially as polyneuropathy with chronic pain [74].

In short, neuropathic pain can occur due to injuries to peripheral nerves, entrapment of these nerves, spinal cord injuries, cerebral infarcts, infections (such as postherpetic neuralgia), multiple sclerosis, and others [75]. Neuropathic pain syndromes may evolve into evoked painful conditions such as hyperalgesia and allodynia [76]. It may be useful to evaluate neuropathic painful conditions based on mechanisms rather than symptomology. For that, a better understanding of the mechanisms of CRPS is needed.

Discussion

Pain specialists generally recognize that a subset of patients present with persistent and sometimes severe neuropathic pain. When this pain becomes centralized but retains a peripheral component, is associated with a variety of other signs and symptoms including but not limited to edema, motor symptoms, skin temperature and coloration changes, and can create moderate to severe and even debilitating pain, it has been tempting to assign it to the category of CRPS. The problem with CRPS—historically as well as contemporaneously—is that it is a very flexible syndrome that can “stretch” to accommodate a wide number of conditions. The pain must be persistent but can be moderate to severe, may be localized or diffuse, may migrate or not, and might remit. Related signs may be changes to hair and nails, changes in sweating, dystonia, and cutaneous abnormalities—which may be mild to severe, may remit or relapse, and may not occur at all. Related symptoms such as hyperalgesia and allodynia, which can be exceedingly troublesome to the patient, occur in any number of neuropathic painful conditions.

If CRPS were a clear-cut condition, it would offer a more precise definition. If it were more precisely defined, its mechanisms and physiopathology might be better elucidated. And if its mechanisms were better understood, targets for drug development might emerge or other effective treatment strategies might become clear. The vagueness of the CRPS diagnostic criteria and our tendency to keep expanding it (by the addition of CRPS-NOS) rather than condensing and refining it has created a condition in which many conditions might—or might not—be CRPS.

In truth, neuropathic pain represents the “frontier” of pain science in that it is not clearly understood and cannot be universally effectively treated. Our understanding of aberrant neural signal processing is mainly descriptive—it is not entirely evident how these neural transmissions might be modified to reduce pain and lower the pain threshold. There is an urgent unmet need in medicine to better come to grips with neuropathic pain, its mechanisms, and treatment. With that, a clearer understanding of CRPS may emerge.

There is no doubt in the mind of pain specialists that patients with complex neuropathic pain (which we currently diagnose as some form of CRPS) present with genuine symptoms and very urgent medical needs for pain control and symptom management. However, it is unclear whether CRPS exists quite the way we think it exists and if our current line of thinking is even helpful. Our attempts to diagnose CRPS have led to a growing awareness—anand clinical frustration—that what we currently call CRPS may represent one or several conditions. Since it is a diagnosis of exclusion, a rush to diagnose CRPS may preclude a more time-consuming, difficult, but accurate diagnosis of a different condition.

Finally, it may be that our broad and rather vague definition of CRPS obscures a multiplicity of other conditions that warrant...
deeper study. For instance, the role of the inciting injury in CRPS requires more investigation, in that a subset of patients develops CRPS with no such trauma or at least no recollection of it. Trophic symptoms, including very pronounced symptoms, might hold a clue to deeper understanding of CRPS but only a subset of patients develops them. Skin temperature changes are often observed in CRPS but they occur in many other conditions as well and may owe to the inflammatory response rather than a specific aspect of CRPS.

Without neglecting the patients in our care, some of whom are in genuine need of pain control as well as reassurance and emotional support in the wake of serious neuropathic pain, attention should be focused on better defining and describing CRPS. Its etiology, pathophysiology, mechanisms, and genetic background should be elucidated. Then better diagnostic categories may emerge. Until such time, the Budapest criteria represent our best—but inadequate—approach to diagnosing these difficult conditions.

Finally, this is not to minimize or trivialize the severe, debilitating, and fundamentally life-altering pain that many patients experience. Such patients may suffer from unrelenting severe pain. It is not unusual for patients with persistent pain to suffer losses on many fronts: loss of function, loss of employment, loss of relationships, and diminished quality of life. These individuals often seek out medical help in a fashion that might only be described as heroic: going from one failed diagnosis to the next and occasionally being accused of malingering or drug-seeking by the healthcare professionals they trusted.

The issue of malingering deserves a special mention here. It is easy to dichotomize pain into those conditions in which there is a structural or physiological pathology toward pain (“real” pain) versus patients who complain about pain but have no such “proof.” The latter has been called a pseudo neurological presentation [77]. Neuropathic pain can be difficult to dichotomize in that a neural lesion or dysfunction can be difficult to prove objectively in some patients. Malingering or intentionally producing or exaggerating physical or psychological symptoms for a goal is not rare.

These goals might include everything from avoiding work, evading military service, obtaining a financial settlement, avoiding criminal prosecution, gaining sympathy, or obtaining drugs. The prevalence of malingers who claim “chronic pain” is high (20% to 31%) [78,79] and most healthcare professionals treating chronic pain patients have encountered such individuals. In a study of 237 CRPS patients, surveillance found that 16 of them (about 7%) were malingering [80].

While we may challenge the utility of the Orlando and Budapest criteria and even raise questions about the authenticity of CRPS Types I and II as clinical categories, it is because there is a real need to help patients who seem to “fall into” this diagnosis and it appears that our efforts are falling short.

Conclusion

The Budapest criteria intended to help clinicians better diagnose CRPS but actually made the syndrome even more diffuse by incorporating a third type of CRPS. Like the Orlando criteria that preceded them, the Budapest criteria, based on consensus and expert opinion, offer a virtual menu of signs and symptoms and result in a syndrome that defies clear understanding of the syndrome. A better knowledge of CRPS, its etiology, and its mechanisms are urgently needed. As a diagnosis of exclusion in a field where many rare and complex conditions predominate, it is likely that many patients diagnosed with CRPS may have other conditions. Treatment of CRPS is challenging and often ineffective. A more thorough understanding of the neuropathy and its origins are urgently needed to better define it, diagnose it, and ultimately treat it effectively.

Conflicts of Interest

To comply with International Committee of Medical Journal Editors (ICMJE) requirements, I disclose the following relationships: Consultant/Speaker and Researcher for: Inspiron, Mallinckrodt, Baxter, Purdue Pharma LLP, Grunenthal GmbH, BDSI, ENDO Pharmaceuticals Iroko, DepoMed and Mundipharma. There was no specific funding related to this project. Ms. LeQuang has nothing to disclose. Dr. Nalamachu has nothing to disclose. Mr. Bigelsen has nothing to disclose. Dr. Taylor has nothing to disclose.

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