Complex regional pain syndrome

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Since the early musings in the mid-1800s of Claude Bernard and his French neurological colleagues on the association of pain with the sympathetic nervous system, complex regional pain syndrome (CRPS) has both fascinated and perplexed practitioners. Some of the clearest and most interesting descriptions of ‘causalgia’ come from the American Civil War by one of Bernard’s students, Silas Weir-Mitchell. The low-velocity, high-mass missiles used in this confrontation (the ‘Minnie ball’) seemed to be particularly effective in inducing neuropathic pain associated with intense autonomic dysregulation. Weir-Mitchell’s depictions are clear and elegant, and as good as any clinical description that can be found in this century.64 Many great minds have struggled with the pathophysiology of what came to be called ‘reflex sympathetic dystrophy’ in the later part of the 1900s and what has, since the Orlando consensus-based workshop of 1999, come to be called complex regional pain syndrome (CRPS) (Table 1).37 63 85 From Leriche46 and his vicious circles we have progressed through Livingston47 and Sunderland88 with the turbulence theory, and finally to the solid physiological information generated by the various animal models of causalgia, especially the chronic constriction injury model of Bennett and Xie.5 Recently, the effort to understand the syndrome has turned towards consensus symposia. The first of these concerned taxonomy, as above.37 85 A second Dahlem-type conference was conducted in regard to the guidelines for therapy,84 and recently the International Association for the Study of Pain (IASP) sponsored a symposium in Cardiff, Wales in 2000 to discuss issues of pathophysiology and to amend the diagnostic considerations.83

The epidemiology of the syndrome is very unclear. Although the syndrome has traditionally been considered rare, its ‘discovery’ by personal injury lawyers in the United States has caused a radical increase in the reporting of the syndrome (at least in the USA). The current diagnostic criteria, as set forth by the Committee of Classification of Chronic Pain of the IASP, have contributed to the liberalization of the diagnosis (Table 1).63 This effort was extremely important in providing standardized diagnostic criteria, and caused a vast improvement in clinical communication and research homogeneity. It provided the hope that results could be generalized across studies, and in fact widespread use of these standardized criteria has helped all these things considerably. These criteria, while being very sensitive, greatly lack specificity.9 21 31 The intent of the Orlando conference in 1994 was that these criteria should evolve on the basis of experience and empirical testing, and that they should be subject to systematic validation research over time.37 62 85 This has been accomplished to some extent, and through a process of internal and external validation the opportunity to improve the specificity of the bedside diagnostic criteria is available.9 21 31 Although the original IASP criteria required only subjective and potentially only historical signs and symptoms, the suggestions for improving these criteria are that some objectification and observed evidence be included. It is recommended that the diagnostic criteria be modified to include at least one symptom in each of the four diagnostic categories derived by factor analysis: sensory (hyperaesthesia), vasomotor (temperature and/or skin colour asymmetry), sudomotor/oedema (reports of asymmetrical oedema in the affected limb and/or a sweating asymmetry), and a new symptom set which was identified by factor analysis: the motor/trophic set (reports of motor dysfunction or trophic changes).9 21 31 Our data also suggest that the patient should display at least one quasi-objective sign (observed by the physician) in two or more of these categories (Table 2).9 31 This approach maintained a sensitivity of 0.70 while increasing specificity to 0.94. This level of specificity is important in research. However, the original IASP criteria could be used if maximal clinical sensitivity was desired. A variety of schemes in which the clinician/researcher can virtually set the sensitivity and specificity, depending on the diagnostic scheme used, have been discussed.9 31
Table 1 IASP diagnostic criteria for complex regional pain syndrome (adapted from Merskey and Bogduk).63 *Not required for diagnosis; 5–10% of patients will not have this

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

Table 2 Proposed modified research diagnostic criteria for CRPS (adapted from Bruehl and colleagues9 and Harden and colleagues31)

| 1 | Continuing pain that is disproportionate to any inciting event |
| 2 | Must report at least one symptom in each of the four following categories: |
| | Sensory: reports of hyperaesthesia |
| | Vasomotor: reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry |
| | Sudomotor/oedema: reports of oedema and/or sweating changes and/or sweating asymmetry |
| | Motor/trophic: reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) |
| 3 | Must display at least one sign in two or more of the following categories: |
| | Sensory: evidence of hyperalgesia to pinprick and/or allodynia to light touch |
| | Vasomotor: evidence of temperature asymmetry and/or skin colour changes and/or asymmetry |
| | Sudomotor/oedema: evidence of oedema and/or sweating changes and/or sweating asymmetry |
| | Motor/trophic: evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin) |

Symptoms

There is great heterogeneity of symptoms endorsed by patients with CRPS.69 It is essentially a disorder characterized by pain and dysfunction of the sympathetic nervous system. The symptoms most frequently mentioned by patients are spontaneous burning and stinging pain. Although burning pain was an essential part of earlier sets of criteria,72 it has recently been found to occur in 81.1% of patients meeting criteria for CRPS31 (all the percentages reported for symptoms and signs in this paper are from this reference). Patients frequently (69%) relate hyperaesthesia in response to the typical mechanical stimuli encountered in their daily lives, such as clothing resting on the affected part, or even draughts blowing on the limb. Patients may relate extreme sensitivity to temperature changes, such as in the environment or in bathing. In CRPS II (which is CRPS associated with major nerve damage63), patients may often complain of symptoms appropriate to the neuropathy, such as brief electrical sensations or shooting pain. In this context, they may also demonstrate an interesting presentation of hypo-aesthesia (negative symptom) in the nerve distribution associated with electrical ‘shocks’ and extreme allodynia (positive symptoms). Other symptoms include asymmetry of the colour or temperature of the affected limb; these are the symptoms most indicative of vasomotor autonomic disturbance (86.9% colour, 78.7% temperature). Sudomotor symptoms can be seen with sweating asymmetry (52.9%), either hyperhidrosis or dryness. Patients may also endorse changes in the skin, nails or hair pattern (trophic changes, 24.4, 21.1 and 18% respectively) and will frequently mention that the limb swells (79.7%) and becomes stiff. Patients frequently also speak of decreased range of motion (80.3%) or loss of motor competence (weakness) in the affected limb (74.6%). They will occasionally notice ‘jumping’, tremors or myoclonic action in the affected part77 01 (about 20% each) and symptoms of myofascial pain in the proximal joint.72

Signs and tests

The examining physician should seek evidence of altered central processing by looking for allodynia (innocuous stimulation that is now painful, 74%) or hyperpathia (slightly painful stimulation that is now significantly painful and/or painful for a prolonged period). Allodynia should be tested using light touch or brushing of the affected part to see if this elicits pain. Temperature allodynia should be sought. This is most easily tested using warm, cool and ambient-temperature test-tubes of water. The test-tubes are presented in a specific order on the affected part. The patient should mentally subtract the sensation/pain of the ambient tube from the pain associated with the cool or hot tube (subjectively). This is most easily done by assessing pain on a verbal Likert scale (0–10) and recording the spontaneous report, the ambient report and the report of the effect of temperature. These signs can be documented formally by quantitative sensory testing.19 28 99 The patient may also report pain on movement of the affected joints (with either passive or active movement). Signs of trophic changes of the skin, nails and hair patterns (19.1, 9.3 and 8.5% respectively) should be observed and documented. Signs of autonomic disturbance (temperature asymmetry 56.3%, colour asymmetry 66.4%) need to be measured and described in terms of apparent sympathetic hypofunction (hot, red and dry) or apparent sympathetic hyperfunction (cold, blue, pale or mottled, and sweaty).

Whether these signs accurately reflect activity of the sympathetic nervous system is questionable.73
Thermography, or at least a spot-temperature measurement (using a thermosensitive tape or spot-temperature device), best documents vasomotor autonomic disturbance. Abnormal activity of the sudomotor side needs to be assessed clinically using the examiner’s touch (24.2%). Dragging a smooth-handled instrument across the affected versus the unaffected part can also give an idea of ‘sweatiness’ (a smooth-handled instrument will glide more easily over a sweaty area than a dry area). Sudomotor abnormalities can be documented by QSART (quantitative sudomotor axon reflex testing). Decreased range of motion (70.3%), weakness (56.1%), dystonia (14.0%) and tremor (8.8%) can also be seen and myoclonic activity has been observed occasionally. An interesting phenomenon of apparent motor neglect is also observed sometimes. We do not find three-phase bone scans to be particularly helpful (sometimes they are actually confusing!). However, we often find sympathetic skin-response testing helps us to define mechanisms better. In some cases the response may be absent or abnormal in early (hot, red, dry) CRPS, but is usually normal in later (cool, blue, sweaty) CRPS.

**Treatment**

A second Dahlem-type conference was held in Malibu to generate consensus about treatment guidelines. All treatments were focused primarily on functional restoration; the use of drugs, blocks and psychotherapy was reserved for patients failing to progress in the functional algorithm (Fig. 1). Interdisciplinary pain management techniques emphasizing functional restoration are thought to be the most effective therapy; they may work by resetting altered central processing and/or normalizing the distal environment.

The principle of functional restoration is based on steady progression from very gentle movements on an active basis to gentle weight-bearing, such as carrying light bags in upper-extremity syndromes or putting partial weight on the lower extremity in gait training. This progresses to movements that involve more active load-bearing such as the scrub-and-carry techniques of Carlson and Watson. Gradual desensitization to increasing sensory stimulus goes along with increased function. This could include such strategies as progressive stimulation with silk, progressing to cloths of other textures, such as towelling, or contrast baths that progressively broaden the temperature difference between the two baths. It is thought that perhaps this gradual increase in normalized sensation tends to reset the altered central processing in the nervous system. It is important to manage oedema, optimize the range of motion and encourage general aerobic activity throughout.

Another basic principle of these functional restoration guidelines is that if patients do not progress through the steps in a reasonable time, then other interventions will be added progressively to give the patient greater comfort or confidence so that they may proceed to the next level. For instance, if the allodynic pain is too great, a sympathetic and/or somatic block may give the patient a window of opportunity to begin to entertain more aggressive therapy or, if the patient has kinesiophobia (fear of movement), then cognitive behavioural techniques could be undertaken to demonstrate to the patient that movement does not necessarily lead to entirely negative consequences. Neural blockade, psychotherapy and drugs are reserved and should be used only when there is failure to progress.

**Occupational therapy**

The roles of occupational therapists and physiotherapists differ in many countries. In the USA, the occupational therapists take the lead in functional restoration, and thereby take the lead in the team for treating CRPS. They begin by initiating gentle active movements and preliminary desensitization techniques. Later, they measure and manage the oedema (using volumetry to measure and bandaging and lymph flow massage to manage). They are also responsible for introducing and maintaining a programme of scrubbing/loading. The scrubbing can literally be accomplished using a scrubbing-brush, and is usually done with the patient on all fours, putting gradually increasing weight on the arm as they actually scrub in circles. There are technical devices that have been designed for this purpose, but they do not seem to hold any particular advantage over the good old-
fashioned scrubbing-brush. A crucial therapeutic point of the scrubbing/loading technique is the weight-loading of the joints in the affected limb, which increases progressively as the scrubbing programme continues. In the upper extremity, the weight-loading part of the treatment continues with small objects carried in the hand, and soon progresses to a handled bag, which can later be loaded with heavier weights.

The lower extremity can be treated with a custom-designed and padded strapping arrangement that attaches a scrubbing-brush like a shoe to the foot. Loading can start in a sitting position, but would gradually progress to standing and putting increasing weight on the foot for brushing. Walking is a relatively advanced loading technique but is clearly one of the most important goals to entertain as early as possible in the treatment of lower extremity CRPS. This therapy may be supplemented by psychology in situations involving post-traumatic stress disorder (PTSD), especially in vocational situations.

**Vocational rehabilitation**

As the patient progresses, the therapist will begin to work on assessing and simulating work activities. A thorough understanding of the prior job description and requirements, and occasionally vocational testing and targeted retraining, are part of vocational rehabilitation. Eventually, vocational rehabilitation can provide work capacities and targeted work-hardening and functional capacity assessment, so that the patient may return to gainful employment, the ultimate functional restoration. It usually requires a methodical, informed, experienced and organized team approach in order to understand and successfully manage the Byzantine social and medicolegal quagmires CRPS patients may find themselves in. This effort is best orchestrated by vocational rehabilitation.

**Physiotherapy**

Physiotherapy obviously has an important role in functional restoration, and the activities in physiotherapy are designed to complement those in occupational and vocational therapy. Beginning with small, gentle active therapies by the patient, the physiotherapist can help the patient begin to extend the range of motion and flexibility through mostly active, gentle activities. These must be done within the patient’s tolerance and never in an insensate situation (such as after a block) or in CRPS type II with hypo-aesthesia. Gradually increasing strength and flexibility with ultimate return to normal use is the goal, and this is accomplished by a series of exercises, devices (e.g. foam rubber balls progressing to spring grip strengtheners) and mat exercises. The physiotherapist is also actively involved in gait training and postural correction. It is important to remember that nearly all patients with advanced CRPS will also have myofascial pain syndrome of the supporting joint. Aggressive treatment of myofascial pain syndrome is the purview of the physiotherapist, and may be critical to recovery. According to some schools of thought, the myofascial pain syndrome must be treated effectively first; if it is treated the entire syndrome may resolve. Occasionally, hands-on techniques can be used effectively to treat the myofascial pain, such as massage and myofascial release. Desensitization techniques, such as rubbing with silk, then cotton, then towelling or contrast baths, can be very useful. In our experience, electrostimulation modalities may occasionally have some use. Ultrasound and diathermy therapies are less effective in our clinic. The physiotherapist may co-treat with psychology to break through PTSD and kinesophobia.

**Recreational therapy**

Often the recreational therapist is the first clinician to be able to get the patient to move freely and with some pleasure. In the context of restoring the patient to a pastime or a game that they once enjoyed, it may be possible to break through the kinesophobia and bracing that so often accompany CRPS. With assisted devices and creativity (such as learning to bowl with the non-dominant hand, ride a bicycle instead of run, etc.), a patient can sometimes break the ice and find enjoyment and socialization in previously lost or new recreational activities.

**Psychology**

Psychology is a critical mainstay of treatment in CRPS, and in some patients may be essential to recovery. There is a high incidence of depression and anxiety in the syndrome, and cognitive behavioural psychotherapy is the most effective psychological intervention for these diagnoses in association with chronic pain. In addition to anxiety and depression, there is a high prevalence of post-traumatic stress disorder (PTSD) and what has been called ‘kinesophobia’. PTSD is often associated with the initial injury and can prevent full recovery because the patient fears re-encountering the circumstances of their injury. Kinesophobia is more an ongoing operant issue associated with negative reinforcement when patients perform particular movements. Patients find that whenever they perform certain manoeuvres they have pain, which acts as a powerful negative reinforcer for performing that movement again. They set up operant patterns that avoid these painful movements, and eventually this avoidance becomes behaviourally set. It is important to demonstrate to patients that the consequences of movement are not always totally negative or painful, and this can be accomplished with a combination of psychotherapy and drug or block therapy. We have learned that normalized movement is critical in the recovery of CRPS patients and a variety of movement therapies, such as the Feldenkrais and Alexander techniques, can be undertaken in the context of psycho-
therapy. Family therapy can also be quite important, with the basic approach of trying to change solicitous family members into coaches.

Medication

There are many medications that have been reported to be helpful in CRPS, but few that have been tested in double-blind, randomized, controlled trials. At this time, a balanced empirical approach involving observation, consideration of possible mechanisms and the use of the best current information to treat these mechanisms, is the most productive clinical approach. Although monotherapy is the ideal, in practice ‘rational polypharmacy’ is often employed. This requires a knowledgeable guess as to the mechanisms responsible for the condition, and then combining drugs that make sense together (i.e. an anti-inflammatory and a centrally acting GABAergic agent). Two basic classes of medications should be entertained: drugs used for prophylaxis (used daily) to manage pain and other symptoms, and abortive drugs (used as rescue agents) for crisis management.

The prophylactic drug selected will often be determined by the presentation of the patient. For example, if a CRPS patient is extremely depressed and/or anxious and insomniac, the clinician may choose a tricyclic antidepressant with significant analgesic, sedative and anxiolytic properties as the drug of first choice. The tricyclics are traditional in neuropathic conditions, and seem to be partially effective in CRPS. Good clinicians should have several tricyclic/quadracyclic drugs in their repertoire as they have varied side-effects that can sometimes be used to the patient’s advantage. Consider the previous example, or consider a patient who is depressed, overweight and hypersomnolent with psychomotor retardation. In such a case it may be useful to select a more noradrenergic agent, such as desipramine, which is activating and may cause some anorexia. Tricyclic and tetracyclic antidepressants have been shown to be effective in other neuropathic conditions, such as post-herpetic neuralgia and diabetic peripheral neuropathy. However, they have never been studied properly in CRPS. Selective serotonin reuptake inhibitors have been disappointing for CRPS in our experience. Certain newer antidepressant agents, such as venlafaxine and mirtazapine, show some benefit in our clinics.

The anti-epileptic compounds are some of the best-studied drugs in neuropathic pain, and currently hold significant promise in the treatment of CRPS. Gabapentin has been studied in large randomized controlled trials in post-herpetic neuralgia and diabetic peripheral neuropathy. The research community’s attention was originally drawn to gabapentin by an anecdotal report in CRPS (called ‘reflex sympathetic dystrophy’ in that report). The mechanism of action in Gabapentin may be of interest in CRPS, but it is incompletely understood. It probably works primarily by enhancing natural γ-aminobutyric acid (GABA) systems in pain modulation but may also have some impact in suppressing excitatory amino acids, such as glutamate. Other GABAergic drugs have not been tested properly in CRPS.

Membrane-stabilizing anti-epileptic drugs such as phenytoin may have some use, particularly where there is nerve damage or a belief that ectopic activity is involved in generating the pain. Lamotrigine has been studied in other neuropathic conditions, but randomized controlled trials, especially in CRPS, are lacking. Carbamazepine, which is membrane-stabilizing as well as tricyclic, has a traditional and perhaps clinically important place in the treatment of CRPS, but there are no specific randomized controlled trials. Oxcarbazepine may be as effective as carbamazepine but has fewer side-effects.

Non-steroidal anti-inflammatory drugs probably have some role in the management of CRPS, as seen in some other neuropathic models, particularly in cases where there is considerable inflammation. Certain drugs in this class may be more useful, such as ketoprofen, which has detectable anti-bradykinin and anti-prostacyclin effects as well as the usual anti-prostaglandin effect. COX-2 inhibitors have not been tested in CRPS. Steroids can be particularly useful in the early/acute phases of CRPS, again particularly when there is significant inflammation. A short course of steroids may be indicated, but longer courses have a questionable risk–benefit ratio.

Opioids may be useful, especially in the acute pain scenario. However, they remain controversial in chronic pain management. We have employed a strategy of trying to use non-opioid medication for prophylaxis and using opioids in crisis management. We often tie the use of opioid therapy to increasing function, and may use an acute or subacute opioid protocol to allow the patient to begin to progress in non-pharmacological therapies. Issues of tolerance and long-term toxicity are unresolved as yet and there is concern that long-term opioid use may actually elicit allodynia and/or hyperpathia. NMDA receptor antagonists (such as MK-801, ketamine and dextromethorphan) have been considered for management of these effects (and for CRPS), but have proved too toxic for regular human use. Low-dose subcutaneous ketamine may have a role.

Many medicines from other fields have proved to be helpful, not only in the management of pain (e.g. clonidine) but also in the management of symptoms associated with CRPS (e.g. nifedipine, which can control the intense vasoconstriction sometimes associated with chronic CRPS). Interestingly, calcitonin is one of the best-studied drugs in the management of CRPS. Unfortunately, the evidence is mixed and our anecdotal experience with this compound is not particularly encouraging.

The lidocaine patch may be useful in some very local or focal CRPS phenomena, such as patch allostynia. EMLA
(eutectic mixture of local anaesthetics) cream has been disappointing in our clinic.\textsuperscript{2} Capsaicin has proved to be intolerably painful early on, messy, and thereby to engender very poor compliance, in our experience.\textsuperscript{5 25 41 67 80}

While a variety of block therapies have been the traditional first line of treatment in CRPS, there is very little scientific evidence to support their use.\textsuperscript{86} We view blocks primarily as providing a pain-free period so that patients may progress in the functional restoration algorithm, and we use them sparingly in that context. Many blocks have been examined, and the most frequently used are paravertebral sympathetic blocks and epidurals.\textsuperscript{86}

Although it appears clinically that there is excessive sympathetic activity in the later phases of CRPS, the peripheral picture (cold, blue, sweaty extremity) may not actually reflect what is going on in the sympathetic efferents to the limb.\textsuperscript{33} Intravenous phenolamine has been reported as useful both therapeutically and diagnostically\textsuperscript{7 71} but is not useful therapeutically beyond the placebo effect in our experience.\textsuperscript{41 92} Intravenous regional sympathetic blockade using guanethidine\textsuperscript{27} or bretylium\textsuperscript{41} seem to be more helpful, and have a longer-lasting effect in our patients. The research available is less enthusiastic.\textsuperscript{36 41} The use of any of these interventions in a frequent or chronic way has never been justified substantially in the scientific literature.

A short trial of a limited number of nerve blocks with very clear goals and time limitations may be indicated ethically and may be cost-effective if the patient fails to progress naturally in a functional restoration effort.

Although sympathectomy has some theoretical support,\textsuperscript{4 40 79} it has not shown any long-term benefit in our patients, and may have a negative impact in some cases.\textsuperscript{3 20 50} Spinal cord stimulation is of controversial utility and until recently had not been properly studied.\textsuperscript{38 43 44 60} A recent randomized controlled trial supports its value in cases where nothing else is helping.\textsuperscript{39} Implanted pumps have not been studied properly, and have no long-term utility in our experience.

Conclusions

The key to the successful diagnosis of CRPS is not only to look for and document those historical/subjective elements that meet IASP criteria but also to search for quasi-objective signs (examiner-witnessed). A more specific approach would be to consider the research criteria proposed in Table 2.

The key to successful treatment of CRPS is a trained, coordinated and experienced interdisciplinary team employing a functional restoration approach (Fig. 1). Guidelines help,\textsuperscript{84} but creativity, compassion and flexibility are essential. Often patients will require diligent pharmacotherapy, blocks or intensified psychotherapy if they are to make substantial progress.

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