"Sensitization": Is There a Cure?

In Volume 3(3) of *Pain Medicine*, Drs. Harbut and Correll present a detailed description of a patient with a nine year history of lower extremity CRPS I, who was successfully treated with sub-anesthetic doses of continuous intravenous ketamine infusion [1]. The patient remains apparently pain free with functional restoration since the time of intervention. This case is striking because of the complete remission of symptoms in an individual who had been seriously disabled by CRPS and had responded only minimally to multiple earlier interventions.

Severe ongoing, paroxysmal and/or evoked pain is one of the most disabling symptoms of Complex Regional Pain Syndrome, Type I (CRPS I) also known as Reflex Sympathetic Dystrophy (RSD). The complexity of presenting symptoms has resulted in difficulty establishing appropriate standardized, reliable diagnostic criteria, which could then potentially decrease inter-rater variability, leading to homogeneity in sample populations for study. Routine use of such criteria would constitute an important methodological advance in promoting studies to better analyze the underlying pathomechanism of the disease as well as the effectiveness of various treatment protocols.

The complexity of CRPS I results from one or a combination of factors, which are described below:

1. The discrepancy between the type, magnitude and, at times, location of the inciting event to the extent and distribution of the CRPS findings. Essentially any injury, even as trivial as a transcutaneous angiocatheter placement, can potentially result in severe CRPS symptom expression involving much of the affected extremity. CRPS contradicts the common human perception that type, extent and location of an injury is directly related to the ensuing damage including the "site & size" of subjective complaints and clinical findings; this is a common misperception with major psychosocial and medical consequences.

2. Co-expression of multiple symptom categories [2-4]; i.e., simultaneous presence of autonomic, sensory, motor, dystrophic and/or emotional-behavioral symptoms and signs indicates involvement of many organ systems at the same time and interestingly enough, as its name indicates, being a "regional syndrome" it is also mostly very localized to the same site. For instance a case of distal extremity CRPS I may include a variety of nervous system, vascular, musculoskeletal and cutaneous findings. This has resulted in a variety of diagnostic and therapeutic approaches between different medical subspecialties. Classically a systemic disease such as vasculitis or osteoporosis is considered to affect the entire vascular tree or the skeletal system respectively; however, coexistence of the above multisystem elements in a strictly localized region does not support this conception.

3. Coexistence of a variety of symptoms in the same symptom category. For example, within the sensory category of neuropathic pain one may experience a variety of pain symptoms, such as spontaneous continuous or paroxysmal pain with or without the presence of evoked pain phenomena [5] such as allodynia, hyperalgesia and hyperpathia. To a variable degree hypesthetic, dysesthetic or hyperesthetic areas may also be present.

4. Inter- and Intra-individual variability in symptom expression, temporal fluctuation and spread. For instance individuals may differ in type, combination and/or intensity of their presenting symptoms between each other or at different time intervals. Edema and autonomic abnormalities may be a prominent feature of the condition in one patient, whereas in others the motor abnormality may dominate the picture. Within the same individual some of the symptoms may only be present on an intermittent basis. Even in individuals with symptom spread this variation continues to persist; e.g. spread of autonomic or motor abnormalities may precede the spread of pain to another body region [6].

5. Effect of gender and age on natural course of the disease. It is well established that the female sex (67%) predominates in CRPS I cases and that the median incidence of the disease in adults is reported to be 41 years of age [7]. It is also known that the condition affects the pediatric patient population less frequently and usually has a more favorable outcome than in affected adults. Indeed, suggested treatment options unequivocally point out to physical therapy in children [8]. One explanation for favorable outcome during childhood is that the disease encounters the biology at an earlier stage of development when they have the highest regeneration poten-

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tial. Therefore affected individuals have a lesser chance of developing the condition. Even once it is developed, considering the usual delay in referral and prior to appropriate diagnosis, children are more likely to undergo spontaneous remission or "grow out of it". This phenomenon contrasts with the decreased incidence of CRPS I in the elderly population. It is conceivable that the condition encounters the individual at a partially degenerated state in which the individual may not be capable of generating the full blown picture of a variety of autonomic and pain phenomena seen in adults; i.e. there is a lack of "positive symptoms". On the other hand, "negative symptoms" such as weakness and dystrophic tissue changes are commonly encountered in patients with a variety of conditions such as peripheral vascular disease or even stroke. In this scenario, due to the absence of pain symptoms or due to them being less prominent in the clinical picture, the diagnosis of a pain syndrome such as CRPS I is not justified, although the presence of "RSD without pain" continues to be mentioned in the literature. Overall, the pattern appears to be that in adults, the organism is still capable of generating and maintaining the disabling "positive symptoms" for quite a while but unable to actively suppress the positive symptoms, as is the case during childhood, possibly demonstrating that older adults have decreased capacity for plasticity and regeneration.

6. Non-unified response to laboratory testing and currently available treatment options. As alluded to above, given the multiplicity of CRPS symptom expression and its temporal fluctuation, it is not surprising that the currently available test methods and therapeutic options are only of limited benefit. As per definition there is no identifiable nerve lesion in patients with CRPS I [9], and therefore conventional EMG/nerve conduction studies are not of any benefit, unless one considers excluding any other types of large fiber neuropathy. Furthermore a dysfunction of the small nerve fibers, which constitute up to 70% of a peripheral nerve and are responsible for transmission of pain, temperature and sympathetic activity, is not assessed in EMG/NCS studies. Autonomic nervous system [7] and quantitative sensory testing [9] on the other hand are more appropriate measures in confirming the clinical findings in neuropathic pain states. Considering that multiple mechanisms can be present in the same individual [5], [10], it is conceivable that a given therapeutic modality would benefit only a selected patient population and probably for a certain period of time. This indicates the dynamic nature of biological systems and their resilience in maintaining a sensitized state. Even in animals, it has been shown that with experimental painful neuropathies multiple abnormal pain sensations are differentially responsive to drugs; this has been demonstrated for the NMDA receptor antagonist dextrorphan [11], an N-type calcium channel blocker [12], magnesium [13], opioids [14], clonidine [15] and gabapentin [16].

The phenomena of primary afferent sensitization and central hyperexcitability are fundamentally involved in pain and tenderness that normally follows tissue damage. There is also evidence suggesting that some (but certainly not all) forms of neuropathic pain may be dysfunctional expression of these normal processes [5]. Despite the above-mentioned difficulties involved in the management of CRPS patients and the several line of experimental evidence primarily from animal pain models supporting a variety of mechanisms underlying the neuropathic pain sensations, the activation of N-methyl-D-aspartic acid (NMDA) receptors in dorsal horn is implicated in the induction and maintenance of central sensitization [17]. There have been several studies addressing the efficacy of NMDA receptor antagonists such as ketamine, dextromethorphan/dextrorphan and amantadine/memantine; however the psychotropic side effects of ketamine in particular, limit its applicability in clinical practice of pain medicine. Hallucinations and dissociative phenomena are the most common limiting adverse effects of this drug. This is present even after a short single dose infusion therapy [5], [11], [18–24].

Ketamine has been in clinical use since 1960's [25]. It has been shown that ketamine acts primarily as a noncompetitive NMDA receptor antagonist by binding to phencyclidine (PCP) binding site [26]. In subanesthetic doses it was found to exhibit analgesic properties [27]. The pharmacodynamic of ketamine has been found to be dose dependent. At concentrations between 0.9-2.5 μmol/L it will exert its affinity to PCP binding site, whereas levels above 28 μmol/L would result in interaction with μ-opioid receptors [28] and concentrations above 50 μmol/L will suppress sodium channels [29]. Levels between 50-100 μmol/L will display local anesthetic properties, whereas above 100 μmol/L ketamine will also affect the voltage operated membrane channels [30]. Inhibition of various characteristics of pain is reported to be obtained by serum

concentrations below 1 μmol/L; i.e 1/10 to 1/5 of an anesthetic dose, which is reported to be above 4-5 μmol/L of racemic ketamine [24].

There have been also case reports of long term neuropathic pain relief (CRPS II) following low dose epidural ketamine infusion (25 $\mu g \cdot kg^{-1} \cdot hr^{-1}$) for 10 days [31]. The paper by Drs. Harbut and Correll describes a significantly different methodology from earlier interventions for CRPS I. To prevent psychotropic adverse effects, these investigators gradually titrated ketamine while the patient maintained an appropriate level of arousal and awareness. Thus they successfully avoided any significant psychomimetic side effects, which have generally limited the routine clinical use of NMDA antagonists as a main analgesic agent. Complete resolution of the pain after several years of suffering from CRPS type I (RSD) indicates the persistent dynamic nature of the process and its responsiveness to therapeutic approaches such as the treatment described here. Obviously any single case report has its limitations in terms of safety and applicability issues in patients with this and other pain disorders at large. Nevertheless it is the first attempt to safely desensitize one of the most intractable chronic pain disorders. Further detailed studies are required to address the issues mentioned above and to test and "fine tune" this potentially powerful treatment strategy in larger patient samples. Ultimately, blinded, controlled studies will be needed. Theoretically the subanesthetic doses of ketamine should be able to primarily limit the degree and extend of secondary sensitization rather than exerting an effect on the primary "injured" site with possible ongoing afferent C-nociceptor input.

If sub-anesthetic intravenous treatment with ketamine proves to be a safe and effective therapeutic modality, it will have implications that transcend the field of pain medicine. With the NMDA receptor being the major excitatory receptor protein it is implicated in a variety of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis and even in epilepsy, stroke, head trauma and schizophrenic disorders [32].

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