**Complex Regional Pain Syndrome: Developing Diagnostic Tools and Treatments from Sympathetic Nervous System, Neuroimmune, and Neuromodulation Discoveries in Neuropathic Pain**

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Though our understanding of complex regional pain syndrome (CRPS) has advanced significantly over the last few decades, reliable diagnostics for identifying this pain condition remain elusive. Our ability to accurately identify CRPS is appropriately rooted in clinical diagnosis as the gold standard, with physical examination and assessment of each patient’s pain experience as key elements in this symptom-based condition. An international group of experts created the Budapest diagnostic criteria for CRPS in an attempt to standardize the diagnosis of CRPS based on four distinct subgroups of signs and symptoms1 This development of common terminology helped build a foundation on which to research the pathophysiology of CRPS. Nevertheless, an improved diagnostic test(s) would be welcome to supplement the clinical diagnosis, differentiate phenotypes in ways that would guide treatment plans and facilitate development of new therapeutics, and help monitor disease progression. Numerous alternate/supplementary diagnostic strategies have been proposed, with dysregulation of the autonomic nervous system, particularly the sympathetic nervous system, often a central theme. In this issue of *Regional Anesthesia and Pain Medicine*, Lee et al.2 investigate the correlation between the results from regional and systemic tests of dysautonomia and (1) Budapest criteria and (2) response to sympathetic nerve blocks. Sympathetic nervous system dysregulation in CRPS was classically thought to mediate the development of chronic pain by altering catecholamine expression and the interaction between the sympathetic and sensory nervous systems. As a result, CRPS signs and symptoms were thought to be mediated by sensitization or dysfunction of nociceptive fibers and sensory neurons in the skin and dorsal root ganglia.3-5 A previous study by Lee et al.6 had already shown that *peripheral* dysautonomia diagnostics (quantitative sudomotor axon reflex test and sympathetic skin response) had 67.6% sensitivity and 40.6% specificity; however, diagnostic tests of *systemic* dysautonomia are less well studied

Lee et al.2 examine the utility of the deep breathing test, orthostatic test, and sympathetic skin response to diagnose CRPS in a South Korean pain center with a focus on military patients. Their study reveals that, individually, these tests have a low sensitivity and high specificity for identifying CRPS. When the authors combine them as a battery of tests, they demonstrate only a marginally higher prevalence of abnormalities in CRPS patients than in non-CRPS patients. We note that results might differ if such investigations were conducted in a more heterogenous CRPS population (gender, age, non-military, geographic region), if data were examined along a continuum (rather than as only positive or negative), or if the testing methods were modified. Nevertheless, the authors’ results suggest that either systemic dysautonomia is not a consistent pathology of CRPS, or that the deep breathing and orthostatic tests do not readily identify CRPS-specific systemic dysautonomia. CRPS is often classified based on duration as either acute—with more severe dysautonomia—or chronic or persistent—with clinically diminished autonomic signs.7 Thus, the timing of these tests in relation to the initiation of CRPS is likely a key variable.

One overarching question highlighted in their study appears to be whether autonomic nervous system dysfunction correlates with CRPS pain throughout disease duration, or whether it is a poor predictor of pain symptoms specifically in persistent CRPS.8 A second question is whether the degree of autonomic dysregulation is predictive of treatment response with agents that modify sympathetic outflow.9 It should be noted, however, that, established regional or systemic tests were originally developed to measure ‘autonomic dysfunction’ in the context of stable structural defects of the sympathetic nervous system, i.e. in autonomic neuropathies. In contrast, the ‘autonomic’ signs observed in CRPS, such as sweating or vasomotor disturbances, are highly variable over time and can occur even in the absence of any structural neuropathy.10 CRPS research has shifted away from assessing sympathetic nervous system function and treatments to instead focusing on alternative, non-sympathetic targets to treat or prevent CRPS.11; 12 Eventually, we may acknowledge sympathetically mediated CRPS, historically known as reflex sympathetic dystrophy, as one of multiple heterogenous variants of CRPS.

Thoughtfully constructed, this work by Lee et al.2 highlights a broader picture wherein the development of a reliable diagnostic test for CRPS is intricately linked to improvement in our understanding of its pain mechanisms, whether that be through autonomic nervous system mechanisms or other pain biology. A number of alternative pain pathways have been proposed as targets for novel drugs. If successful, these drugs may provide a catalyst for developing new diagnostic strategies that can target processes similar to those that mediate the drug treatment response—pain inhibition. Because CRPS is a rare disease, defined by the Orphan Drug Act of 1983 as a disorder or condition that affects less than 200,000 persons, the U.S. Food and Drug Administration has provided pharmaceutical companies with financial incentives to develop therapeutics under special Orphan Drug status. This status has supported clinical trials of CRPS with non-sympathetically targeted treatments such as (1) bisphosphonates neridronate and zoledronic acid,13 (2) a cannabinoid-based drug previously used for cancer pain, PPP001 drug [delta-9-tetrahydrocannabinol (9.5%) and cannabidiol (2.5%)],14 and (3) a novel N-methyl-D-aspartate receptor antagonist also being studied for neuropsychiatric disorders, BHV-500015.

Repurposing existing therapeutics for CRPS is another promising approach that avoids many of the regulatory and financial challenges of new drug development. Intravenous immunoglobulin is one example of a drug that was used to suppress inflammation in a wide variety of indications prior to investigations that demonstrated its potential to improve CRPS symptoms,16 although it was later proven ineffective.17

An autoimmune contribution to CRPS highlights further potential for developments in new therapeutics and diagnostics. Purified serum immunoglobulin G from patients was recently found to mediate pain by increasing pro-inflammatory cytokines that sensitize sensory neurons, likely in combination with pain mediated by direct immunoglobulin G and sensory neuron cross-talk.18 This finding suggests that an autoantibody-mediated autoreactive process is underpinning CRPS. Neuroimmune signaling initiated by peripheral tissue injury is receiving attention from a number of pain research groups that study seemingly distinct pain conditions; however, their commonality appears to be an immune upregulation that leads to increased neuronal excitability during the initiation and maintenance phases of chronic pain.19-21

A similar discussion is ongoing regarding the neuroimmune mechanisms of spinal cord stimulation (SCS), currently the only analgesic treatment with evidence-based efficacy for refractory CRPS.22 A new CRPS diagnostic based on the neuroimmune system could also help clinicians to predict SCS treatment response and improve the current ‘trialing’ process that typically precedes permanent lead implantation. Though SCS is frequently linked to sympathetic nervous system antagonism through supraspinal, spinal, and peripheral mechanisms,23 a number of recent studies have noted that SCS modulates many of the neuroimmune mediators associated with neuropathic pain conditions and may treat CRPS by reducing neuroinflammation.23-26 In their study, Lee et al.2 insightfully exclude patients with SCS implants from autonomic nervous system function testing because SCS is associated with sympathetic nervous system inhibition; nevertheless, they compare subsequent SCS implantation rates based on their outcome (failed or successful) to sympathetic nerve block and note an increased trend of implantation in patients with failed blocks.2 Though the response to SCS is unknown in these patients, a recent retrospective study concluded that there was no correlation between the effects of sympathetic blocks and outcomes with SCS.27 Interestingly, they also found that the therapeutic benefit achieved with sympathetic nerve block is not dependent on preprocedural temperature.27

Although the traditional understanding of CRPS pathology will take time to reshape, it is increasingly apparent that gaps are present in clinician-reported diagnostic criteria, objective diagnostic testing, and our fundamental understanding of CRPS mechanisms. Approaching these gaps in CRPS knowledge with a fresh slate, often catalyzed by outside experts and disciplines, may be key to reorienting our trajectory towards innovation and development of successful CRPS therapeutics and diagnostics.

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