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

Eellan Sivanesan, MD,1\* Andreas Goebel, PhD2

1Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD, USA.

2Pain Research Institute, University of Liverpool, and Department of Pain Medicine, Walton Centre NHS Foundation Trust, Liverpool L9 7AL, United Kingdom

**Correspondence:** Eellan Sivanesan, MD, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, School of Medicine, Baltimore, Maryland, 21287, USA. Phone: 410-955-1822; Fax: 410-614-2019; E-mail: esivane1@jhmi.edu.

**Funding Statement:** This study was subsidized by a grant from the Foundation of Anesthesia Education and Research (FAER) (E.S.). Andreas Goebel was supported by the Pain Relief Foundation, Liverpool <https://painrelieffoundation.org.uk/> . Funders had no role in conceptualizing this editorial or in the decision to submit the work for publication.

**Conflicts of Interest:** E.S. has no conflicts of interest to declare.A.G. reports no conflicts of interest with regard to this editorial.

**Running Head:** Complex Regional Pain Syndrome Developments

**Prior Presentations:** Not applicable

**Author contributions:** E.S. and A.G. conceptualized this work; E.S. wrote the first manuscript draft; E.S., and A.G. wrote the final manuscript. Both authors read and approved the final manuscript.

**Word count (excluding title page, abstract, and references)**: 1277

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.

1. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. *Pain medicine* 2007;8:326-331.

2. Lee H-J, Lee KH, Moon JY, Kim Y-C. The prevalence of dysautonomia in complex regional pain syndrome. *Regional Anesthesia & Pain Medicine* 2020.

3. Tominaga M, Wada M, Masu M. Potentiation of capsaicin receptor activity by metabotropic atp receptors as a possible mechanism for atp-evoked pain and hyperalgesia. *Proceedings of the National Academy of Sciences* 2001;98:6951-6956.

4. Opree A, Kress M. Involvement of the proinflammatory cytokines tumor necrosis factor-α, il-1β, and il-6 but not il-8 in the development of heat hyperalgesia: Effects on heat-evoked calcitonin gene-related peptide release from rat skin. *Journal of Neuroscience* 2000;20:6289-6293.

5. McLachlan EM, Jänig W, Devor M, Michaelis M. Peripheral nerve injury triggers noradrenergic sprouting within dorsal root ganglia. *Nature* 1993;363:543-546.

6. Lee H-J, Kim SE, Moon JY, Shin J-Y, Kim Y-C. Analysis of quantitative sudomotor axon reflex test patterns in patients with complex regional pain syndrome diagnosed using the budapest criteria. *Regional Anesthesia & Pain Medicine* 2019;44:1026-1032.

7. Goebel A, Barker C, Birklein F et al. Standards for the diagnosis and management of complex regional pain syndrome: Results of a european pain federation task force. *European Journal of Pain* 2019;23:641-651.

8. van Eijs F, Geurts J, van Kleef M et al. Predictors of pain relieving response to sympathetic blockade in complex regional pain syndrome type 1. *Anesthesiology* 2012;116:113-121.

9. Ali Z, Raja SN, Wesselmann U, Fuchs PN, Meyer RA, Campbell JN. Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. *Pain* 2000;88:161-168.

10. Oaklander AL, Rissmiller JG, Gelman LB, Zheng L, Chang Y, Gott R. Evidence of focal small-fiber axonal degeneration in complex regional pain syndrome-i (reflex sympathetic dystrophy). *Pain* 2006;120:235-243.

11. Russo M, Georgius P, Santarelli DM. A new hypothesis for the pathophysiology of complex regional pain syndrome. *Medical Hypotheses* 2018;119:41-53.

12. Birklein F, Ajit SK, Goebel A, Perez RS, Sommer C. Complex regional pain syndrome—phenotypic characteristics and potential biomarkers. *Nature Reviews Neurology* 2018;14:272.

13. Kapural L, Goebel A, Serpell M, Jones A, Kaye R, Tabuteau H. (429) create-1 study: A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of axs-02 (disodium zoledronate tetrahydrate) administered orally to subjects with complex regional pain syndrome type 1 (crps-1). *The Journal of Pain* 2016;17:S81-S82.

14. Safety and efficacy of inhaled cannabis for the uncontrolled pain releif in patients with advanced cancer. Available at: <https://ClinicalTrials.gov/show/NCT04042545>. Accessed November 21, 2020.

15. Biohaven announces initiation of clinical development for bhv-5000, a novel low-trapping nmda antagonist. PRNewswire. Available at: <https://www.prnewswire.com/news-releases/biohaven-announces-initiation-of-clinical-development-for-bhv-5000-a-novel-low-trapping-nmda-antagonist-300584389.html>. Accessed November 21, 2020.

16. Goebel A, Baranowski A, Maurer K, Ghiai A, McCabe C, Ambler G. Intravenous immunoglobulin treatment of the complex regional pain syndrome: A randomized trial. *Annals of internal medicine* 2010;152:152-158.

17. Goebel A, Bisla J, Carganillo R et al. Low-dose intravenous immunoglobulin treatment for long-standing complex regional pain syndrome: A randomized trial. *Annals of internal medicine* 2017;167:476-483.

18. Helyes Z, Tékus V, Szentes N et al. Transfer of complex regional pain syndrome to mice via human autoantibodies is mediated by interleukin-1–induced mechanisms. *Proceedings of the National Academy of Sciences* 2019;116:13067-13076.

19. Liang Z, Hore Z, Harley P et al. A transcriptional toolbox for exploring peripheral neuroimmune interactions. *Pain* 2020;161:2089-2106.

20. Sekiguchi F, Domoto R, Nakashima K et al. Paclitaxel-induced hmgb1 release from macrophages and its implication for peripheral neuropathy in mice: Evidence for a neuroimmune crosstalk. *Neuropharmacology* 2018;141:201-213.

21. Jain A, Hakim S, Woolf CJ. Unraveling the plastic peripheral neuroimmune interactome. *The Journal of Immunology* 2020;204:257-263.

22. Kemler MA, Barendse GA, Van Kleef M et al. Spinal cord stimulation in patients with chronic reflex sympathetic dystrophy. *New England Journal of Medicine* 2000;343:618-624.

23. Sivanesan E, Stephens KE, Huang Q et al. Spinal cord stimulation prevents paclitaxel-induced mechanical and cold hypersensitivity and modulates spinal gene expression in rats. *Pain Reports* 2019;4.

24. Sato KL, Johanek LM, Sanada LS, Sluka KA. Spinal cord stimulation reduces mechanical hyperalgesia and glial cell activation in animals with neuropathic pain. *Anesthesia and analgesia* 2014;118:464.

25. Kriek N, Schreurs MW, Groeneweg JG et al. Spinal cord stimulation in patients with complex regional pain syndrome: A possible target for immunomodulation? *Neuromodulation* 2018;21:77-86.

26. McCarthy KF, Connor TJ, McCrory C. Cerebrospinal fluid levels of vascular endothelial growth factor correlate with reported pain and are reduced by spinal cord stimulation in patients with failed back surgery syndrome. *Neuromodulation* 2013;16:519-522.

27. Cheng J, Salmasi V, You J et al. Outcomes of sympathetic blocks in the management of complex regional pain syndrome: A retrospective cohort study. *Anesthesiology* 2019;131:883-893.