

LETTER TO THE EDITOR

Nerve Injuries and the Fixed Dystonias of CRPS

Nerve injury is a known precipitant of complex regional pain syndrome (CRPS). However, is nerve injury a primary cause of CRPS dystonia? In 2009, Oaklander and her colleagues [1] reviewed peripheral aspects of CRPS, asking whether diverse symptoms of this neuropathic pain disorder are linked to small-fiber neuropathies. These authors also described a possible role for large-fiber neuropathies in the etiology of CRPS-fixed dystonias. This hypothesis adds a valuable new perspective to one of the most controversial topics in neurology: the fixed dystonias of CRPS.

During, and after, the American Civil War, Dr. Silas Weir Mitchell described both intense burning pain (causalgia) and fixed dystonias in a subset of wounded Union soldiers, as well as civilians, who had suffered nerve injuries [2]. In a number of these patients, remission of the CRPS comorbidities occurred within days to weeks after therapies were initiated (e.g., passive movement and splinting of inflamed/immobilized joints, massage and electrical stimulation of contracted muscles, and chemical blistering of causalgic skin). The rapid onset and rapid remission of CRPS causalgia and dystonia are consistent with the onset and attenuation of peripheral and spinal neuroinflammation, a view first forwarded by Silas Weir Mitchell [1].

Despite the original reports of Mitchell [1], a role for nerve injury as an antecedent to CRPS dystonia remains controversial [3]. On one hand, an epidemiological analysis by Birklein et al. [4] found that 48% of CRPS type II patients with confirmed nerve injuries ($N = 11/23$) exhibited dystonic muscle contractions or myoclonic jerks, whereas 27% of CRPS type I patients with no confirmed nerve injury ($N = 33/122$) had these movement disorders. In striking contrast, a study by Verdugo and Ochoa [5] reported that dystonia was entirely absent in CRPS type II patients who had documented nerve injury ($N = 0/307$).

A new needlestick model for fixed dystonia, recently developed by Oaklander and Fields [1] in rodents, offers new opportunities to address open questions about fixed dystonia arising from nerve injury. For instance, is coupling between spinal and supraspinal levels necessary for fixed dystonia to occur? Do fixed dystonic postures relax in response to spinalization? Do the fixed postures remit in response to pharmacological agents that attenuate neuroinflammation (e.g., glial attenuators)?

In discussing the review of Oaklander and Fields [1], Lang and Chen [3] have argued that the author's focus on large-fiber axonopathies in rodents does not adequately explain the generation of CRPS dystonias in humans.

From a mechanistic standpoint, this is true. However, Oaklander and Fields were discussing a possible etiology for CRPS dystonia in their review, not the entire set of neurophysiological processes by which fixed dystonic postures could be generated and maintained. Overall, the review by Oaklander and Fields moves the discussion of CRPS dystonia etiology in the right direction, correlating key cellular features of peripheral nerve injury with the onset of fixed dystonia. Whether the fixed dystonias arising from needlestick nerve injury in rodents [1] arise from the same mechanisms as fixed dystonia in CRPS type I or CRPS type II patients remains to be determined.

The central question remains: Why do some individuals with peripheral trauma develop fixed dystonia, and others do not? At the supraspinal level, Espay et al. [6] have elegantly shown that there are definitive neurophysiological characteristics in the cortex of patients with posttraumatic fixed dystonias, which they define as psychogenic dystonias. Espay et al. [6] have suggested that such abnormal cortical traits could allow psychological or environmental factors to precipitate a further decrement of already-deficient intracortical inhibition, causing these predisposed individuals to adopt fixed dystonic postures.

An alternative hypothesis is possible. Positron emission tomography (PET) imaging has shown that neuroinflammation (i.e., microglial activation) can spread from site to site within the neuraxis via neuronal projections [7]. In both CRPS type I and CRPS type II patients, a retrograde spread of neuroinflammation, from spinal levels to the motor cortex, could occur via corticospinal neurons. In predisposed individuals, functional changes in the motor cortex could ensue in response to cortical neuroinflammation. This could lead to a focal decrement of intracortical inhibition in the motor cortex, a condition known to foster fixed dystonic postures [8]. If this hypothesis is true, PET imaging of neuroinflammation should reveal focal microglial activation in the motor cortex of patients with CRPS dystonia, regardless of how the CRPS was initially established at the spinal level.

Lang and Chen [3] have argued that psychosomatic perspectives need to be used to understand the heterogeneous characteristics of CRPS dystonias. Oaklander and her colleagues [1], on the other hand, have generated a powerful rodent model of fixed dystonia, triggered by a defined peripheral nerve injury. Researchers in The Netherlands, focusing on immune etiologies for CRPS, have correlated the occurrence of fixed dystonia in CRPS patients with certain human leukocyte antigen profiles [9]. These researchers raise the possibility of an autoimmune etiology for CRPS dystonia [9].

With these currently disparate viewpoints, one thing is certain. As knowledge about nerve injury, neuroinflammation, and central sensitization continues to expand, existing views about spinal and supraspinal contributions to CRPS dystonias will continue to be challenged, integrated, and modified.

MARK S. COOPER, PhD
*Associate Professor, Department of Biology
University of Washington
Seattle, Washington, USA
E-mail: mscooper@u.washington.edu*

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