Editorial

Motor dysfunction in CRPS and its treatment

Complex Regional Pain Syndrome (CRPS) is a relatively new term for a clinical entity first described during the American Civil War almost a century and a half ago. Historically, the diagnostic criteria have focused on the sensory (pain, allodynia, hyperalgesia) and autonomic (sudomotor and vasomotor disturbances) features associated with this syndrome (IASP terminology Refs. [10,14]. However, recent epidemiological reports and studies attempting to validate the International Association for the Study of Pain (IASP) diagnostic criteria have documented that motor dysfunction is common in CRPS [1,4,13,19]. An expert consensus panel has proposed revised diagnostic criteria for CRPS which include the presence of motor signs and symptoms [7].

The majority of patients with CRPS exhibit a variety of motor symptoms and signs including weakness, tremor, decreased range of movement, difficulty in performing complex movement patterns, dystonia, and myoclonus [1,8,11,19]. Focal distal limb dystonia and myoclonic jerks have been reported in 30% of patients [1]. The prevalence of motor disorders may increase with prolonged duration of the disease and may reach as high as nearly 50% of patients [11,19]. In late stages, contractures from guarding of the affected limb and fibrosis of palmar and plantar fascia may also be observed. Although these motor symptoms are restricted to the affected limb in most patients, in a subset of patients these symptoms spread to other extremities [11].

Among the motor dysfunctions seen in patients with CRPS, dystonia is often disabling and presents a therapeutic challenge [18]. Dystonia, a neurological movement disorder, is characterized by sustained muscle contractions that result in twisting and repetitive movements or abnormal postures [2]. Although many dystonias have no known cause and are termed primary dystonias, numerous hereditary neurodegenerative disorders, such as Parkinson's disease, Huntington's disease, Wilson's disease, and Rett syndrome, are associated with secondary dystonias. Many drugs, including levodopa, dopamine agonists, antipsychotic drugs, anticonvulsant agents, and serotonin-reuptake inhibitors, also can cause dystonias [15]. Studies in patients with dystonia have indicated that the disorder might result from alterations in the sensorimotor circuitry that integrates sensory input and motor output [2]. Imaging studies in patients with secondary dystonias have commonly revealed damage to the basal ganglia, but multiple other regions including the thalamus, brainstem, parietal lobe, and cerebellum may also be involved [6,9]. Impaired inhibition at multiple levels of the central nervous system has been suggested as potential pathophysiological mechanisms for dystonia [2]. Possible examples include disruption of the striatal dopaminergic and cholinergic neurotransmitter systems and a loss of GABA-mediated inhibition.

Plastic changes in central sensory and motor nervous systems have similarly been reported in CRPS patients [3]. Functional imaging studies have shown shrinkage of cortical hand representation in the somatosensory cortex. In addition, researchers using transcranial magnetic stimulation reported a bilateral disinhibition of the primary motor cortex in patients with CRPS [12]. Kinematic analysis and fMRI imaging studies revealed motor defects suggestive of an impaired integration of visual and proprioceptive inputs in the posterior parietal cortex and adaptive changes indicative of significant reorganization of the central motor circuits in CRPS patients [8]. Recently, regional gray matter atrophy and abnormal gray–white matter interactions, including decreased connectivity between the ventromedial prefrontal cortex and basal ganglion have been observed [5]. It is unclear whether these plastic changes in the sensory and motor cortex are responsible for CRPS-associated motor dysfunctions, such as dystonia, but the possibility is worthy of further investigation.

In this issue of the journal, van Rijn et al. [17] report their observations on the efficacy and safety of intrathecally administered baclofen in CRPS patients with wide-spread dystonia. Inclusion criteria included a failed trial of oral baclofen therapy. In an earlier paper published by this group, the investigators reported that intrathecal baclofen was efficacious in a small number of patients [16]. The present study includes a group of 42 patients with long-standing CRPS (mean duration >10 yrs); more than 80% of them have symptoms in three or more extremities, and two thirds of them have dystonia in three or more extremities. These patients may not be the typical ones seen in most pain clinics in North America. It is not clear whether this group represents a select subset of patients with recalcitrant CRPS or is reflective of CRPS that has been allowed to progress for a long duration without aggressive treatment.

This report provides a useful dose-escalation paradigm for the conduct of an intrathecal baclofen trial. The study design consisted of a 2-day, single-blinded placebo run in period that was followed by a daily step-wise dose escalation (200–800 µg) till a preset responder criterion was met or side effects prevented further dose escalation. The study demonstrates the efficacy of intrathecal baclofen therapy in this difficult-to-treat group of CRPS patients, as evidenced by a reduction in dystonia scores by 33% and 45% in the lower and upper extremities, respectively, over a 12-month period. The decrease in dystonia also correlated with a reduction in the patients' pain severity.

Several observations made by the investigators are worth highlighting. The earlier report [16] suggested that an intrathecal bolus dose of 25–75 µg baclofen helped predict the subsequent response to continuous intrathecal baclofen infusion. In this study, however, despite a considerably higher peak dose of intrathecal baclofen during the blinded dose-escalation period, only 47% of patients who responded to the infusion trial improved by more than 50%, and none of the tested variables predicted the response to the open-labeled intrathecal baclofen treatment period. The

intrathecal dose was increased by 35% between month 3 and month 12, and the median daily intrathecal dose of baclofen (615 µg/day at the end of the year), although similar to that used to treat other types of dystonia, might be considerably higher than that used to treat spasticity. Several drug-related and device-related complications occurred. Forty-three device-related complications were observed in 33 patients and included post-dural puncture headache, catheter dysfunction, pump-related pocket infections, and pain at the pocket site. Six of the 36 implanted pumps were explanted during the 1-year follow-up period.

This cohort study provides information that is likely to benefit interventional pain practitioners who treat patients with CRPS-associated dystonia that is resistant to conventional, conservative therapies. However, given the frequency of the adverse events that occurred in this population, intrathecal baclofen therapy should be limited to carefully selected patients and conducted by physicians with considerable experience in the implantation and care of intrathecal devices.

References

[1] Birklein F, Riedl B, Sieweke N, Weber M, Neundorfer B. Neurological findings in complex regional pain syndromes-analysis of 145 cases. Acta Neurol Scand 2000;101:262–9.
[2] Breakefield XO, Blood AJ, Li Y, Hallet M, Hanson PI, Standaert DG. The pathophysiological basis of dystonias. Nat Rev Neurosci 2008;9:222–34.
[3] Fechir M, Geber C, Birklein F. Evolving understandings about complex regional pain syndrome and its treatment. Curr Pain Headache Rep 2008;12:186–91.
[4] Galer BS, Bruehl S, Harden RN. IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study. Clin J Pain 1998;14:48–54.
[5] Geha PY, Baliki MN, Harden RN, Bauer WR, Parrish TB, Apkarian AV. The brain in chronic CRPS pain: abnormal gray–white matter interactions in emotional and autonomic regions. Neuron 2008;60:570–81.
[6] Geyer HL, Bressman SB. The diagnosis of dystonia. Lancet Neurol 2006;5:780–90.
[7] Harden RN, Bruehi S, Stanton-Hick M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007;8:326–31.
[8] Maihofner C, Baron R, DeCol R, Binder A, Birklein F, Deuschl G, Handwerker HO, Schattschneider J. The motor system shows adaptive changes in complex regional pain syndrome. Brain 2007;130:2671–87.
[9] Marsden CD, Obeso JA, Zarranz JJ, Lang AE. The anatomical basis of symptomatic hemidystonia. Brain 1985;108:463–83.
[10] Merskey H, Bogduk N. Complex regional pain syndrome type 1 (reflex sympathetic dystrophy). In: Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. IASP Press; 1994. p. 41–2.
[11] Schwartzman RJ, Kerrigan J. The movement disorder of reflex sympathetic dystrophy. Neurology 1990;40:57–61.
[12] Schwenkreis P, Janssen F, Rommel O, Pleger B, Volker B, Hosbach I, Dertwinkel R, Maier C, Tegenthoff M. Bilateral motor cortex disinhibition in complex regional pain syndrome (CRPS) type 1 of the hand. Neurology 2003;61:515–9.
[13] Sharma A, Agarwal S, Broatch J, Raja S. A web based cross-sectional epidemiologic survey of complex regional pain syndrome. Reg Anesth Pain Med 2009;34:in press.
[14] Stanton-Hicks M, Janig W, Hassenbusch S, Haddox JD, Boas R, Wilson P. Reflex sympathetic dystrophy: changing concepts and taxonomy. Pain 1995;63:127–33.
[15] Tarsy D, Simon DK. Dystonia. N Engl J Med 2006;355:818–29.
[16] van Hilten BJ, van de Beek WJ, Hoff JI, Voormolen JH, Delhaas EM. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. N Engl J Med 2000;343:625–30.
[17] van Rijn MA, Munts AG, Marinus J, Voormolen JHC, de Boer KS, Teepe-Twiss IM, van Dasselaar NT, Delhaas EM, van Hilten JJ. Intrathecal baclofen for dystonia of complex regional pain syndrome. Pain 2009. doi:10.1016/j.pain.2009.01.014.
[18] van Rijn MA, Marinus J, Putter H, van Hilten JJ. Onset and progression of dystonia in complex regional pain syndrome. Pain 2007;130:287–93.
[19] Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993;342:1012–6
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