Movement Disorders in Complex Regional Pain Syndrome

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Abstract

About 25% of the patients with complex regional pain syndrome (CRPS) suffer movement disorders, including loss of voluntary control, bradykinesia, dystonia, myoclonus, and tremor. These movement disorders are generally difficult to manage and add considerably to the disease burden. Over the last years, interesting findings have emerged that show how tissue or nerve injury may induce spinal plasticity (central sensitization), which alters sensory transmission and sensorimotor processing in the spinal cord and is associated with disinhibition. These changes, in turn, set the stage for the development of movement disorders seen in CRPS. There are no randomized control studies on the treatment of movement disorders in CRPS but findings from fundamental and clinical research suggest that strategies that enhance the central inhibitory state may benefit these patients.

Key Words. Complex Regional Pain Syndrome (CRPS); Dystonia

Introduction

Complex regional pain syndrome (CRPS) is characterized by poorly controllable pain, swelling, and changes in skin blood flow and sweating that usually develop in the distal extremities [1]. The syndrome is commonly preceded by a minor to severe trauma or surgical intervention [1]. There is compelling evidence that patients with CRPS may develop movement disorders (MDs) including loss of voluntary control, bradykinesia, dystonia, myoclonus, and tremor. These MDs may occur early in the disease course and occasionally precede the onset of the more typical features of CRPS [2–4]. Findings from different studies indicate that 9–49% of the CRPS patients may develop MDs [2–5]. The prevalence of MDs increases as the disease duration lengths [6,7].

Movement Disorders in CRPS: Neurological Entity or Psychogenic?

In the field of movement disorders, several issues contributed to a long-lasting ambiguity concerning the neurological or psychiatric origin of the MDs in CRPS. First, the failure to demonstrate abnormalities in routine neurophysiological studies in CRPS type 1 patients with MDs [8]. Second, the concept that ultimately became dogma and related MDs like dystonia to dysfunction of the basal ganglia-thalamocortical circuitry. Because in CRPS, MDs are frequently preceded by peripheral trauma, basal ganglia involvement was neither demonstrated nor obvious from a clinical point of view. Consequently, MDs that occurred in the absence of basal ganglia involvement were for a long period considered non-organic. However, a unique psychological profile was never demonstrated in CRPS patients with MDs [9,10].

The Clinical Profile of MDs in CRPS

The execution of voluntary movement in patients with CRPS is commonly impaired, but these motor disturbances frequently remain unnoticed or are attributed to the presence of pain. Loss of voluntary control is frequently experienced by patients suffering weakness or dystonia. Typically, these patients report “My mind tells my hand/foot to move, but it won’t work” [2]. This so-called loss of voluntary control has been reported in other causes of dystonia [11] and has been ascribed to both dysfunction of attention and abnormal sensorimotor integration [12,13].

Bradykinesia or slowness of movement is very common in CRPS patients and is evaluated by means of repetitive finger or foot tapping. In CRPS patients, the performance of these movements are typically slowed and frequently associated with hesitancies. Interestingly, patients with unilateral upper extremity CRPS, may also show bradykinesia on the non-affected extremity [14].

Dystonia occurs in approximately 20% of patients with CRPS and is characterized by fixed flexion postures of the fingers (Figure 1), wrist, and feet that may vary in severity [2,15]. In less affected patients without overt dystonia, this may be provoked by repetitive tasks. Dystonia of the lower extremity is usually characterized by inversion and/or plantar flexion of the foot, with or without clawing or scissoring of the toes [2,15]. Dystonia may worsen by effort of the involved extremity, under circumstances of cold temperatures and humidity, and in the more severely affected patients, by tactile and auditory stimuli. Contractures, which frequently are also characterized by flexion postures...
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molecular level, central sensitization is associated with
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inflammation in CRPS [21,22]. Because neurogenic
inflammation is initiated by sensory nerves, it remained
frequently reported by CRPS patients with dystonia but
rarely may occur as the sole or predominant MD [14].

**MDs in CRPS: Mechanisms of Disease**

Compelling evidence suggests that in CRPS, different mechanisms may play a role. Similarities between the classical symptoms of inflammation and the clinical features of CRPS have led several investigators to suggest that inflammation must play an important role in the syndrome [17–19]. Tissue injury stimulates C and Aδ-fibers of sensory nerves, which causes the release of the inflammatory neuropeptides substance P and Calcitonin-gene-related-peptide from the afferent nerve endings [20]. These neuropeptides may induce local vasodilatation and increased capillary permeability causing edema and an increase of skin blood flow, a process known as neurogenic inflammation [20]. Indeed, several studies confirmed that this mechanism is involved in the perturbed regulation of inflammation in CRPS [21,22]. Because neurogenic inflammation is initiated by sensory nerves, it remained unclear how MDs may evolve in CRPS. However, nociceptive neurons in the dorsal horns of the spinal cord may become sensitized (central sensitization) by peripheral tissue or nerve injury [23]. In central sensitization, there is an increased sensitivity of spinal neurons, despite a lack of change of afferent input. As a result, pain becomes chronic and non-noxious stimuli become painful [23]. On a molecular level, central sensitization is associated with changes in the release of neuropeptides, neurotransmitters, prostaglandine E2, and the expression of N-methyl aspartate receptors in particular [23]. It seems unlikely that central sensitization only involves pathways that deal with the perception of pain and not those that mediate a response to pain. Indeed, two lines of research now show that central sensitization may influence spinal motor circuitry. First, findings from a recent study suggest that the induction of central sensitization causes a spinal learning deficit with respect to simple motor responses to shock [24]. Second, cutaneous afferents which mediate neurogenic inflammation are also linked to spinal interneuronal circuits that mediate nociceptive withdrawal reflexes (NWR) [25]. Animal models of neurogenic inflammation have shown that SP released at the dorsal horn of the spinal cord, enhances NWRs [26,27]. In withdrawal reflexes, flexor muscles play a prominent role, and interestingly, in dystonia of CRPS there is a conspicuous involvement of flexor postures, which may hint towards the involvement of spinal motor programs that mediate NWRs [15]. Neurophysiological studies have shown that central disinhibition is a key characteristic of central nervous system involvement in CRPS patients with and without dystonia [28–31]. Both SP-sensitized NWRs in animal models and dystonia in CRPS patients respond to baclofen, a gamma-aminobutyric acid (GABA) B receptor agonist which enhances spinal GABA-ergic inhibition on the spinal cord [32,33]. Collectively, findings from different sources of research suggest that peripheral tissue or nerve injury may induce central sensitization, which is associated with spinal changes that may contribute to the development of MDs.

In CRPS, there is a conspicuous tendency for dystonia to spread to other extremities. In two studies, 37 and 67% of the CRPS patients had two or more extremities affected by dystonia [34,35]. Interestingly, the hazard of dystonia in subsequent extremities in patients with CRPS increases with the number of extremities already affected by dystonia [7]. Apparently, once triggered, the underlying mechanism of dystonia in CRPS has the capacity to facilitate the occurrence of dystonia in other body parts. This accelerated disease course is a typical feature of maladaptive neuronal plasticity, as has been documented for pain [36]. CRPS occurs more frequently in women (~75%). The gender imbalance is further increased in CRPS patients with dystonia (~85%) [2,7,35]. These findings may indicate that the female gender is a risk factor for clinical manifestations of maladaptive neuronal plasticity.

Although most evidence seems to indicate that dystonia in CRPS occurs in the context of central sensitization in the spinal cord, the question remains if supraspinal involvement may contribute to the development of MDs in CRPS. Two functional magnetic resonance imaging (fMRI) studies evaluated cerebral network function during the execution of voluntary movement in patients with CRPS with and without MDs [37,38]. One study that evaluated finger movements in CRPS patients without MDs revealed a significant reorganization of central motor circuits with increased activation of the primary motor cortex and supplementary motor cortices, and increased activation of the ipsilateral motor cortex [38]. Activity of the posterior parietal cortices, supplementary motor cortices, and

**Figure 1** Shows examples of upper and lower extremity dystonia in CRPS patients.
primary motor cortex correlated with the degree of motor dysfunction as assessed by the maximum finger tapping frequency. Another fMRI study on voluntary and imaginary hand movements in CRPS patients with dystonia showed altered ipsilateral and contralateral cerebral activation during imaginary movement of the dystonic hand [37]. Collectively, these studies provided important new insights on the involvement of cortical circuitry in voluntary and imaginary motor tasks in patients with CRPS. However, it remains unclear if these findings play a role in the MDs of CRPS since Maihoffner et al. found that pain by itself is sufficient to induce these cortical changes [38]. However, given the important role of supraspinal sensorimotor networks in the execution of movement, it is not unlikely that supraspinal changes may contribute to some of the clinical characteristics of MDs in CRPS.

**MDs in CRPS: Treatment Options**

There are no randomized controlled studies of physical therapy, occupational therapy, or oral pharmacotherapy in treatment of MDs in CRPS [39]. Splints or plaster casts are often ineffective or may even worsen the dystonic postures of CRPS [39]. Benzodiazepines and high doses of baclofen may be beneficial in the treatment of dystonia and spasms in patients with CRPS but the extent of improvement is rarely described. Also, no controlled studies exist on the use of botulin toxin in dystonia in CRPS-I patients [39]. One study reported on the beneficial effects of intrathecal baclofen therapy in a small number of patients with CRPS-I and dystonia [33]. However, given the complexity of this treatment, it should only be considered for patients with CRPS-I if dystonia is a major problem and conventional therapy has proven ineffective [39].

**References**


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