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Complex Regional Pain Syndrome: Time to Study the Supraspinal Role?

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The International Association for the Study of Pain (IASP) defines complex regional pain syndrome (CRPS) as a spontaneous or stimulus-induced pain that is disproportionate to the inciting event and is accompanied by a wide variety of autonomic and motor disturbances, in highly variable combinations. As noted in the definition, there are a number of possible causes for CRPS. These include tissue damage, nerve damage, casting, traumas, fractures, burns, frostbites, strokes, and other non-identifiable causes. The symptoms of reflex sympathetic dystrophy that do not accompany nerve damage are generally classified as CRPS type 1, while those accompanying nerve damage — such as causalgia — are classified as CRPS type 2. Although various reports have suggested different incidence rates, the condition has generally been found in 20-30 cases per 100,000 persons; the incidence rate of CRPS type 2 is reported to be 0.82 cases per 100,000 persons.

Thus far, pathophysiological studies on CRPS have investigated a wide range of physiological processes, including psychological factors, immobilization, the sympathetic nervous system for vasomotor disturbance, This also includes pain processing, neurogenic inflammation, neuropeptides, cytokines, deep tissue microvascular pathology, small fiber neuropathy, genetic predisposition, autoimmunity, and central processing changes [1]. Existing treatment modalities include pharmacological agents (antipsychotics, antidepressants, corticosteroids, and opioids), physical and occupational therapy, sympathetic blocks, medullary stimulation, psychological pain management, and ketamine [2]. Despite these various treatment modalities and vigorous studies on the pathophysiology, the treatment of CPRS type 2 patients still remains ineffective; some patients are even driven to suicide as their pain increases by the day.

This indicates that the known etiological factors and treatment modalities of chronic pain remain insufficient to address CRPS pain. As many may be aware, pain transmission and sensation processes are not simply confined to the somatosensory pathways. Modulation, sensitization, inhibition, and convergence occur, and psychological factors also wield an influence on the process through which pain is transmitted, perceived, and responded to. Most prior studies on pain have focused on the peripheral nervous system and the spinal cord, with few studies considering the supraspinal region—i.e., the brain. Given that chronic pain is closely associated with emotions and memories, treatment for refractory chronic pain— CRPS pain that persists despite treatment— should target the brain, the ultimate executive organ for the transmission, integration, and ordering of all information.

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The existing supraspinal studies on CRPS pain can be classified into two categories: studies on cortical representation changes due to peripheral pain stimulation, and those on supraspinal sensitization in pain processing [1].

To study the central processing of CRPS patients, brain mapping (D1, D2, and D5) was conducted using magnetoencephalography from tactile stimulation on CRPS affected upper extremities, The response in the contralateral primary somatosensory cortex (S1) area was significantly increased in affected hands, compared to that in the hands of healthy individuals or in unaffected hands. However, the response area (D1–D5 distance) was greatly reduced and seemed to have shifted to the cortical representation region of the lips [3]. The degree of cortical reorganization was associated with the amount of CRPS pain and the severity of the pinprick hyperalgesia. Thus, it can be implied that central sensitization and cortical reorganization are correlated [4]. On the other hand, the findings of the functional MRI (fMRI) during electrical stimulation showed that when the index finger of the affected hand was stimulated, the signal strength was decreased in S1 and S2 compared to that of healthy individuals. The degree of signal change was shown to be correlated with the degree of tactile discrimination impairment [5].

The degree of cortical reorganization as measured with cortical mapping was shown to revert to normal as the clinical symptoms improved [6]. However, functional magnetic resonance imaging (fMRI) tests on pediatric CRPS type 1 patients revealed that the brain's response to stimulation was maintained in the postcentral gyrus, posterior cingulate cortex, basal ganglia, and amygdala even after the pain symptoms had improved [7]. This variant stimulation–response phenomenon was thought to be associated with symptom relapse.

Meanwhile, motor cortex reorganization also occurs in CRPS patients. The amplitude and size of the motor-evoked potential of the long extensor muscle of the fingers were significantly reduced in the motor cortex of the affected side, compared to that in the contralateral side [8]. The results of the fMRI during taping of the CRPS-affected area revealed that the degree of response in the primary motor cortex, supplementary motor area, and posterior parietal cortices, was associated with the extent of the motor dysfunction [9]. A study using transcranial magnetic stimulation demonstrated that abnormal activation in the classical motor area and posterior parietal cortex area was associated with the degree of motor impairment; the same study suggested that increased neural activity in the M1 area was caused by functional impairment of the inhibitory GABA-nergic circuit [10].

A study suggested that the roles of the posterior parietal cortices, which control the body schemas for the visual, tactile, proprioceptive, and vestibular input and for limb movement, are related to CRPS symptoms. Moreover, in a fMRI study on CRPS I patients with symptoms of tonic dystonia, an affected dominant hand showed decreased activity in the contralateral inferior parietal area compared to that of an unaffected hand [11].

In summary for cortical representation change, the anomalies observed in the supraspinal brain area of CRPS patients included cortical reorganization of the S1, S2, and M1 of the brain, functional disturbances in the posterior parietal cortex, disturbed body schema, and altered perception of the affected limb. These phenomena are suggested as contributory factors to the sensory-motor dysfunction and pain enhancement in CRPS patients [1].

The primary and secondary somatosensory, insular, and anterior cingulate, the prefrontal cortex, and the thalamus (also known as the 'supraspinal pain neuromatrix'), are activated in pain stimulation on the fMRI; When the unaffected hand of a CRPS type 1 patient is given a brush-evoked mechanical stimulation, the S1, S2, and insula are activated. The M1, parietal cortex, insula, frontal cortices, and cingulate cortex are additionally activated when the affected hand is given allodynia or pinprick hyperalgesia stimulation. This confirms that not only nociceptive processing, but also motor and cognitive processing, are involved in CRPS pain [12].

In experimental capsaicin-induced hyperalgesia, the thalamus and brain stem were observed to be specifically associated with central sensitization [13]. The application of painful stimuli and innocuous stimuli to CRPS type 1 patients strongly activated their ipsilateral posterior cingulate cortex and stimulated their contralateral and ipsilateral posterior opercula [14].

The amygdala plays a significant role in the affective dimensions of the pain response. In an animal experiment, a noxious visceral stimulation was shown to increase the c-fos in the amygdala. The amygdala is also involved in the psychological symptoms (e.g., anxiety and depression) that frequently accompany chronic pain [15].

A number of studies have also surveyed the changes in the brain morphometry of CRPS patients, observing atrophy in the gray matter areas involved in pain process-

ing, namely the ventromedial prefrontal cortex, anterior portion of the insula, and nucleus accumbens. In the white matter, the functional connectivity between the prefrontal cortex and insula was increased, while the connectivity with the basal ganglia was decreased. Furthermore, the anterior portion of the insula was specifically activated during allodynia and hyperalgesia [16].

The response of the pain suppression task was reduced in the periaqueductal gray and anterior cingulate cortex in CRPS type 1 patients. As the periaqueductal gray is involved in descending pain modulation, it can be presumed that CRPS patients experience an impairment of their endogenous pain modulation [17].

Hence, we can deduce that the supraspinal brain area, which is involved with the cognitive/emotional components, is also associated with CRPS pain and central sensitization. We can also infer that anatomical changes in the areas associated with chronic pain and functional impairment of the descending inhibitory pathway further intensify the pain.

Peripheral sensitization and central sensitization are the two main causes of chronic pain. Several studies have investigated the numerous changes occurring in the process through which pain stimulation sprouts from the peripheral nociceptor and ultimately lands in the spinal dorsal horn. As noted in the definition of pain suggested by the IASP, pain also includes 'emotional experiences'. This has been clinically demonstrated, as long-term chronic patients — including CRPS patients — have complained of depression, insomnia and anxiety in addition to the pain. Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and sedatives have also been found to relieve the degree of chronic pain. These findings suggest that central sensitization and cognitive/emotional modification occur in the supraspinal brain area in refractory CRPS pain. Therefore, more vigorous research on the pain-associated supraspinal brain areas is required for the successful management of chronic refractory pain.

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