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EDITORIAL

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New Treatments for Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy was first described by Mitchell, in 1864.[1] It has been difficult for clinicians to diagnose this disorder because it has many variations, often follows minor injury, and evolves and spreads over time.[2,3] There are five main types of symptoms: pain, autonomic dysfunction, edema, a movement disorder, and dystrophy and atrophy. A new classification of this disorder and a new name, the complex regional pain syndrome, have been proposed in an effort to describe its clinical features more accurately and avoid the implications of the name "reflex sympathetic dystrophy." The role of the sympathetic nervous system in many aspects of the illness is not clear, and dystrophy may not occur in all patients. In complex regional pain syndrome type 1, all the features of reflex sympathetic dystrophy are present, with no definable nerve injury; in type 2 (formerly called causalgia), a definable nerve injury is present.[4]

In the early stages of reflex sympathetic dystrophy, the pain is more severe than would be expected for the degree of tissue damage, and the pain spreads progressively from a nerve or dermatomal distribution to a regional distribution. The pain is often characterized as a constant burning from its onset, is diffuse both superficially and deeply, and has a palmar or plantar predominance. Spontaneous pain is frequent, and most patients initially have hyperalgesia (more pain than that which would be expected from a painful stimulus) and allodynia (pain from an innocuous stimulus). Later in the course of the disorder, there is hyperpathia (an increased threshold to pain that, once exceeded, results in pain that reaches its maximal intensity too quickly and is not stimulus-bound). The nails become ridged, thickened, and brittle; the hair darkens and grows rapidly in the affected area. In the distal portion of the affected extremity, there may be increased or decreased skin temperature, hyperhidrosis, livedo reticularis, dusky cyanosis, delayed capillary refill, and diffuse mottling. Spasms, increased reflexes, and weakness are common. In approximately 20 percent of patients, the affected area is initially painful, warm, and red.

As the illness evolves, the constant burning pain, hyperalgesia, and allodynia intensify and may be accompanied by disruption of sleep, anxiety, and depression. The skin may show brawny edema and is usually hyperhidrotic, cool, cyanotic, and mottled. Loss of hair occurs in areas where its growth was previously stimulated. The bones may undergo cystic and subchondral erosion, as well as diffuse osteoporosis (Sudeck's atrophy).

After several years, the illness is characterized by ever-increasing pain, dystrophy, and atrophy. A small percentage of patients report pain throughout the body. In some patients, the disorder remains stable for years, whereas in others it progresses rapidly. The symptom complex may be dissociated in any stage of the illness — for example, there may be pain in one hand and autonomic dysfunction in the other.

In its early stages, reflex sympathetic dystrophy may be maintained by sympathetic neural activity, but with time it becomes independent of sympathetic activity. There is no evidence that affected patients have a personality disorder, but the severity of the pain and the disruption of the patient's life can lead to depression and anxiety.[5] There is some evidence of a genetic predisposition.

In general, reflex sympathetic dystrophy is caused by direct trauma to soft tissue, bone, or a major nerve or plexus in which nociceptive terminals are injured. Studies in animals have shown that allodynia, thermal hyperalgesia, sympathetic maintenance (in which case sympathetic blockade relieves the pain), dystonia, and altered pain behavior are consistent with lowered pain thresholds.[6]

The pain in patients with reflex sympathetic dystrophy is consistent with the mechanisms of activity-dependent plasticity in which nociceptive terminals innervating the damaged area and the central pain-projecting nerves of the dorsal horn undergo changes in physiologic function as the result of a complicated series of intracellular enzyme cascades, receptor modifications, and novel gene expression. This modulation results in the central sensitization that amplifies the pain response of the central nervous system.[7] The edema that often accompanies reflex sympathetic dystrophy may be a manifestation of neurogenic inflammation in which C fibers that innervate blood vessels in the affected area release vasoactive neuropeptides that cause vasodilatation and increased permeability, with consequent transudation of fluid and protein.[8]

Recent clinical studies of autonomic function in patients with reflex sympathetic dystrophy have demonstrated a profound abnormality of respiratory and thermoregulatory sympathetic neurogenic reflexes early in the course of the disorder that clears with clinical recovery, as well as abnormalities in sweat output and skin temperature at rest and in microcirculatory responses to both peripheral and central autonomic stimuli. The clinical findings indicate that patients with reflex sympathetic dystrophy have autonomic dysfunction within the central nervous system.[9]

The movement disorder that is characteristic of reflex sympathetic dystrophy has five main components: an inability to initiate movement, weakness, tremor, muscle spasms, and dystonia.[10,11] These motor manifestations may precede the pain, may appear suddenly, and may occur on the contralateral side of the body. Rarely, both the arms and the legs may be affected. In the upper extremity, the dystonia starts with flexion and contraction of the fourth and fifth fingers of the hand and evolves into adduction and flexion of the arm and wrist. In the lower extremity, the foot is inverted, with plantar flexion. A few patients have dystonic extensor postures. The process is devastating and renders the extremity nonfunctional. These motor manifestations may be alleviated by sympathetic blockade but only in the early stages of reflex sympathetic dystrophy. The mechanisms that cause the dystonia are unclear. There may be enhancement of nociceptive flexor withdrawal reflexes and decreased presynaptic inhibition of nociceptive afferents by γ-aminobutyric acid–employing (GABAergic) inhibitory neurons.[12,13]

Two fine clinical studies of novel treatments for the pain and dystonia of reflex sympathetic dystrophy are reported in this issue of the *Journal*. Kemler and colleagues describe a randomized trial of spinal cord stimulation.[14] In an intention-to-treat analysis, the patients assigned to receive this treatment had greater improvement in scores for the intensity of pain and the perceived effect of treatment than did the patients assigned to the control group. The health-related quality of life improved only in the patients who actually underwent spinal cord stimulation. Unfortunately, the patients had no functional improvement as a result of this treatment. Kemler et al. note that complications occur in 20 to 75 percent of patients who undergo spinal cord stimulation. In most patients, the complications are associated with unsatisfactory positioning of the electrode. The authors make a case for total coverage of the affected area with induced paresthesias in order to obtain a good result. Spinal cord stimulation is an invasive but safe and effective treatment for the relief of intractable pain in patients with reflex sympathetic dystrophy.

Also in this issue of the *Journal,* van Hilten and colleagues report on their double-blind, randomized crossover trial comparing intrathecal baclofen, a GABA-receptor agonist (type B), with placebo for the treatment of dystonia in patients with reflex sympathetic dystrophy.[15] In six of seven patients, bolus injections of 50 and 75 μg of baclofen resulted in complete or partial resolution of dystonia of the hands, but little improvement was noted in dystonia of the legs. The patients whose hands were affected regained normal function with prolonged therapy. Pain and violent spasms were also relieved in some patients. The results of this study strongly support the role of GABAergic inhibitory neurons in the pathophysiology of reflex sympathetic dystrophy. The widespread use of baclofen pumps for spasticity has established their safety for long-term treatment.

Reflex sympathetic dystrophy is a devastating, life-altering illness that frequently affects young people. My suggestions for its management are early diagnosis, treatment of any underlying cause, treatment with sympathetic blockade when appropriate, and intensive physical therapy. If these measures fail, the use of dorsal-column stimulation may be helpful, particularly if the disorder is limited to one extremity. My experience also supports the finding of van Hilten et al. that intrathecal baclofen can help relieve dystonia in patients with reflex sympathetic dystrophy, but high doses are usually needed. Although the use of a baclofen pump and dorsal-column stimulation involve invasive procedures, they are welcome additions to the treatment options for patients with severe reflex sympathetic dystrophy.

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