Is Reflex Sympathetic Dystrophy/Complex Regional Pain Syndrome Type I a Small-Fiber Neuropathy?

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Neurologist S. Weir Mitchell first described "causalgia" following wartime nerve injury, with its persistent distal limb burning pain, swelling, and abnormal skin color, temperature, and sweating. Similar post-traumatic symptoms were later identified in patients without overt nerve injuries after trauma. This was labeled reflex sympathetic dystrophy (RSD; now complex regional pain syndrome type I [CRPS-I]). The pathophysiology of symptoms is unknown and treatment options are limited. We propose that persistent RSD/CRPS-I is a post-traumatic neuralgia associated with distal degeneration of small-diameter peripheral axons. Small-fiber lesions are easily missed on examination and are undetected by standard electrophysiological testing. Most CRPS features—spreading pain and skin hypersensitivity, vasomotor instability, osteopenia, edema, and abnormal sweating—are explicable by small-fiber dysfunction. Small fibers sense pain and temperature but also regulate tissue function through neuroeffector actions. Indeed, small-fiber–predominant polyneuropathies cause CRPS-like abnormalities, and pathological studies of nerves from chronic CRPS-I patients confirm small-fiber–predominant pathology. Small distal nerve injuries in rodents reproduce many CRPS features, further supporting this hypothesis. CRPS symptoms likely reflect combined effects of axonal degeneration and plasticity, inappropriate firing and neurosecretion by residual axons, and denervation supersensitivity. The resulting tissue edema, hypoxia, and secondary central nervous system changes can exacerbate symptoms and perpetuate pathology. Restoring the interest of neurologists in RSD/CRPS should improve patient care and broaden our knowledge of small-fiber functions.

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"You have to have the imagination to look for new phenomena!"

Raymond D. Adams, M.D, while discussing complex regional pain syndrome with the authors on July 19, 2007.

S. Weir Mitchell and his colleagues Morehouse and Keen first reported that about 10% of American Civil War soldiers with major limb nerve or plexus injuries developed burning pain distal to their injury (causalgia).[1] Some had colocalizing edema, temperature asymmetry, abnormal skin perfusion, and excessive sweating. Most recovered, but a few had persistent severe ongoing pain and pain triggered by light touch or strong emotion. Symptoms often spread beyond the innervation territories of the injured nerves, sometimes even to the "mirror" site on the contralateral uninjured limb. Mitchell followed some patients for up to 28 years. Case 51 from *Injuries of Nerves and their Consequences*—David Schiveley, age 17; examined 4 years after bullet injury to his right brachial plexus at Gettysburg on July 2, 1863—shows that Mitchell's insight extended even to the psychosocial effects of causalgia.

"The left hand, which . . . was also eczematous, is painful on pressure or touch, especially in the palm. Both hands are kept covered with loose cotton gloves, which he wets at brief intervals. He is . . . nervous and hysterical to such a degree that his relatives suppose him to be partially insane. It is difficult even to examine him properly on account of his timidity, and his whole appearance exhibits the effects of pain . . . and want of rest."[1]

Causalgia remains a significant problem after combat injuries, but a very similar clinical picture is far more common in civilians with traumatic limb injuries that do not cause obvious damage to major nerves (Fig 1). In 1901, Sudeck described this syndrome and proposed that it reflected prolonged regional inflammation from incomplete healing that sensitized nearby axons.[2] In

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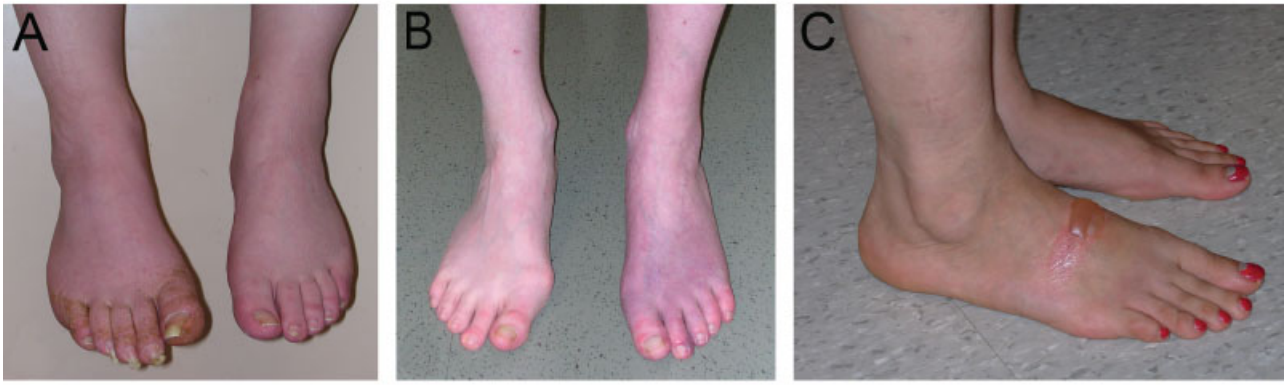

Fig 1. Reflex sympathetic dystrophy/complex regional pain syndrome type I (CRPS-I) is a complex of symptoms of varying severity and location, most commonly affecting the distal limbs. Few patients have all symptoms, and these usually gradually abate so that many patients pass from a CRPS diagnosis to one of simple neuralgia en route to recovery, evidence that unifies these conditions. (A) A laborer in his 30s 4 years after right foot crush by a steel beam. Premorbid neurological history showed childhood megacolon. Severe ongoing and touch-induced pain in his great toe spread to his entire foot, which he guarded from contact even with bathwater. Poor hygiene, mild edema, color change, and toe dystonia are visible. His history and a persistent Tinel's sign at his right fibular head suggested peroneal-nerve injury, but he declined electromyography/nerve conduction velocity testing. (B) A researcher in her 30s with chronic pain, edema, and vasodysregulation in her left foot and lower leg following bunionectomy several years ago. She also developed benign ectopic bone growth of her proximal left tibia. Her history is notable for migraines and asthma, linked through epidemiological study to CRPS.[9] (C) An otherwise healthy woman in her 40s several years after a well-healed 2nd degree burn from hot coffee spilled on her right foot. Ever since, any prolonged contact triggers severe pain and blister formation (shown), and the resulting ulcer takes weeks to heal. Her inability to wear a shoe precludes employment.

1946, Evans described 32 cases of what he termed reflex sympathetic dystrophy (RSD), mostly triggered by orthopedic problems, but he did not evaluate his patients for nerve damage.[3] Although he included pain relief from sympathetic block as part of his diagnostic criteria, later studies showed that sympatholytics do not help most patients with persistent RSD.[4] This provided the impetus to change the name from reflex sympathetic dystrophy, and to search for other mechanisms of pain persistence. The current International Association for the Study of Pain nomenclature and diagnostic criteria (Table) date from 1994, preceding most of the discoveries reviewed here.[5] Complex regional pain syndrome type I (CRPS-I) replaced RSD for patients without known nerve injuries, and CRPS-II replaced causalgia for patients with documented nerve injuries. Some 90% of CRPS patients are categorized as CRPS-I, yet few of these patients have undergone the neuromuscular consultation optimal for detecting or excluding subtle nerve injuries. Correlation between the old and new terminology is imperfect, and the new criteria are less specific. In practice, even they are often ignored, and the CRPS-I label is applied indiscriminately.

Epidemiological studies have contributed important insights about this rare condition. As methods improved, the initial annual incidence of 5.5[6] was increased to 26.2 new CRPS-I cases per 100,000.[7] Fractures and sprains are the most common precipitants, and CRPS-I is more common in middle adulthood and among women, with a remarkable 4:1 sex ratio. Children are especially likely to recover quickly,[8] and most adults eventually recover as well, leaving CRPS rare in the elderly. Examination of preincident comorbidities has linked CRPS-I to asthma and to focal and generalized neuropathies, but not to psychological illness.[9]

Small-Fiber Neurobiology

As knowledge emerged of the efferent and trophic functions of axons previously classified as purely sensory, it lessened functional distinctions between somatosensory and autonomic peripheral axons and led to a unified concept of small-fiber function. Mixed peripheral nerves contain motor, sensory, and postganglionic sympathetic axons. "Small fibers" are the thinly myelinated (A-delta) or unmyelinated (C-fiber) and sympathetic axons that comprise some 80% of peripheral axons.[10] Somatic small fibers detect and transmit information triggered by potentially injurious mechanical, thermal, and chemical stimuli. In addition, they have critical vasomotor and trophic efferent functions that may contribute to CRPS, for instance by antidromic release of vasoactive neuropeptides, including calcitonin gene-related peptide (CGRP) and substance P (SP).[11] Small fibers are particularly sensitive to some types of injury. Small-fiber degeneration and pain often precede degeneration of myelinated fibers in sensorimotor polyneuropathies.[12] After traumatic injury to rat sciatic nerve, the cell bodies of small-diameter axons in

Table. **The Current (1994) Diagnostic Criteria of the IASP for CRPS-I and CRPS-II**[5]

IASP Diagnostic Criteria for CRPS-I (Reflex Sympathetic Dystrophy)
1. The presence of an initiating noxious event, or a cause of immobilization.
2. Continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event.
3. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.[a]
IASP Diagnostic Criteria for CRPS-II (Causalgia)
1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve.
2. Evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of pain.
3. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.[b]

Modifications have been proposed for research and clinical use.[84,85]
[a]Criteria 2-4 must be satisfied.[5]
[b]All three criteria must be satisfied.[5]
CRPS = complex regional pain syndrome; IASP = International Association for the Study of Pain.

the dorsal root ganglion and their central axons degenerate preferentially.[13] This may explain how trauma can cause small-fiber–predominant axonal degeneration, dysfunction, and CRPS without apparent large-fiber injury.

The hypothesis of small-fiber involvement in CRPS emerges from its clinical similarity to the generalized small-fiber–predominant polyneuropathies (SFPNs).[14] SFPN patients do not develop weakness, muscle atrophy, or hyporeflexia, and their neurological signs are easily missed if not specifically sought. SFPN is characterized by combinations of symmetrical distal loss of pain and temperature sensation, often preceded by pain and hypersensitivity. Bilateral burning foot pain is the most common complaint, but careful history, examination, and testing often reveal accompanying distal limb edema, vasodysregulation, and disordered sweating, as in CRPS.[15] Effects of SFPN on non-neural tissues, including skin and bone, can be as severe as in CRPS. Although qualitatively similar, SFPN symptoms are not triggered by trauma and typically affect both sides equally. SFPN can progress to involve all limbs, whereas CRPS predominates in the originally injured limb. Mitchell also named and characterized an SFPN phenotype, erythromelalgia, that shares some of CRPS' dramatic features.[16,17]

Objective Evidence of Small-Fiber–Predominant Axonal Injuries in CRPS-I

Electromyography is unrevealing in SFPN because small fibers do not activate muscles. Furthermore, their compound action potentials are undetectable by surface nerve conduction study, because small axons have low extracellular amplitude and slow and variable conduction velocities. Until recently, ultrastructural analysis of nerve biopsies was the only objective test for small-fiber axonopathy, but invasiveness and technical complexity limited use. Diagnosis and understanding of small-fiber diseases has been revolutionized by a minimally invasive method that permits light-microscopic visualization of intraepidermal axons. Small skin biopsies are immunolabeled against axonal markers. Intraepidermal neurites are mostly nociceptors,[18] making this method particularly useful for neuralgia. Repeatable and safe, skin biopsies are even more sensitive than nerve biopsies for detecting small-fiber axonopathy, as they sample the most distal axon, which degenerates earliest.[19] Density of intraepidermal nerve fibers is reduced in many neuralgic conditions.[20,21]

In 1998, a Dutch group pathologically evaluated legs amputated from 8 CRPS-I patients. They found muscle atrophy and severely thickened capillaries but no consistent abnormalities of myelinated axons. In contrast, ultrastructural quantitation revealed C-fiber degeneration in 4 of 8 sural nerves.[22] Two recent studies of CRPS-I patients corroborate and extend these findings.[23,24] Pathological examination of skin from amputated limbs revealed reduced epidermal, sweat-gland, and vascular small fibers, loss of vascular endothelial integrity, and blood-vessel hypertrophy (Fig 2).[23] Remaining small fibers innervating hair follicles, superficial arterioles, and sweat glands had altered neuropeptide profiles. A study of 19 more-typical patients showed average losses of 29% of intraepidermal neurites from subjects' CRPS-affected sites as compared with unaffected control sites.[24] Nine symptom-matched osteoarthritis subjects lacked neurite losses, suggesting that chronic limb pain, edema, and disuse alone cannot explain CRPS axonopathy. These 3 stud-

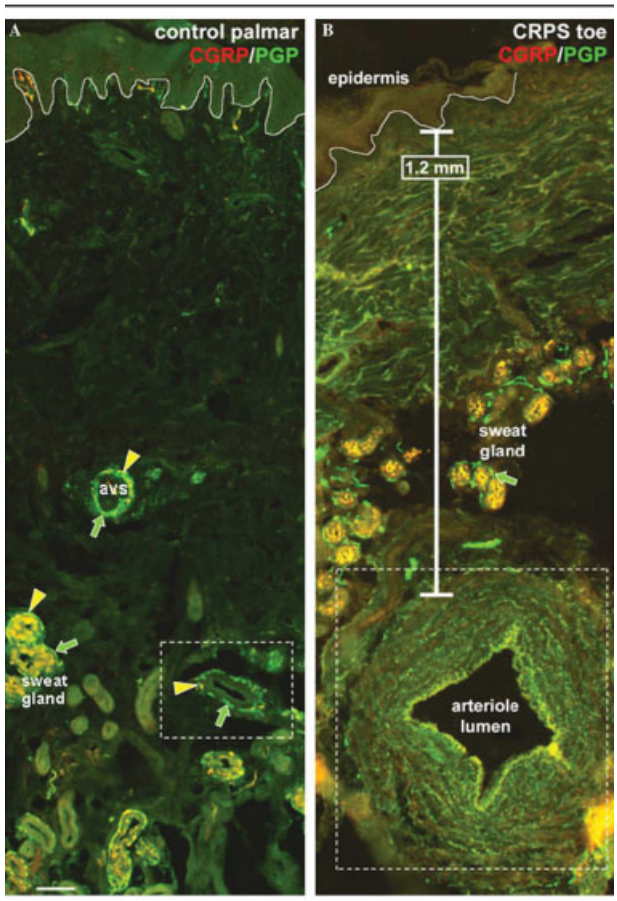

Fig 2. Calcitonin gene-related peptide (CGRP) (red) and protein gene product (PGP) 9.5 (green) immunolabeling of cutaneous innervation. (A) Control palmar skin demonstrating normal abundant innervation of sweat glands, arteries (box), and arteriovenous shunts (avs) located within 2 mm of the epidermis (basement membrane delineated by the white line). All contain abundant PGP^+ innervation (arrows) and some coexpress CGRP (arrowheads). (B) In contrast, complex regional pain syndrome (CRPS)-affected skin contained sweat glands with reduced PGP^+ innervation (arrow), no coexpression of CGRP, and denervated arteries (box) that are extremely hypertrophied. Scale bar = 100 μm. Reproduced with publishers' permission.[23]

ies established the presence of chronic focal axonal degeneration in CRPS-I and showed that both CRPS I and II are associated with nerve injury. Persistent CRPS-I may represent a small-fiber–predominant mono- or oligoneuropathy that is initiated by a limb trauma. In some cases, the treatment of trauma (eg, tight casts, surgery, injections) may be a contributing factor.

How Can Loss of Nociceptive Axons Cause Chronic Pain?

It seems counterintuitive to link fewer nociceptive axons with increased pain. Overall, most patients with sensory axonal damage from trauma or illness do not complain of associated pain, but a significant minority of patients with neuropathies from diabetes, chemotherapy, shingles, or trauma develop neuralgic pain in the territory innervated by damaged nerves. As Hughlings Jackson stated, dead or disconnected neurons cannot directly cause positive symptoms such as pain. As with other neural injuries, conditions that kill some small fibers, or tissue changes triggered by partial axonal loss (eg, upregulation of growth factors), can cause neighboring survivors to malfunction. Surviving small fibers with reduced thresholds for ectopic firing[25] have been termed angry or irritable nociceptors.[26,27] Damage to peripheral axons of primary afferents usually affects their central axon as well and triggers diffuse glial activation and abnormalities of postsynaptic neurons in the dorsal horn and higher centers.[28] Reduced activity of inhibitory interneurons in the dorsal horn appears particularly important in triggering the abnormal firing of central pain neurons that is the final common pathway of neuropathic pain. Neuropathic pain is truly a systems disorder.

Microvascular Dysregulation and Neurogenic Inflammation

Colocalizing distal limb microcirculatory abnormalities distinguish CRPS from simple post-traumatic neuralgia. These persist after healing of the original injury, consistent with a neural cause. Their presence and severity varies between patients, and with activity or limb position. Although often assumed to reflect sympathetic dysfunction, nociceptive C- and A-delta somatosensory axons also innervate blood vessels, and their degeneration or neuroeffector secretions can produce signs of inflammation when there is no infection or acute injury, which is known as neurogenic inflammation.[11] Some dermal vessels entirely lack sympathetic innervation,[29] so peripheral microvascular dysregulation does not always implicate sympathetic involvement or dysautonomia.

The distal limbs contain many arteriovenous shunts (AVS, Fig 2A), used mostly for rapid cooling. Dense innervation, predominantly sympathetic, maintains tonic smooth muscle contraction to keep AVS closed and direct blood through capillary beds where gases and nutrients are exchanged. Normally AVS open only transiently, however, if the nervi vasorum degenerate, they can remain open, permitting blood to chronically bypass the capillaries. Although CRPS-affected skin can appear flushed and hyperemic, the tissues below may be paradoxically ischemic. Indeed, ^{31}P nuclear magnetic resonance spectroscopic study of muscles from CRPS-I patients documents hypoxia.[30] The nervi vasorum do not respect anatomical boundaries defined by cutaneous sensation, so traumatic mononeuropathy (injury to one nerve) can trigger neurogenic microvascular dysregulation outside the cutaneous distribution

of that nerve, and at worst, involve the entire distal limb. Sometimes CRPS-affected limbs appear vasoconstricted (blue and cold, Fig 1B). Vasodilation and constriction can alternate in different conditions, influenced by supersensitivity of denervated vessels to circulating catecholamines.

Neurogenic edema, another facet of CRPS, can be caused by inappropriate release of peptides contained in somatic polymodal C-fibers, including those that innervate cutaneous venules.[11,31] Denervated venules lose endothelial adhesion markers,[23] permitting plasma leakage.[32] If subcutaneous tissues are scant, blisters can form (Fig 1C). Severe edema, although rare, can cause pain by stretching tissues and can hinder gas and nutrient exchange.

Small-fiber axonopathies can produce other aspects of inflammation as well. Plasma extravasation produces intraluminal hemoconcentration that promotes adhesion and diapedesis of white blood cells. Neuropeptides released from small-fibers also directly recruit and activate immunocytes including lymphocytes, macrophages, and mast cells. Their cytokines amplify local inflammation and can sensitize nearby primary afferent nociceptors in a vicious neural-immune cycle. Tryptase, a mast-cell–specific product, is increased in CRPS-I–affected skin,[33] and proinflammatory cytokines are increased in tissue fluid[34] and serum[35] from CRPS patients and patients with painful SFPN.[36]

Skin Abnormalities in CRPS

The skin is densely innervated and regulated by small fibers, and cutaneous abnormalities are common in CRPS. Changes known historically as "trophic effects" include abnormal growth of hair and nails, and thin glossy skin. These are consistent with nerve injury; experimental axotomy of cutaneous nerves slows keratinocyte mitosis and causes epidermal thinning and hair loss.[37,38] These changes also develop distally in SFPN.[15] CRPS-I–affected skin contains abnormal dense small-fiber innervation around hair follicles,[23] a potential substrate for touch hypersensitivity (mechanical allodynia).[27]

Some CRPS patients report regional sweating abnormalities, usually hyperhydrosis. Sweating is currently measured quantitatively by three tests: 1) resting sweat output (RSO), which measures subthreshold, nonthermoregulatory baseline sweating; 2) thermoregulatory sweat testing (TFT), which measures combined central and peripheral sweat control; and 3) quantitative sudomotor axon reflex testing (QSART), which measures sweat produced by local administration of cholinergic agents. These test results can be surprisingly discordant,[39] so composite scores that include any abnormal value are often used for diagnosis. A 1995 Mayo Clinic study of 53 RSD patients found increased RSO in 85%,[39] but a 1999 Mayo study of 102 CRPS-I subjects found RSO to be increased in only 22% of subjects, reduced in 7%, and normal in 71%.[40] This study also found normal QSART results in 38% of subjects, reduced sweating in 38%, and increased sweating in only 24%.[40] By comparison, a Mayo QSART study of 129 well-characterized SFPN patients found distal leg or foot hypohydrosis in only 49%, although 98% had at least one abnormality in QSART or TFT.[41] These details belie a common impression that hypohydrosis is the characteristic sweating abnormality of SFPN, whereas hyperhydrosis characterizes CRPS-I. Sweating abnormalities, usually subclinical, are common in both, but they vary, and the same patient can have areas of hypohydrosis and hyperhydrosis,[42] or different sweating abnormalities in different situations. A partially denervated gland may sweat insufficiently from direct neural stimulation, but sweat excessively in response to circulating catecholamines. Pathological study of sweat glands from amputated limbs of 2 CRPS-I patients revealed widespread sweat gland denervation and ectopic sprouting from nervi vasorum.[23]

Bone and Joint Abnormalities

Many CRPS patients complain of deep pain in their affected bones or joints, and imaging reveals objective correlates. Magnetic resonance imaging (MRI) can show bone marrow edema, and hyperperfusion can emerge on early phases of bone scintigraphy. Some x-rays show endosteal and intracortical excavations or spotty subperiosteal and trabecular bone demineralization or resorption.[43] These reflect excess osteoclast activity, visible as increased tracer uptake in the late phase of bone scans.[43] To reabsorb bone, osteoclasts reduce local pH to 4, low enough to activate nociceptors. This may explain why bisphosphonates and other inhibitors of bone resorption can reduce CRPS pain.[44] The osseous abnormalities of CRPS, which often localize to the sclerotome of the injured nerve, further implicate small-fiber axonopathy.

Bone is densely innervated, mostly by nociceptive small fibers, as demonstrated by the painfulness of fractures. Bone fracture is such a common cause of CRPS-I that it raises the question of whether bone fracture alone transects enough interosseous axons to trigger changes more typically associated with overt nerve injury. Small-fiber secretions are critical for bone formation and maintenance, and bone is profoundly influenced by small-fiber axonal degeneration.[45,46] Nerve injuries are the leading cause of malunion of apposed fractures,[47] and surgical denervation of bone was used experimentally for decades to model osteopenia, an effect apparently regulated by substance P secretion from nociceptive axons.[48] Neurofibromatosis I and leprosy are other neurological diseases in which focal small-fiber axonopathies disrupt bone innervation, producing maldevelopment in children and focal osteope-

nia, bone cysts, and pathological fractures in adults. SFPN commonly damage distal bone and contribute to osteomyelitis, Charcot joints, and digit resorption in advanced cases, even without overuse or injury.

Dystonia and Other Movement Disorders in CRPS

Most CRPS patients report difficulty moving their affected limb.[49] Some causes are nonspecific and secondary, for example, pain, disuse, and contracture. Others, such as muscle atrophy, may reflect concomitant motor axonopathy, and yet others reflect secondary central dysfunction. The most characteristic CRPS-associated movement disorder is tonic distal limb dystonia. Other involuntary movements are rare and usually accompany dystonia. CRPS/dystonia manifests as subtle (Fig 1A) or overt (Fig 3A) abnormal distal limb postures. It develops in under 10% of CRPS-I patients, usually in women.[50] It is distinct from the classical childhood-onset dystonias or other acquired dystonias that are usually proximal and centrally mediated. It differs from acquired phasic or activity-triggered limb dystonias and does not respond to sensory tricks. CRPS/dystonias are stereotyped, with flexion of ulnar-innervated digits most common in the hand and equinovarus deformity predominating in the foot (Fig 3A). Some postures persist during sleep, complicating distinction from secondary contracture. Although movement disorder specialists consider tonic limb dystonias (particularly of the lower limbs) psychogenic,[51] study of 103 tonic limb dystonia patients (20% of whom fulfilled CRPS criteria) found that 45% of subjects had no evidence of psychogenic causality.[52] Some physicians apply the term CRPS/dystonia to dystonias that appear up to several years after the causal injury, to generalized dystonias, or to dystonias that arise spontaneously without trauma, but this complicates interpretation. Patients with pure small-fiber polyneuropathies never develop dystonias, implying that neither small-fiber dysfunction nor its central consequences cause this. Data from animal models suggest that abnormal hind paw postures are more common after large than small axotomies, perhaps reflecting motor axonopathy.[53] If so, CRPS/dystonia may implicate concomitant large-fiber damage.

Spread of CRPS Symptoms

Patients with CRPS typically report distal unilateral limb pain outside the cutaneous distribution of a single nerve, although many patients identify an epicenter within a single nerve territory.[54] Small-fiber neurobiology affords multiple opportunities for regional spread of abnormalities. In addition to axonal spread along blood vessels (see above), peripheral mechanisms include electrical coupling of adjacent small-diameter axons,[55] and effects on nearby "bystander" axons within the same nerve, plexus, or root.[56] Opportunities for symptom spread continue in the central nervous system. Nociceptive axons send collaterals rostrally and caudally in Lissauer's tract before entering the gray matter, spreading nociceptor activity extrasegmentally. In rats, even partial distal nerve injuries can produce extrasomatotopic changes in inhibitory interneurons, perhaps even in the contralateral spinal cord.[57] Experimental nerve injury also activates spinal cord microglia and astrocytes in areas extending outside segmental or nerve territories.[57,58] Pain may be perceived in body

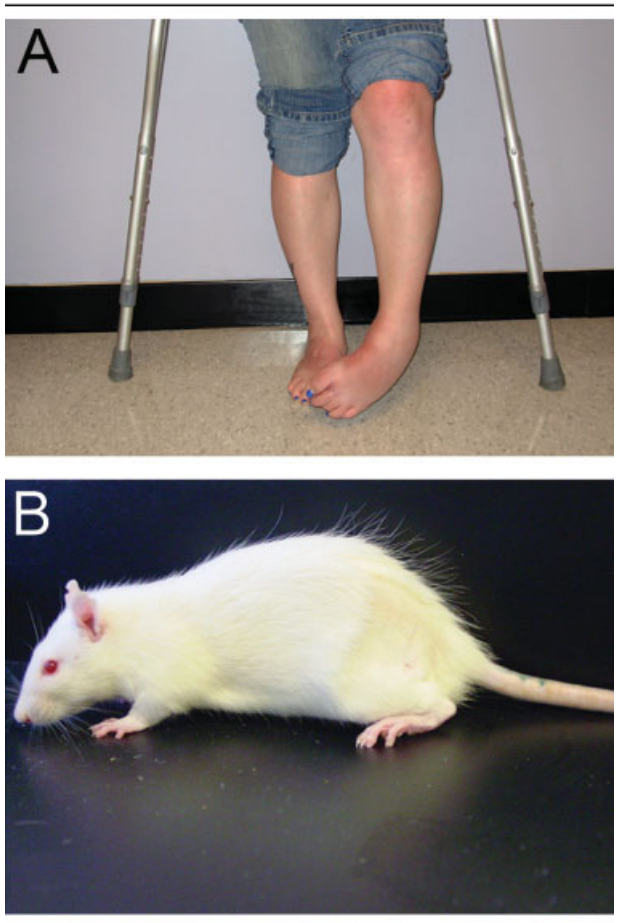

Fig 3. (A) A previously healthy 24-year-old photographed 6 weeks after onset of left lower leg pain, swelling, discoloration, and dystonia immediately after arthroscopic meniscectomy of her left knee. Examination revealed widespread sensory loss to pin in her left lower leg and foot that later regressed to the territory of the left infrapatellar branch of the saphenous nerve. Nerve conduction study revealed only absent left saphenous nerve conduction. Electromyography revealed continuous coactivation of tibialis anterior and posterior muscles. Ultrasound showed no venous thrombosis; magnetic resonance imaging showed intramuscular edema. (B) A rat with tonically abnormal left hind paw posture 10 days after 18-G needlestick penetration through its left tibial nerve.[54] [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

areas with representation adjacent to the cortical territory of an injured nerve.[59]

"Mirror" spread of pain and other symptoms to a matching location on the opposite uninjured limb is a little-understood feature of CRPS and other conditions.[54] Neurally mediated mirror-contralateral effects are common and inadequately recognized.[60] They implicate central pathways receiving converging input from peripheral axons that innervate symmetrical tissues and can activate efferent functions in those tissues. For instance, normal development and remodeling of bone is mirror-symmetric,[61] and bilaterally symmetric joint involvement is characteristic of rheumatoid arthritis.[62] Experimental manipulation of one kidney alone causes both kidneys to alter their urine output in parallel. Abolition of this "renorenal reflex" by capsaicin confirms mediation by nociceptive axons.[63] Some experimental unilateral nerve injuries produce bilateral small-fiber effects, including pain behaviors[53] and plasma extravasation.[64] Unilateral experimental tibia fracture produces bilateral mirror-symmetric periarticular bone loss, as in CRPS.[43]

Localizing Nerve Injuries in CRPS-I

Localizing nerve injuries in CRPS-I patients requires careful history and neurological examination. Even minor procedures, including phlebotomy and knee arthroscopy, can damage specific sensory nerve branches.[65] Because the axonopathy of chronic CRPS-I typically causes only some of the axons within a nerve to degenerate, sensation may be preserved. Currently there are no good objective diagnostic tests for localizing small-fiber injuries. Surface electrophysiological studies are insensitive, but useful when they confirm injuries that damage large fibers as well. Imaging is similarly specific but insensitive. Standard MRI protocols are not optimized to visualize nerves in the way made possible by magnetic resonance neurography, which is available at specialized centers.[66] Axial fat-saturated T2-weighted images can be useful from standard MRIs. Imaging can also help localize bone, joint, and tissue edema to a particular sclerotome or myotome. But overall, lesion localization in CRPS depends on the classical skills of the neurological examination.

Treatment of CRPS

Other symptoms such as dystonia may require treatment, but pain is the biggest problem. Evidence-based reviews show that the same medical and surgical treatments are effective in CRPS-I, CRPS-II, traumatic neuralgia, and SFPN; this is consistent with the idea that CRPS pain is neuropathic.[67,68] Rehabilitation and physical therapy are critical, not only for preventing secondary weakness, contractures, weight gain, and depression, but to minimize pathological cortical remodeling.[69] Most CRPS patients with chronic moderate or severe pain should be offered pain medications. The uncertainty surrounding the diagnosis of CRPS-I has precluded conduct of high-quality clinical trials, and there are no drugs approved by the US Food and Drug Administration for treatment of CRPS (by any name).

In this climate, we are guided by the results of randomized controlled trials for other neuralgias. Trials for postherpetic neuralgia (PHN) may be most relevant, because PHN and CRPS both involve focal one-time peripheral nerve system injuries in otherwise healthy patients. A superb recent meta-analysis of PHN trials enables comparison of medication safety as well as efficacy.[70] Additional medications have been found efficacious for acute CRPS, including calcitonin, bisphosphonates, and vitamin C, but these are untested in chronic CRPS and other neuralgias.[71] Early treatment with corticosteroids and nonsteroidal anti-inflammatory drugs may warrant controlled study. In the first controlled trial of sympathetic blockade in CRPS-I, early relief was similar after saline and local anesthetic sympathetic ganglion blockade, but it lasted significantly longer after local anesthetics.[72] Later work found sympatholytic treatment more helpful in acute than chronic CRPS-I, suggesting minimal sympathetic contribution to pain in chronic patients.[73] Accordingly, meta-analysis does not support use of local anesthetic sympathetic blockade,[4] nor of oral sympatholytics such as clonidine in persistent CRPS.[67]

If rehabilitation and medications are ineffective, surgical options should be considered. As with other mononeuropathies, one should consider the possibility of nerve impingement or entrapment, for instance by scar, blood vessel, or bone callus. Rare patients, particularly those with a spontaneous nontraumatic onset, may have a tumor, vascular malformation, or infection in or near their nerve. Similar to trigeminal neuralgia, surgical decompression may provide the most effective pain relief.[74] However, such lesions must be clearly localized and characterized to make nerve exploration appropriate. Ablative (nerve cutting or neurodestructive) procedures are not indicated except for the rare cases in which a well-defined mechanosensitive neuroma requires relocation. Spinal cord stimulators have documented efficacy, and CRPS-I is a common indication for their use.[75,76] A percutaneous stimulator trial can provide valuable evidence of efficacy and tolerability to aid in selecting candidates for implantation. Implanted nerve stimulators have better long-term success rates (63 to 80%) than most other options.[77] Again, these can only be considered for patients with anatomically and electrophysiologically localized nerve injuries. In the most severe cases, ulcers or infection may prompt consideration of limb amputation. However, because stump pain persisted in 28 of 34 amputations performed for CRPS, amputation is ineffective and not indicated for pain.[78] CRPS patients that do not im-

prove with time and treatment should be periodically re-evaluated for ongoing treatable neuropathic injury, such as from diabetes mellitus or thyroid dysregulation.

Summary

Today few neurologists treat CRPS patients, but evidence that CRPS-I, like CRPS-II, is a neurological disorder is compelling. Much pathophysiology remains to be clarified, but the hypothesis that persistent dysfunction of small-diameter primary afferent nociceptor axons distal to trauma is causal is consistent with many CRPS clinical features and experimental models. Some signs and symptoms may be due to loss of function, whereas others appear to reflect denervation hypersensitivity or hyperactivity of nearby intact but malfunctioning small-fiber afferents. Pathological evidence of nerve damage in patients classified as CRPS-I obviates distinction between CRPS-I and CRPS-II and revives Mitchell's formulation of a complex form of post-traumatic neuralgia. Perhaps his terms "minor" and "major" nerve injury should be reconsidered.

If pain in CRPS-I arises "as a direct consequence of a lesion or disease affecting the somatosensory system," it meets the criteria for a peripheral neuropathic pain syndrome,[79] and the consensus diagnostic criteria for CRPS should be modified to reflect this and to conform to neurological standards. Revising neurological diagnostic criteria is common, as pathology, pathophysiology, and genetics are defined and new tests become available. The qualifiers "definite," "probable," or "possible" have clinical and research utility and conform to current recommendations for diagnosing neuropathic pain syndromes.[79] The CRPS and post-traumatic–neuralgia diagnoses, currently separate, need to be related. Many patients fall between the extremes, with mild or occasional CRPS signs or symptoms accompanying post-traumatic neuralgia. Given that patients with either diagnosis are treated identically, and that CRPS-specific signs fluctuate and often resolve leaving only neuralgia, these diagnoses should no longer be viewed as entirely separate. One possibility, modeled on the parkinsonian syndromes, would be to classify CRPS as a "post-traumatic neuralgia plus" syndrome until better criteria are established. The rare patients with internal traumas (eg, infarction) need to be accommodated in any future scheme, yet the link to focal injury or illness preserved. Patients with regional or widespread chronic pain, no evidence of axonopathy, and no history of focal injury or disorder should pursue other diagnoses. Better classification should also help establish and validate animal models for screening potential therapies.

Epidemiological study hints that CRPS is a complex disorder that is environmentally triggered in susceptible individuals. Many types of pain are genetically influenced, with median heritability for pain traits averaging 50% in animal studies.[80,81] Similar heritability, including for post-traumatic neuralgia, is present in humans.[82] The age and sex distribution and inflammatory features of CRPS raise the possibility of autoimmune involvement, especially in the early stages, an idea strengthened by comorbidity with asthma.[9] Recognition of the ties between RSD and causalgia should return neurologists to a central role in caring for these patients. Translation of strategies from other neurological disorders offers the possibility of advancing the standards of care beyond pain palliation toward disease modification and cure.

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