Clinical Note

Treatment of Tremors in Complex Regional Pain Syndrome

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Abstract

A 14-year-old girl presented with Complex Regional Pain Syndrome, Type I (CRPS-1) of the left ankle after a remote history of sprain. Allodynia, pain, temperature and color changes, and swelling were successfully treated with physical therapy, transcutaneous electrical nerve stimulation (TENS), gabapentin, amitriptyline, and tramadol. Five weeks later, she presented with a continuous, involuntary, intermittent coarse tremor of the left foot causing increased pain. The electromyogram showed rhythmic discharges of 3 Hz frequency lasting 20–80 milliseconds in the left tibialis, peroneus and gastrocnemius, suggestive of either basal ganglia or spinal origin. Tremor and pain were controlled with epidural bupivacaine, but the tremor reappeared after discontinuing epidural blockade. Carbidopa/levodopa 25/100 (Sinemet®) was started and the tremor disappeared after two days. With continued physical therapy, pain and swelling resolved within two months and carbidopa/ levodopa was discontinued after five weeks with no recurrence of the tremor. Our success in the treatment of CRPS-associated tremor in this young girl with carbidopa/levodopa suggests that this patient may have had underlying movement disorder which was unmasked by the peripheral injury. J Pain Symptom Manage 2003;25:386–390.

Key Words

Reflex sympathetic dystrophy, parkinsonism, movement disorder, carbidopa-levodopa

Introduction

Complex Regional Pain Syndrome (CRPS) is a clinical disorder, which is usually characterized by severe burning pain, swelling, and vasomotor, sudomotor, dystrophic and trophic changes in the affected body parts.[1] The incidence of CRPS ranges from 1–2% after various fractures and 2–5% after peripheral nerve injuries.[2]

CRPS may be accompanied by movement disorders, including dystonia or tremor.[3–7] Tremors at various frequencies have been documented in many CRPS patients,[3,5] and various medical and surgical treatment options have been used, with limited success, to treat CRPS-associated tremors.

We present a case of severe tremors in a 14-year-old girl with post-traumatic CRPS Type 1,

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which were successfully controlled with medical management.

Case Report

A 14-year-old athletic girl, 80 kg and 180 cm, was evaluated for complaints of pain and discoloration of her left ankle after multiple injuries to that ankle. The initial trauma, which was a Grade I ankle sprain, occurred while playing basketball twelve months prior to the presentation. After brief immobilization, she returned to regular activities, but reinjured the ankle six times. She complained of intense pain in her left ankle, which prevented her from bearing weight. The pain was 9/10 on a numeric rating scale and was aggravated by light touch and improved by hanging the left ankle off the side of the bed. Acetaminophen with codeine provided no relief. Her foot turned purple occasionally.

On examination, the left ankle appeared swollen and purplish when compared to the other foot. The temperature of the affected foot was 85.2° F compared to 93.7° in the right foot. Range of motion was decreased in her left ankle (dorsiflexion 40°, plantar flexion 60°, eversion 30°, and inversion 30°). Muscle spasm and intense allodynia were present.

Radiographs showed osteochondritis of the talus. The magnetic resonance imaging of left ankle showed Grade-I osteochondral lesion of posteromedial talar dome and a small amount of fluid along posterior tibialis tendon. The radionucleide three-phased bone scan showed diminished radionucleide delivery to left ankle.

Treatment included transcutaneous electric nerve stimulation, gabapentin (900 mg three times a day), amitriptyline (25 mg at bedtime), and as needed tramadol (50 mg). Physical therapy was started three times per week. In three weeks, there was improvement in symptoms.

After five weeks, she presented with a two-day history of continuous involuntary twitching of her left foot, with increased pain and discoloration of the left ankle. There was a twenty-degree difference in temperature between the two feet, left being warmer than the right. Neurological examination was notable for an intermittent coarse rest tremor of the left foot, primarily at the ankle, with a frequency of three to four Hz. Muscle tone, bulk, and strength of all muscle groups, sensation, deep tendon reflexes and plantar responses in the lower extremities were normal and symmetric. The magnetic resonance image of the spine was normal.

She was admitted to the hospital and treated with an initial dose of 20 ml of 0.25% bupivacaine via a lumbar epidural catheter. This resulted in resolution of the tremor. She then received an infusion of 0.125% bupivacaine at 10 ml/hr, but every time the epidural infusion was decreased or discontinued, the tremor reappeared. The epidural infusion was held for twelve hours for an electromyogram that showed rhythmic discharges of three Hz frequency lasting twenty to eighty milliseconds in the left tibialis (Fig. 1), peroneus and gastrocnemius muscles, suggestive of either basal ganglia or spinal origin. The nerve conduction studies showed no evidence of mononeuropathy, polyneuropathy or radiculopathy.

Carbidopa/levodopa 25/100 (Sinemet®) was started twice daily. Eighteen hours after carbidopa/levodopa was started, a decrease in tremor was noted. The tremor totally disappeared in three days. With continued physical therapy, the CRPS symptoms resolved within two months. The carbidopa/levodopa was discontinued five weeks after discharge from the hospital, with no recurrence of the tremor.

Discussion

In 1888, Gowers suggested that movement disorders could be produced not only by central, but also by peripheral trauma.[8] Recent observations have confirmed this.[9,10] In 1988, Jankovic and colleagues described five patients with the onset of tremors within one day to nine months after peripheral injury.[3] They noted that 65% (15 out of 23 patients) had common 'predisposing' factors like family history of essential tremor or dystonia, perinatal injury, or a prior exposure to dopamine receptor blocking drugs that could have increased the risk of tremor.[3] In 1995, Cardoso et al. studied patients in whom the onset of tremor, parkinsonism or both was anatomically or temporally related to local injury.[11] They noted the onset of tremor within two months after the injury in 21 out of 28 patients.[11]

In 1991, Deuschl and colleagues studied postural hand tremor in twenty-one patients suffering from unilateral reflex sympathetic dystrophy (CRPS Type 1) in the upper extremity.

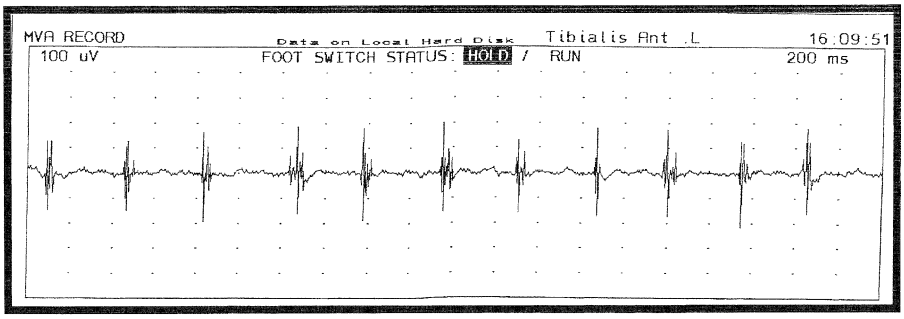

Fig. 1. EMG showing rhythmic discharges of 3 Hz frequency lasting 20–80 milliseconds in the left tibialis.

They noted, on the affected side, an enhanced tremor amplitude, with a mean tremor frequency of 7.2 Hz in 57% of patients.[12] This tremor decreased with loading and the investigators concluded that the tremor in reflex sympathetic dystrophy should be regarded as a form of enhanced physiological tremor.

It has been proposed that peripheral trauma alters the sensory input and induces cortical and subcortical reorganization generating a movement disorder in patients with CRPS.[11] This hypothesis might explain why the peripherally-induced movement disorders have a tendency to spread beyond the original site of injury. The neuronal networks in the thalamic ventralis lateralis nucleus, which receive input from the basal ganglia, may be involved in the generation of the tremor.[11,13] Cohen et al. have shown that the transcranial magnetic stimulation in the patients with unilateral limb amputations evoked larger motor evoked potentials, recruited larger percentage of motoneuron pool and elicited motor-evoked potentials at lower intensities of stimulation in muscles ipsilateral to the stump than in contralateral muscles.[14]

The mechanism by which the altered peripheral input can produce central effects is poorly understood. Some of these changes seem to be mediated by retrograde axonal transport of trophic factors such as ciliary neurotrophic factor.[15] Neural plasticity in response to peripheral trauma also may be mediated also by immediate early response genes (e.g., c-jun and c-fos), resulting in secondary chemical changes. The expression of these genes seem to be markedly increased in the spinal cord after peripheral nerve lesion (axotomy).[8,16]

The tremor, difficulty in the initiation of movement, and increase in reflexes and muscle tone may also be directly related to the change in the activity of the sympathetic nervous system in CRPS. It has been suggested that the interaction between substance P and sympathetic nervous system directly initiates the intense and prolonged depolarization of anterior horn cells that may underlie dystonia of this condition.[17,18] A similar hypothesis can be extended to explain other movement disorders, including tremors, associated with CRPS. Deuschl and colleagues noted that their patients with enlarged tremor amplitudes displayed a greater degree of electromyographic synchronization in the affected arm, and a higher coherence, compared with the healthy side or normal subjects.[12] They suggested that such synchronized discharges of the motor neurons must be due to common central or peripheral inputs on the motor neuron pool.[12]

Enhanced proprioceptive reflexes have been proposed as a major peripheral input causing synchronization and thereby, tremor.[19] Since gain of reflexes can be enhanced by sympathetic sensitization of muscle spindles, most likely by their influence on beta 2-receptors,[20] the enhanced tremor in reflex sympathetic dystrophy could be explained by this mechanism and their reduction following sympathetic blockade.[12] Mechanisms acting at the spinal level have also been proposed to account for the synchronization.[14] For example, the gain of the flexion reflex is enhanced by the stimulation of the C-fiber afferents from the muscle, which is probably mediated by substance P released from the nociceptive primary afferents.[21]

An alternative hypothesis is that trauma may cause a movement disorder by indirectly triggering or accelerating the progression of preexisting subclinical movement disorder.[8,11] Motor symptoms may be transiently exacerbated in patients with Parkinson's disease after motor

vehicle accident or stress.[22] This is also supported by animal models. For example, rats previously treated with neurotoxin 6-hydroxy dopamine to produce subclinical damage to substantia nigra developed Parkinsonism signs after receiving a series of tail shocks.[23]

Treatment of post-traumatic action tremors is challenging.[8,24–27] Botulinum toxin injections into muscles involved in tremor may provide temporary relief up to four months.[28] Ventrolateral thalamotomy may sometimes produce improvement in tremor[29] but tremor may recur in 20% of the patients. Also, there is a considerable risk of of contralateral hemiparesis, hemianesthesia, ataxia, speech disturbance, and other potential complications.[8] Tremor can also be relieved by high frequency thalamic stimulation,[30] particularly in elderly patients and when bilateral effects are desirable.[31] These procedures are not free of risks. The treatment for post-traumatic Parkinsonism is essentially the same as idiopathic Parkinsonism,[32] but the response to dopamine and anticholinergic drugs is less predictable.[9]

The onset of tremor in our patient, while already receiving amitriptyline and gabapentin for the treatment of CRPS, suggested that these tremors were not peripheral in origin. The typical EMG pattern of rhythmic discharges of 3 Hz frequency lasting 20–80 ms suggested spinal or basal ganglia origin. The resolution of tremor with the epidural blockade and its reappearance on discontinuation of the blockade pointed to a possible spinal or a more central origin of the tremor. After the complete resolution of the epidural blockade, carbidopa/levodopa was initiated, with gradual improvement in the tremor and its complete resolution in three days. Our success in the treatment of CRPS associated tremor with carbidopa/levodopa, which essentially increases dopamine levels in the central nervous system, suggests that this patient may have had underlying 'subclinical' Parkinsonism which was unmasked by the peripheral injury.

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