Pain Physician 2007; 10:573-578 • ISSN 1533-3159

Case Report

Treatment of CRPS with ECT

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Disclaimer: No external funding was provided for this study.
Conflict of interest: None

Manuscript received: 04/16/2007
Revisions accepted: 06/04/2007
Accepted for Publication 06/20/07

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Background: Electroconvulsive therapy (ECT) is a well-established treatment method for medically refractory depression. ECT has also been used in the treatment of pain for over 50 years. The mechanism of action of ECT is still unknown, although several observations have been made regarding the effect of ECT on pain processes. It has been reported that several patients with medically refractory depression and Complex Regional Pain Syndrome who were treated with ECT for their depression were also cured of their CRPS symptoms.

Objective: We report a case of CRPS in a patient who also suffered from medically refractory depression. She was treated with ECT for her depression and subsequently was relieved of all her CRPS symptoms.

Case Report: A 42 year-old female patient underwent a series of 12 standard bitemporal electroconvulsive therapy treatments for medically refractory depression. Physical examination and Quantitative Sensory Testing was done before and after the patient's treatment with ECT. This standard treatment procedure for refractory depression completely resolved the patient's depressive symptoms. In addition, the patient's CRPS symptoms were also reversed. Physical examination as well as Quantitative Sensory Testing done before and after the ECT treatment correlated with her CRPS symptom improvement.

Conclusion: ECT was effective in the treatment of severe refractory CRPS in this patient.

Key words: limpedance, posture change, spinal cord stimulation

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Pain perception is a matrix that combines both affective and discriminative components (1). However, the division of a pain matrix into distinct sensory-discriminative and affective-motivational components is evolving in complexity due to recent brain imaging advances (2-3). Treede et al (4) propose a division of central nociceptive pathways into 2 major systems. The lateral system, primarily involved in the discriminative component of pain, is composed of lamina I and V of the dorsal horn that projects to the ventrobasilar complex of the thalamus and SI and SII of the cortex (5-8). This discriminative component inscribes the intensity, localization, and quality of pain. The affective component involves the emotional reaction, stimulus-related selective attention, and the motor drive to avoid further pain. The anatomy of this medial system includes Laminas I, V, and the deeper layers of the dorsal horn, VMpo, MDvc, parafasicular, and intralaminar thalamic nuclei as well as the insula and anterior cingulate cortex. The CL component of

the intralaminar thalamus is also linked to SI and SII of the lateral system (5-8). The insular cortex also projects to the amygdale (9), another component of the limbic system, which modulates emotion. In addition to the medial cortex, the prefrontal cortex is important for affect, emotion, and memory (10).

The pain matrix is modulated by the Diffuse Noxious Inhibitory Controls (DNIC) system, which limits the intensity and spread of pain (11-12). Stimulation of the rostroventromedial medulla (RVM) nuclei of this system can inhibit and/or facilitate nociceptive and non-nociceptive input. This is a major relay for the DNIC, which has input from the cortex and the periaqueductal gray (PAG) (13-18). In this nucleus, ON cells, which fire after a pain stimulus, and OFF cells, which fire after pain is blocked, are thought to be important in the maintenance of chronic pain (19-22).

Electroconvulsive therapy (ECT) has been used in the treatment of pain for over 50 years. In 1946, Pisetsky (23) successfully treated a patient with phantom limb pain and depression with ECT and more recently, Rasmussen and Rummans (24) presented 2 patients with phantom limb pain that improved with ECT treatment. Complex Regional Pain Syndrome (CRPS) and comorbid depression have also been treated successfully with ECT (25-26), which has analgesic properties that are independent of the improvement of depression (27).

In this report, we present a patient who meets all the IASP diagnostic and research criteria for CRPS in all her extremities who had failed conventional treatment modalities for 5 years (28). ECT administered for refractory depression induced immediate improvement in the affective component of her pain and a gradual complete reversal of CRPS signs and symptoms. Quantitative sensory testing correlated with her clinical recovery.

Case Report

A 42-year-old female patient was involved in a motor vehicle accident in 1997 in which she suffered a flexion-extension injury of her neck. She had immediate pain in the C2 and C3 distribution of her neck as well as in the C4 distribution across the trapezius ridge. She continued working, but her pain gradually spread to all distributions of both the cervical and brachial plexus on the left side. She was treated with nonsteroidal anti-inflammatory agents, anticonvulsants, opioids and intense physical therapy with minimal benefit. Her pain was associated with weakness and difficulty initiating voluntary movement of the left upper extremity. She suffered with severe generalized mechanical dynamic and static allodynia, hyperalgesia, and cold allodynia, which had spread from her left arm to all extremities. She also noted the spread of a pinprick and cold stimulus to a portion of a dermatome on the entire ipsilateral side of the body after an extremity was stimulated. She noted hyperhidrosis, swelling, and increased hair growth of the affected left arm and hand.

The patient was involved in a second automobile accident in 2000 in which she fractured her right wrist that required open reduction and internal fixation. Prior to this accident, the patient led a very active lifestyle and was working as a judge. Her generalized pain, autonomic dysfunction, and difficulty with movement progressed and she eventually became too ill to work.

By 2001, four years after the initial injury, she had complex regional pain syndrome (all components of 2005 IASP criteria) in all her extremities, back, and face. On physical examination in 2001, the patient presented with mechanical dynamic and static allodynia of 8/10 pain (Likert Numeric Rating Scale/NRS, 0 being no pain and 10 being the worst pain imaginable) and 8/10 NRS pain to deep compression of the muscles in her left upper extremity. Small joint pain was 8/10 on a NRS in all extremities and was associated with cold allodynia. She exhibited hyperalgesia to a pinprick of all extremities, the face, and back which was associated with spread of the stimulus of >6 cm and lasted for >30 seconds. The patient was weak (4-/5) in both proximal and distal muscles of all extremities and had difficulty initiating movement. She had cold hyperhidrotic cyanotic extremities that demonstrated dilated veins and livedo reticularis.

The patient had the following studies: CT of the head, multiple CTs of the cervical and lumbar spine, CT of the abdomen and pelvis, abdominal ultrasound, multiple MRIs of the cervical and lumbar spine, an MRI of the brain with gadolinium, and multiple EMGs, which were negative. An EEG done to evaluate an episode of shaking and dysarthric speech showed left anterior midtemporal slowing and excessive beta activity. A DEXA scan demonstrated osteopenia of the lumbar spine and both hips. ENG showed nonspecific central vestibular pathology. General bloodwork, including CBC, liver profile, sed rate, single and double stranded DNA, SS-A and SS-B antibodies, rheumatoid panel and Lyme's antibody titers was negative. Cardiac

evaluation, including a dobutamine stress echo test, was negative. Endoscopy, colonoscopy, ERCP, 24-hour pH study and gastric emptying study were undertaken to evaluate constipation and demonstrated persistent gastroparesis. The patient had undergone a fundoplication procedure in 2001. Her eating schedule was altered and she was treated with Zelnorm and Miralax for irritable bowel syndrome, which was partially successful.

The patient was treated with the following medications for her pain and depression: Topamax, Celebrex, Neurontin, Oxycontin, Oxy IR, Flexeril, Lamictal, Reglan, Vioxx, Klonopin, Ambien, Effexor, Xanax, Paxil, Wellbutrin, Lithium, Prozac, and Seroquel. A series of spinal epidural steroids for back pain and cervical botox injections for neck pain were administered. The patient underwent a 4-day course of inpatient IV lidocaine, which was gradually titrated to the cardiac arrhythmic dose of 5 mg/L. All of the above treatments did not relieve her pain. It is worthy to note that the patient did not receive a stellate ganglion block. However, although widely used, this technique has little proven value in diagnosing or treating CRPS. Quantitative Sensory Testing (QST) of her upper extremities done in 2002 showed severe cold allodynia and heat hyperalgesia. Her Autonomic Sensory Testing (AST) showed normal capillary flow and normal sympathetically mediated vasoconstrictor reflexes in the hands.

The patient was examined in 2003, one month after having received a series of 12 treatments with bitemporal electroconvulsive therapy under standard anesthesia for her severe, medically refractory depression. On physical examination, the patient related 1/10 NRS mechanical dynamic and static allodynia and 3/10 NRS mechanical allodynia with deep compression of the muscles. The patient stated that she had evoked pain with arm movement 3/10 on a NRS, but had no deep joint pain. She exhibited 5-/5 strength in her extremities, had no hyperalgesia or spread to pinprick or a cold stimulus, and had no dysautonomic features (normal temperature, no hyperhidrosis, and no livedo reticularis). Her major complaint on this visit was short- term memory loss. The patient described having had no spontaneous or evoked pain immediately after the ECT. Repeat QST in 2003 after the ECT showed cold allodynia and heat hyperalgesia in the hands. AST was normal.

The patient was seen again in 2007. On physical examination, she had no criterion factors for CRPS. She had 0/10 NRS mechanical dynamic and static allodynia, no hyperalgesia to pinprick or a cold stimulus and exhibited none of the inflammatory aspects of CRPS. There was no autonomic dysregulation; she had normal temperatures in her extremities, was not hyperhidrotic, and demonstrated no erythema. She had minimal difficulty initiating movements and minimal 5-/5 weakness bilaterally in her dorsal and volar interosseii and abductor pollicis brevis. The patient was no longer depressed. QST done in 2006 was normal in the hands. AST showed a baseline capillary flow that was slightly high but otherwise was normal in the hands.

Table I demonstrates cold and warm detection thresholds and cold and heat pain thresholds during Quantitative Sensory Testing on 3 separate occasions during the patient's illness. The first set of data, acquired in 2001 before her ECT treatment, show that her cold detection thresholds were within the normal 1-2° C change in temperature. The patient's warm detection thresholds were minimally high with a +4° C change. In 2003, several months after her ECT treatment, her cold and warm detection thresholds remained normal, although the warm detection thresholds slightly improved. By 2006, her detection thresholds were completely normal.

The patient's cold pain threshold was highly abnormal in 2001. The <10° C change in temperature was well below the normal >22° C change that most people experience. The +5° C change in heat pain threshold was also well below the normal >10° C range. Her second set of data from 2003 taken after the ECT treatment showed minimal improvement in her cold and heat pain thresholds. However, by 2006, both pain thresholds were well within the normal range.

After 4 years of intractable pain and failed treatment attempts, following ECT, the patient made a full physical and social recovery. She no longer requires any pain or depression medication. She now leads a normal life and has returned to working full-time as an attorney.

Discussion

In 2005, the IASP proposed changes to its diagnostic criteria for Complex Regional Pain Syndrome. Current clinical evidence for CRPS in a patient should include:

1) continuing pain disproportionate to any inciting event,
2) At least one symptom in 3 of 4 categories- sensory (hyperesthesia and/or allodynia), vasomotor (temperature asymmetry and/or skin color changes

Table I. Quantitative Sensory Testing. Threshold Changes in degrees C from Baseline of 32°C

Test site	Date of Exam	Cold Detection Threshold	Actual Temp. (°C)	Warm Detection Threshold	Actual Temp. (°C)	Cold Pain Threshold	Actual Temp. (°C)	Heat Pain Threshold	Actual Temp. (oC)
Lt Thenar	2001	-1.2	30.8	+3.7	35.7	-11.1	20.9	+4.3	36.3
	2003	-1.0	31.0	+1.8	33.8	-11.0	21.0	+4.9	36.9
	2006	-0.9	31.1	+1.8	33.8	-22.4	9.6	+13.4	45.4
Lt Hypothenar	2001	-1.3	30.7	+3.5	35.5	-6.2	25.8	+5.9	37.9
	2003	-1.1	30.9	+2.5	34.5	-6.5	25.5	+5.2	37.2
	2006	-1.4	30.6	+2.5	34.5	-21.2	10.8	+9.9	41.9
Rt Thenar	2001	-2.2	29.8	+4.3	36.3	-8.9	23.1	+6.0	38
	2003	-1.5	30.5	+2.1	34.1	-4.3	27.7	+2.7	34.7
	2006	-1.5	30.5	+3.4	35.4	-25.2	6.8	+13.6	45.6
Rt Hypothenar	2001	-1.3	30.7	+4.2	36.2	-5.2	26.8	+5.2	37.2
	2003	-1.3	30.7	+3.1	35.1	-9.2	22.8	+4.8	36.8
	2006	-1.2	30.8	+2.5	34.5	-24.5	7.5	+14.3	46.3

and/or skin color asymmetry), sudomotor/edema (edema and/or sweating changes and/or sweating asymmetry) and motor/trophic (decreased range of motion and/or motor dysfunction such as weakness, tremor, dystonia and/or trophic changes in hair, nails, skin),

3) must display at least one sign at time of evaluation in 2 or more of the following categories (as described above): sensory, vasomotor, sudomotor/edema, motor/trophic and
4) There is no other diagnosis that better explains the signs and symptoms (28).

As noted earlier, our patient satisfied all the diagnostic criteria for CRPS, but after her treatment with ECT, she currently remains asymptomatic.

Just as revisions to the diagnostic criteria for CRPS are occurring to improve therapeutic outcomes, concepts of pain perception are evolving as well. However, at present, pain perception is often compartmentalized into an affective component measured by a patient's response to validated neuropsychological tests, such as the McGill pain questionnaire, while the discriminative component may be measured by a Likert numeric rating scale of hyperalgesia, allodynia and spontaneous pain as well as QST and AST (29,30). Most patients with CRPS will have both components affected to some degree, which was the case with this proband prior to ECT. She had both a high number on her Likert scale for spontaneous pain, mechanical dynamic and static allodynia and hyperalgesia as well as an abnormal QST. After her treatment with ECT, our patient's affective component was immediately improved; however, her QST showed no improvement of her cold allodynia and heat hyperalgesia in her hands. Over the next few years, her Likert numbers still remained low for discriminative CRPS factors, but her QST pain thresholds improved to the normal range. It is important to note that her temperature detection thresholds were within the normal range both before and after her ECT treatment, which rules out small fiber neuropathy as a cause of her decreased pain sensation after ECT. As with any treatment, a placebo effect must be taken into consideration. However, given the often naturally progressive course of chronic CRPS, it is highly unlikely that the placebo effect was causative in the recovery of this patient (31).

The mechanism of action of ECT is still unknown, although several observations have been made regarding the effect of ECT on pain processes. King and Nuss (25) and McDaniel (26) both postulated that massive quantities of neurotransmitters are released during ECT that induce changes in CNS post-synaptic receptors throughout the nervous system. The neurotransmitters affected include serotonin, dopamine, norepinephrine

(27), substance P, neuropeptide Y, somatostatin, TSH, and CRH (26). Other neuromodulators, including enkephalin, immune-reactive dynorphin, and beta-endorphins, have also been implicated in the effects of ECT on pain (26,32,33). King and Nuss (25) and Abdi et al (32) have postulated that the electrical current transmission through the thalamus and hypothalamus which occurs during bilateral ECT alters pathways for pain sensation and perception. Wasan et al (27) suggested that disrupted affective processing of pain in CRPS leads to enhanced receptive fields, intensified pain perception and increased pain sensory input. ECT may interrupt this inappropriate processing of pain by disrupting the memory for pain. In addition, Wasan et al (27) have postulated that ECT may stimulate the lateral thalamic structures involved in descending pain inhibition. Fukui et al (33) have studied the effect of ECT on regional cerebral blood flow. They found that patients with chronic neuropathic pain have decreased blood flow to the thalamus. After treatment with ECT, one of their patients had increased regional cerebral blood flow to the thalamus and a dramatic reduction in pain.

Functional changes in the brains of CRPS patients have been described with functional MRI (fMRI). Maihofner et al (34) have shown that activation of the contralateral SI, bilateral SII, and insular cortex all contribute to the encoding of non-painful stimuli. Deactivation of the ipsilateral SI and the primary visual cortex was found in CRPS patients. However, CRPS patients with allodynia have widespread cerebral fMRI activation that includes the ipsilateral and contralateral SI, the primary motor cortex, the contralateral parietal association cortex, bilateral SII, insula, and frontal cortex as well as the anterior and posterior cingulate cortex. Deactivations were detected in the ipsilateral superior frontal cortices, contralateral inferior frontal cortices, visual cortices, and the contralateral temporal and posterior insular (vestibular) cortices. In addition, Maihofner et al (35) have also used magnetic source imaging to show that the brain reorganizes with pain in CRPS, particularly in the primary somatosensory cortex, and recovers from cortical reorganization when CRPS pain is reduced. Therefore, it is possible that ECT may trigger the recovery process of the brain that has been reorganized by CRPS pain to its original form. Because our patient's symptoms did not immediately completely improve, it can be postulated that ECT may begin the process that restores the brain to its normal functional somatotopic processing capacity, but it may require a prolonged period of time to completely recover.

Conclusion

Further controlled randomized studies will be necessary to elucidate possible mechanisms involved in ECT for the benefit of severe refractory CRPS.

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