



Successful Treatment of Long Standing Complex Regional Pain Syndrome with Hyperbaric Oxygen Therapy

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Abstract

Complex regional pain syndrome (CRPS) is a devastating posttraumatic neuroinflammatory condition with both autoinflammatory and autoimmune features, characterized by unrelenting severe pain and disability, with the majority of affected patients being unable to function socially or vocationally. Remission is more likely in children than adults, and if treatment is started early. Once established, there are no universally effective treatments, and these are desperately needed. A single limb is often involved, but there can be multi-limb spread, and systemic autonomic manifestations. We describe a case of long-standing CRPS with multi-limb spread and systemic autonomic features, controlled only with very high dose oral corticosteroids, which led to several complications. Multiple other treatment modalities failed or were insufficient to control the CRPS and allow tapering of the corticosteroids, but the patient had a dramatic response to hyperbaric oxygen therapy (HBOT), allowing a reduction in prednisone dose to just over the physiologic range. When symptoms started to increase several months later, a second course of HBOT treatments allowed reduction in prednisone dose into the physiologic range while still controlling CRPS symptoms. This case is unique in that it shows that HBOT can be effective in long-standing CRPS, both initially, and for subsequent flares, and adds to the evidence supporting HBOT as a potential treatment for this condition.

Keywords Complex regional pain syndrome · Hyperbaric oxygen

To the Editors,

Complex regional pain syndrome (CRPS) is a post-traumatic neuroinflammatory condition that has both autoinflammatory and autoimmune features (Clark et al. 2018). Clinical features include chronic pain, tissue swelling, skin changes, sweating, and motor dysfunction (Harden et al. 2007), leading to significant disability. Less than 20% of patients are able to return to full time vocation (Agarwal et al. 2005). There is impaired microcirculation (Schurmann 2001) that contributes to reduced tissue perfusion, and atrophy of skin, muscle and bone. Skin breakdown and recurrent infection can lead to gangrene and amputation. Chronic intractable pain can lead to suicidal ideation in almost half of patients (Agarwal et al. 2005), with 15% acting on these impulses,

giving CRPS the name “the suicide disease”. At present, there is no universally effective treatment for this devastating and heterogeneous disorder, though some modalities may be partially effective in subsets of patients Fig. 1.

Hyperbaric oxygen therapy (HBOT) is an intermittent inhalation of 100% oxygen in a hyperbaric chamber at a pressure higher than 1 absolute atmosphere (ATA). It is a safe and reliable treatment with very few contraindications and side effects. HBOT has been shown to have antinociceptive and analgesic effects in animal models of nociception, as well as modulatory effects in animal models of inflammatory and neuropathic pain (Sutherland et al. 2015; Li et al. 2011). Furthermore, it decreases inflammation and hyperalgesia in a rodent models and human studies (Rasmussen et al. 2015; Ding et al. 2018). The positive effect of HBOT on allodynia and hyperalgesia is postulated to be through inhibition of endoneuronal TNF- α production (Li et al. 2011). Hyperbaric oxygen causes reduction of IL-1 β and IL-18 and suppresses mRNA and protein expression of NLRP3 inflammasome components, especially reducing NLRP3 expression in microglia in animal models of traumatic brain and spinal cord injury (Liang et al. 2015). There is preliminary evidence that

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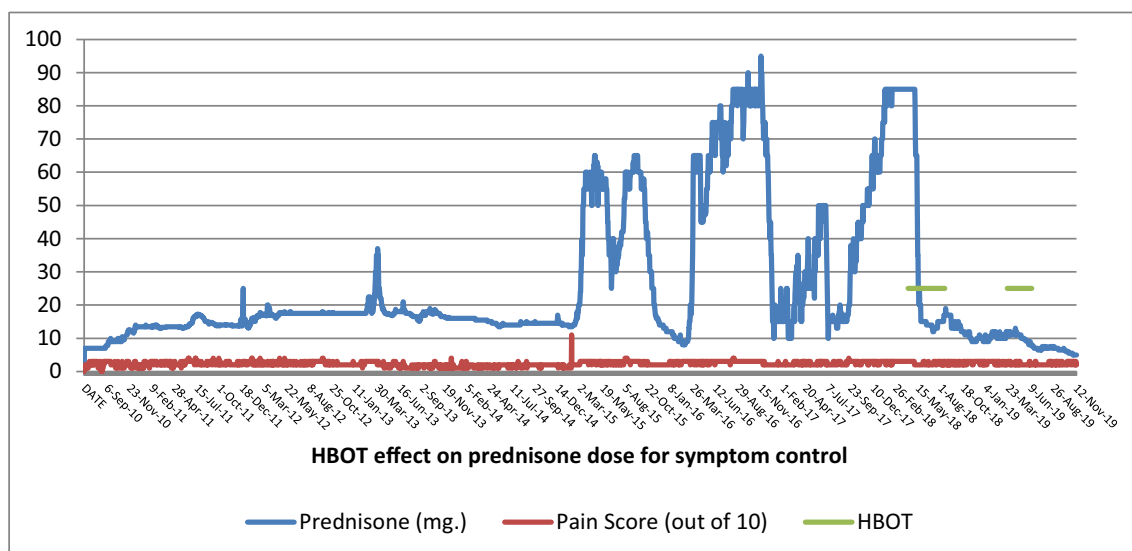


Fig. 1 HBOT effect on prednisone dose for symptom control

HBOT is effective in CRPS (Kiralp et al. 2004; Sutherland et al. 2015; Katznelson et al. 2016), particularly if used early. We wished to determine if it could be effective in well established cases.

Case Report

The patient was 50 years of age when she developed CRPS after an otherwise trial hairline fracture of her left fifth proximal phalanx. A delay in diagnosis and casting of the non-healing fracture for 3 months likely contributed to the poor outcome. Her initial course has been reported previously (Binkley 2013), but to summarize, she failed to respond to various conventional and unconventional treatments, except for prednisone. Initially responding to short bursts, she required higher and more frequent courses of prednisone, and finally required continuous prednisone, in escalating doses, up to 95 mg a day. Symptoms initially involved the left foot, but spread to involve the entire left leg, with pain, cyanosis, swelling, weakness, increased sweating, and decreased nail growth. Later, the left arm became involved with weakness, tremor, and some pain, eventually spreading to the right side of the body and left side of the face. Motor symptoms with weakness, tremor, fasciculations, and, at times, frank jerking of the limbs, predominated over pain later in the course. At various times with severe flares, she developed systemic autonomic symptoms with palpitations, diaphoresis and presyncope (Schwartzman 2012).

Multiple predictable complications arose from corticosteroid use, including weight gain, impaired glucose tolerance, (despite adherence to a low glycemic diet and regular moderate exercise, thrice daily), hyperlipidemia (treated with statins and ezitnibe), insomnia (treated with trazadone or amitriptyline), hypertension (treated with various agents), skin

breakdown, with extensive purpura and bruising, increased susceptibility to infection, with recurrent episodes of cellulitis (treated with antibiotics), recurrent herpes labialis and one episode of zoster, (treated with anti-viral agents), chronic tinea corporis (treated with a topical anti-fungal agent), reduced bone density (treated with bisphosphonates), and bilateral cataract development, requiring bilateral extraction and lens implantation. Multiple treatments that were attempted throughout her course to reduce prednisone use, but were ineffective or insufficient to accomplish this, are detailed in Table 1.

The condition and its treatments had a significant impact on the patient’s quality of life and ability to continue working. Not only did the patient have to take extensive time off work for physician appointments and treatments, but poor sleep and fatigue reduced her ability to keep up with her usual highly productive schedule. During severe flares, she was unable to work at all because of tremours so severe that motor control was insufficient to be able to write, type or function at work. She had trouble opening medication bottles, doing up buttons or zippers to dress herself, or holding utensils steadily enough to feed herself. Working hours per week dropped from her usual 60 to 80 hours to 30–35 on average, with periods of complete absence from work during flares, treatment or treatment complications (ICU stay 1 week for ketamine, 3 weeks of daily 4 h ketamine treatments, daily IVIG treatments for 1 week, 4 weeks off secondary to severe anemia from IVIG induced hemolysis, 2 days off work for each lens replacement surgery, etc.)

HBOT was administered as part of the patient’s ongoing clinical care. Since it is within the purview of any treating physician in Canada to use an existing treatment for a condition for which it has not been approved (so called “off-label use), as long as the patient is fully informed of such and consents, as was the case here, Research Ethics approval was not required.

Table 1 Treatments ineffective or insufficient to control symptoms

Physical modalities:
Physiotherapy
Transcutaneous nerve stimulation
Repetitive transcranial magnetic stimulation
Transcranial direct current stimulation
Low level light therapy
Neural, glial and/or immuno-modulators
ketamine (oral, topical, and intravenous)
Lidocaine (intravenous and topical)
Amitriptyline
Pregabalin
Apremilast
Ibudilast
Mexilitene
Low and standard dose naltrexone
Lithium
Memantine
Clonidine
Alpha blocker
Metprolol
High dose magnesium and vitamin B2 (as per migraine prophylaxis)
Sympathetic blocks
Capsacin (topically)
Immunomodulators/ anti-inflammatory agents
Etanercept
Anakinra
High dose IVIG
Mycophenolate
Palmitoylethanolamide
Statins
Hydroxychloroquine
Bisphonates
Montelukast
NSAIDs
Pentoxifylline
Cimetidine
Complementary
Meditation
Hypnosis
Accupuncture
Massage therapy
Miscellaneous
Spironolactone
Calcitonin
High dose vitamin C
N-Acetyl cysteine
Amlodipine
Diltiazem
Bumetanide

HBOT at 2.4 ATA for 90 min at pressure, with a 5 min air break mid-treatment, three times a week, was started in April 2018 when the patient required 85 mg of prednisone a day to partially control CRPS symptoms. Claustrophobia was managed by the hyperbaric technicians with reassurances, and by maintaining close proximity to the chamber throughout the treatments. Symptom improvement occurred after 10 treatments, and prednisone tapering then began. Forty treatments were completed by August 2018. Prednsione was tapered to successfully to 9 to 10 mg a day by mid November 2018. Low dose naltrexone, 4.5 mg daily was continued throughout.

Hydroxychloroquine had been added in August 2018, with the hopes that its anti-inflammatory actions would prolong remission (V.Tawfik, personal communication).

Symptoms such as dull ache, partial numbness, stiffness, loss of fine motor control, and tremor, all worse on the left, began to flare around February 2019, and prednisone was increased to 10 to 12 mg a day, and HBOT, at 2.0 ATA for 90 min at pressure with a 5 min air break mid-treatment was started in March 2019, when the patient required 13 mg of prednisone to partially control her CRPS symptoms. The patient noticed no improvement after 15 treatments, when it came to our attention that hydroxychloroquine can inhibit the effects of HBOT (Liu et al. 2017). Hydroxychloroquine was immediately discontinued, and after 4 to 5 additional sessions when improvement such as reduction in tremor, improved motor control, and decreased stiffness became apparent. After 33 treatments, HBOT was discontinued, and prednisone was gradually tapered to 5 mg, while maintaining control of CRPS symptoms. This is within the range of requirement for physiological replacement, which may now be required for life, given previous long-term adrenal suppression.

The patient's Cushingoid appearance and weight gain have reversed completely, lipid-lowering and antihypertensive agents have been discontinued, and hypnotic agents for insomnia have been drastically tapered. Fasting blood sugar and hemoglobin A1c levels have returned to well within the normal range. Improvement in these multiple cardiovascular risk factors due to reduction in prednisone dose has undoubtedly added years to her life expectancy. Tinea corporis has completely resolved after several years, and topical anti-fungal treatment has been discontinued. Skin integrity has improved so that purpura have disappeared, bruising has returned to normal, and her epidermis no longer shears off with the slightest friction. The patient has experienced a dramatic improvement in her quality of life, and is returning to the active work schedule she maintained before her illness.

Discussion

Inflammation in CRPS initially involves the peripheral nervous system in the affected limb. The release of these

inflammatory substances causes vasodilation and extravasation, leading to the typical clinical findings of the acute phase of CRPS – edema, erythema and increased temperature.

Later, inflammation becomes centralized in the spinal cord. Activated microglial cells contribute to, and astrocytes may help maintain the inflammation (Schwartzman et al. 2006), and its spread along contiguous spinal segments, causing involvement of ipsilateral limbs, and spread to adjacent spinal segments, causing involvement of contralateral limbs (Edinger et al. 2013). Spreading of symptoms occurs in more than 50% of patients (Agarwal et al. 2005). Inflammation can extend to various regions in the brain itself, including the basal ganglia (Jeon et al. 2017). Movement disorders, including tremour, fasciculations, dystonias, and frank tonic clonic jerking can occur in 25% of patients (van Hilten 2010), and are more common in those with multi-limb spread (van Rooijen et al. 2012), as occurred in our patient. There may be an HLA association with the development of dystonia in CRPS (van Rooijen et al. 2012). The development of auto-antibodies to adrenergic (Kohr, 2011) and muscarinic (Hendrickson et al. 2016) receptors are found in the majority of CRPS patients and, in concert with inflammation of sympathetic tracts, could contribute to movement and systemic autonomic symptoms including gastrointestinal paresis, bladder disturbances, impaired sweating responses, postural hypotension, chest pain, and cardiac arrhythmias, including the increased risk of sudden cardiac arrest (Schwartzman 2012), many of which occurred in our patient. These auto-antibodies are likely to be pathogenic, and when patient serum has been injected into mice, have been demonstrated to recapitulate features of CRPS in the recipients (Helyes et al. 2019).

Psychological support to deal with the impact of the condition may be helpful, though CRPS is not precipitated by pre-existing psychological or psychiatric factors (Farzad et al. 2018). Moreover, the increasing realization that CRPS is inflammatory and has an autoimmune component, has led to the exploration of therapies directed at their suppression. The NMDA receptor antagonist ketamine (thought to attenuate microglial activation and inflammation), given intravenously, and sometimes orally, intranasally or applied topically, can be helpful in some patients (Schwartzman et al. 2011). Corticosteroids can be effective early (Bianchi 2006, Kumowski et al. 2019), and in longstanding CRPS (Barbalinardo et al. 2016), as in the case presented here. Some patients with high dose intravenous immunoglobulin (Tamburin et al. 2014), plasma exchange (Aradillas et al. 2015; Hendrickson et al. 2016), and mycophenolate (Goebel et al. 2018). Anti-TNF agents may be useful (Dirckx et al. 2016), and our patient did respond to etanercept early in the course, but not when the CRPS had become long-standing. Animal experiments with the anti-IL-1 agent, anakinra, suggest that this may occur because inflammation initially present in the peripheral nervous system, becomes centralized, i.e., in the spine and brain (Wei et al. 2016). Acutely, animals responded to anti-

IL-1 given peripherally, but in the chronic phase, they responded only when anti-IL-1 was given intrathecally, presumably because anti-IL-1 and etanercept are relatively large molecules that cannot pass the blood-brain barrier effectively to reach inflamed tissue within the CNS. Therefore, while there are many monoclonal antibodies directed against various inflammatory mediators, their large size and inability to effectively cross the blood-brain barrier may preclude their future use in CRPS.

Our patient's response to prednisone is consistent with an underlying autoinflammatory process driving her CRPS. While autoantibodies have been reported in the majority of CRPS patients, they were not measured in this case. The initial immune response to an insult involves the innate immune system and inflammation, only followed later with activation of the adaptive immune system and production of antibodies. Suppression of initial inflammation in this patient with prednisone was started early after diagnosis, just over 3 months after symptoms began, and was repeated and/or increased with each flare. We could therefore speculate that in this patient, due to the suppression of the innate immune system, the adaptive immune system was never fully engaged, thus preventing the formation of autoantibodies. This could possibly explain the patient's lack of response to therapies directed at altering T and B cell responses, including high-dose immunoglobulins and mycophenolate, while a dramatic response was observed to prednisone and HBOT, which both exert multiple anti-inflammatory actions.

Hyperbaric oxygen has several advantages over other modalities directed against autoinflammation and autoimmunity in CRPS. It is generally well tolerated, and does not have the immunosuppressive side effects with increased risk of infection and long-term increased risk of malignancy, compared to other immunosuppressive regimes. Disadvantages include the fact that it is time and resource intensive, as multiple consecutive sessions, often 20–40, each 110 to 120 min in duration, are required. However, this must be compared against the impact of CRPS on the patients, their families, and the cost to the healthcare system.

A double-blind, randomized, placebo-controlled study was performed at a military hospital to assess whether HBOT was superior to placebo in treating patients with post-traumatic CRPS of the wrist (Kiralp et al. 2004). It was concluded that HBOT was an effective method in patients with CRPS, however, it was not clear that these results can be generalized to other populations. The sample size was relatively small, and consisted of young members of the military. Additionally, all patients received HBOT within 1.5 months of the original injury. Our group has previously reported a post-traumatic CRPS patient who responded to HBOT. This individual underwent 15 sessions of HBOT and improved after suffering the CRPS symptoms for 12 months (Katznelson et al. 2016). This is the first report of the successful use of HBOT in longstanding CRPS.

Although classified as a rare disorder (prevalence less than 200,000), it is posited that there may be at least 50,000 new cases a year in the United States (Reflex Sympathetic Dystrophy Syndrome Association). These patients become disproportionately high consumers of healthcare, as they visit multiple physicians and attempt multiple different treatment regimens, including many that are invasive and expensive. In addition to the high cost to the healthcare system, many treatments are considered off label or experimental, and individuals must pay exorbitant fees out of their own pockets. Most patients fail multiple treatments, and many contemplate suicide, with suicidal ideations reported in 49.3% at some point during their illness in one study (Agarwal et al. 2005), with 15% acting on these impulses. Seventy four 4% were at high risk of suicidal ideation in another study (Lee et al. 2004). Therefore if effective for CRPS, HBOT may improve the quality of life for many and may be an economically viable option.

In summary, we describe a patient with long-standing CRPS, multi-limb spread and systemic autonomic features who required high-dose corticosteroids to control symptoms and failed multiple other treatments, but had a dramatic response to HBOT, and when symptoms began to flare, responded to a second round of HBOT treatment that allowed tapering of corticosteroid doses to that may simply reflect physiologic replacement required due to her long-term adrenal suppression. This report adds to the growing literature documenting the usefulness of HBOT for CRPS, and suggests it may even be effective in chronic, recalcitrant cases with widespread, multisystem involvement. Further studies are urgently needed, so that if these findings are confirmed, HBOT could become an insured service, thereby becoming available to alleviate the suffering of more CRPS patients.

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Compliance with Ethical Standards

Conflict of Interest The authors have no conflicts of interest to declare.

Informed Consent Informed consent was obtained from the participant.

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