Identification and Treatment of New Inflammatory Triggers for Complex Regional Pain Syndrome: Small Intestinal Bacterial Overgrowth and Obstructive Sleep Apnea

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Complex regional pain syndrome (CRPS) is evoked by conditions that may be associated with local and/or systemic inflammation. We present a case of long-standing CRPS in a patient with Ehlers-Danlos syndrome in which prolonged remission was attained by directing therapy toward concomitant small intestinal bacterial overgrowth, obstructive sleep apnea, and potential increased microglia activity. We theorize that cytokine production produced by small intestinal bacterial overgrowth and obstructive sleep apnea may act as stimuli for ongoing CRPS symptoms. CRPS may also benefit from the properties of low-dose naltrexone that blocks microglia Toll-like receptors and induces production of endorphins that regulate and reduce inflammation. (A&A Case Reports. 2015;XXX:00–00.)

Complex regional pain syndrome (CRPS), formally known as reflex sympathetic dystrophy, is a neuropathic pain disorder that may fail to respond to current therapy including a variety of medications, nerve blocks, and ketamine infusions.[1,2] The incidence of CRPS is uncertain because there are few epidemiological studies. In a Mayo Clinic study, the rate was 5.46 per 100,000 person-years compared with a 6-fold larger study in the Netherlands where the rate was 26.2 per 100,000 person-years.[3,4] A marked female predominance was noted in each study. A familial occurrence of CRPS has been described.[5] The natural history of CRPS varies widely. The Mayo Clinic reported that 56 of the 74 patients with CRPS for 1 month to 5 years had complete remission after various treatments. Spontaneous remission was observed when the initial symptoms were mild.[3] By way of comparison, there were no remissions in 656 Drexel University patients who had CRPS for 1 to 46 years.[6] Pain had only modest improvement with their treatments. No spontaneous remissions occurred in 102 Dutch database patients who had CRPS for 2.1 to 10.8 years.[7] Progressive disease was reported in 16%, and permanent disability was present in 31% of the Dutch patients.

Pathophysiologic consequences of cytokine release, microglia activation, central sensitization, and autonomic nervous system dysfunction result in regional pain along with vasomotor, motor/trophic, and sudomotor/edema dysfunction.[1,2,8,9] Microglia cells are an integral part of the anatomic framework of the nervous system with attachments to astrocytes.[10] They act as neuromodulators, which alter central nervous cell and spinal sensory neuron excitability. Various syndromes marked by hyperalgesia including fibromyalgia and CRPS may be mediated by microglia cell activation as a consequence of proinflammatory cytokines.[11,12] Events known to trigger the onset of CRPS include bone fractures, sprains, trauma (injections, nerve injury, surgery, burns, and frostbite), nerve injury, infection, pregnancy, myocardial infarction, and stroke.[1,2] Some of these triggers may be associated with local and/or systemic inflammation.[13–17] In stroke-associated CRPS, inflammation from the stroke has been theorized as one of several possible pathophysiologic mechanisms.[17]

In light of the complex pathophysiology of CRPS and that no single therapy is completely effective, it is desirable to consider all theories. We theorize that cytokine release by various triggering events and disorders could initiate CRPS through the activation of microglia via inflammation. We also propose that underlying unrecognized chronic inflammatory conditions may allow CRPS to persist. Parkitny et al.[18] performed a systematic and meta-analysis review of the role of inflammation in acute and chronic CRPS. In the former, serum interleukin-8 and tumor necrosis factors were increased. In the latter, there were many inflammatory markers in serum, blister fluid, and the cerebrospinal fluid. All of the Mayo Clinic patients reported an antecedent event, with bone fracture being the most common trigger (46%).[3] Fractures are associated with increased cytokines and C-reactive protein in animal models.[13] Chronic systemic

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inflammation has been shown to be an independent risk factor for bone fractures in humans[14]; thus, in this instance, a fracture that precipitates CRPS may stem from a pre-existing chronic inflammatory state.

We present a case of long-standing CRPS in a patient with Ehlers-Danlos syndrome in which prolonged remission was attained by directing therapy toward concomitant small intestinal bacterial overgrowth (SIBO), obstructive sleep apnea (OSA), and potential increased microglia activity. Written consent was obtained from the patient to publish this article.

CASE REPORT

A 56-year-old woman had continuous severe leg pain with episodic pain in the arms and nose since May 2005. Pain first started in the right groin after a cardiac catheterization for evaluation of atypical chest pain. After 5 months, the pain had spread down her leg. Asymmetric, shiny skin with fluctuating temperature changes (up to 10°F), color change, and edema developed. The continuous leg pain worsened 2 years later when she had a spontaneous right ankle fracture. Severe skin blistering occurred beneath the cast. Mild-to-moderate arm and nose pain subsequently occurred mainly in cold weather. A diagnosis of CRPS was confirmed by 4 pain management centers. The patient failed sympathetic ganglion blocks and gabapentin. Prolonged use of opioids worsened the pain.

A 45-year history of irritable bowel syndrome (IBS) was characterized by postprandial bloating, excessive and foul flatus, and diarrhea. Fatigue, anxiety, and a sleep disorder were present for several years before the onset of CRPS. A 2010 sleep laboratory polysomnography evaluation was reviewed. This had been performed to evaluate snoring, daytime hypersomnolence, morning headaches, and awakening with gasping for breath. The apnea–hypopnea index was 15 with a respiratory disturbance index of 58 (documentation of desaturation was not available). In 2010, implementation of nasal mask continuous positive airway pressure (CPAP) at 12 cm H_2O was performed. Despite the CPAP use, symptoms of sleep apnea continued, and intolerance of the device resulted in reduction of CPAP use. Periodic use of alprazolam, bupropion, and nortriptyline increased the depth of sleep and reduced anxiety but did not improve fatigue and sleep apnea symptoms.

In October 2013, the patient returned for a second evaluation for atypical chest pain and fatigue. The sleep medicine clinic was asked to consult again. The gastroenterology clinic was consulted for the first time. Her arterial blood pressure was 130/80 mm Hg and heart rate was 80 beats per minute. Her body mass index was 29.3 kg/m^2. There was diffuse mild abdominal tenderness. Edema, blue discoloration, and tenderness were present in the right leg (Fig. 1). She exhibited joint hypermobility with the Ehlers-Danlos syndrome and Beighton joint flexibility score of 8 of 9. The patient met 3 major criteria and 5 minor Villefranche criteria diagnostic for the hypermobility type of Ehlers-Danlos syndrome.[19] This diagnosis was supported by her family history in which 3 generations had many features of Ehlers-Danlos syndrome. Her C-reactive protein was increased at 3.9 mg/L (normal range, 1.0–3.0 mg/L). A hiatus hernia was diagnosed by endoscopy. SIBO was diagnosed by a lactulose breath test. A repeat sleep laboratory evaluation was performed, and bilevel positive airway pressure (BiPAP) titration was completed with optimal settings of 15/11 with a nasal mask. Rifaximin was given for SIBO (1650 mg/d/2 week), and long-term low-dose naltrexone (LDN; 4.5 mg/d) was prescribed based on the success in a previous publication.[20]

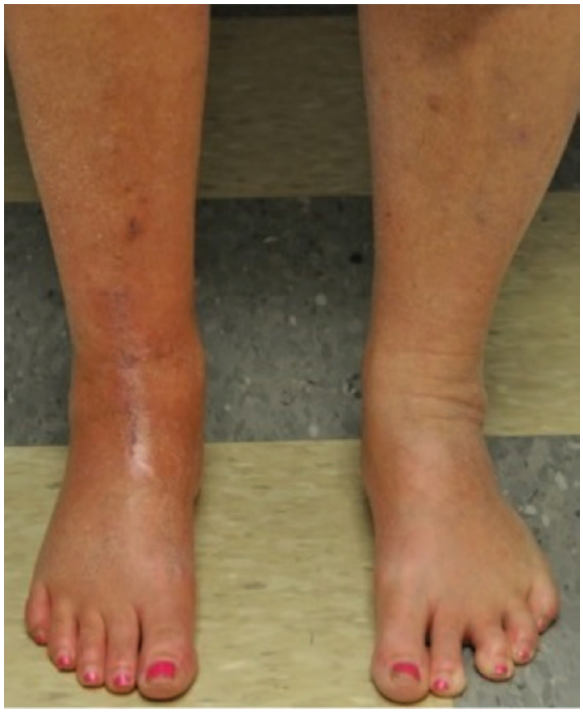

Figure 1. October 2013: asymmetric edema and discoloration in the right leg.

At the 1-month gastroenterology clinic visit, she reported a marked improvement in her leg and bowel symptoms. LDN was continued long term. At the 3-month sleep medicine clinic visit, interrogation of the sleep apnea device over 90 days revealed 82% use >4 hours with 6 hours average use per night. At a 16-month gastroenterology clinic visit, she returned with reports of 1 month of bloating, fatigue, and episodic minor attacks of pain in the arms and nose in cold weather. Inadequate treatment of sleep apnea was suspected because the patient revealed she would often have nightmares, and in the morning, she would find her BiPAP device on the floor. There was mild diffuse abdominal tenderness. Complete remission of CRPS was noted in her right leg (Fig. 2). LDN was continued, and 3 therapies were added: (1) rifaximin (1650 mg/d for 1 month) to retreat SIBO; (2) erythromycin (50 mg/night long term, which acts as motilin-like hormone to stimulate the small intestinal migrating motor complex, which reduces SIBO relapse)[20]; and (3) clonazepam (1 mg/night) to reduce nightmares and reduce the urge to remove the BiPAP device. At the 6-month sleep medicine clinic visit, interrogation of the BiPAP device over 30 days documented improvement to 100% use >4 hours with >7 hours average use per night. Multiple communications over the following 9 months revealed that there had been rapid and sustained remission of all CRPS pain, bowel symptoms, and fatigue.

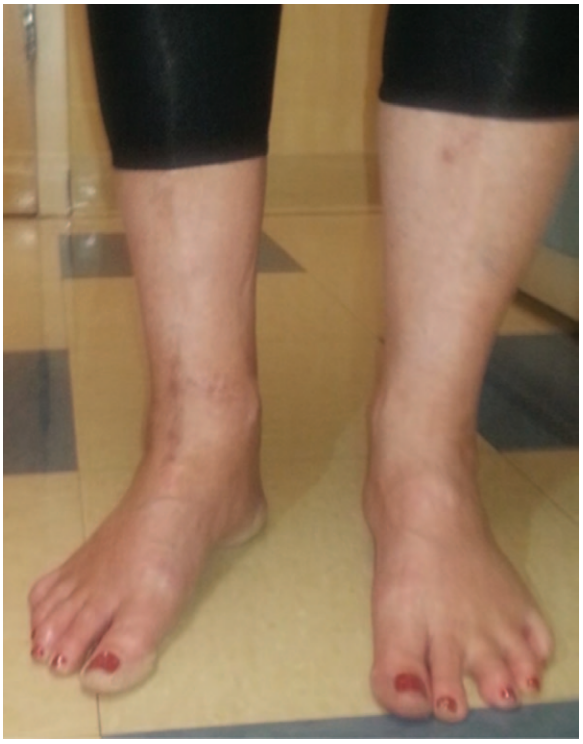

Figure 2. December 2014: signs of complex regional pain syndrome have resolved. The scar from ankle surgery is better visualized.

DISCUSSION

In this case, remission of CRPS was attained by directing therapy toward SIBO, OSA, and potential increased microglia activity. We theorize that cytokine production including tumor necrosis factor produced by SIBO[21] and OSA[22] may act as stimuli for ongoing CRPS symptoms. Experimental therapy of unregulated inflammation and microglia activation using LDN has been reported in pain disorders including 2 cases of CRPS.[11,20]

Systemic pain disorders have been reported in association with SIBO, and thus, this inflammatory state may also play an additional role in CRPS in a patient who has the appropriate phenotypic risk and/or had one of the classic initial inciting triggering events (as was seen in this patient). Pain disorders associated with SIBO include IBS with diarrhea predominance (IBS-d), fibromyalgia, restless legs syndrome, interstitial cystitis, and chronic prostatitis.[21] Finally, inflammation and immune disorders in general have been observed to be present in 95% of the 38 highly associated causes, disorders, and triggering factors for secondary restless legs syndrome.[23]

There is a known relationship of CRPS and the gastrointestinal tract. Dysbiosis (alterations of the microbiome) and increased intestinal permeability (which is present in SIBO) have been reported in CRPS, and these 2 conditions also cause chronic systemic inflammation.[24–26] IBS is common in CRPS although the relationship has hitherto not been elucidated.[27] In multiple studies, SIBO was found to be present in up to 50% of IBS-d patients.[21] Treatment of both SIBO and IBS with rifaximin, a nonabsorbed, gut-directed antibiotic, has been extensively studied, and use of rifaximin for IBS-d was approved by the U.S. Food and Drug Administration in May 2015.[28] Increased levels of substance P are present in IBS-d and are more pronounced in women.[29] This observation might have significance because there is a bidirectional gut–brain connection between the microbiome and substance P.[30] This neuropeptide is thought to play a role in CRPS,[31,32] and women are also more prone to have CRPS as previously noted. Finally, SIBO may also play a role in CRPS by means of lipopolysaccharide translocation through SIBO-induced increased intestinal permeability, which then could activate microglia activity.[33]

Ehlers-Danlos syndrome is a dominant inherited systemic disorder, and the incidence may be as high as 2% of the population.[19] This syndrome is commonly missed in childhood, and adults may present with a unique set of problems that may leave physicians confounded as seen in our patient and her kindred. Thus, published reports of concomitant CRPS and Ehlers-Danlos syndrome are far rare.[20,34] The authors of a case series with 4 patients proposed that Ehlers-Danlos syndrome contributed to CRPS via stretch injury to the nerves traversing hypermobile joints, increased fragility of nerve connective tissue, and/or nerve trauma from more frequent surgery.[34] Subsequently, both syndromes have been subsequently concurrently diagnosed in approximately 25% of 1 of the author's pain management practice.

Three alternative mechanisms whereby Ehlers-Danlos syndrome contributes to CRPS are proposed. Ehlers-Danlos syndrome causes OSA owing to connective tissue laxity,[35] and thus, subsequent chronic hypoxia-induced inflammation[22] may contribute to CRPS activation. This mechanism appeared to play a role in our patient because complete remission of all CRPS symptoms was not attained until sleep apnea therapy was completely optimized. Gastrointestinal symptoms are common in both CRPS and Ehlers-Danlos syndrome.[27,36] In Ehlers-Danlos syndrome, SIBO and small intestinal motility changes have been reported: dilated small intestinal diameter, small bowel diverticulosis, small intestinal motility disorders, and loose connective tissue in the mesentery that allows for drooping of the small intestine to create a relative blind loop.[37–40] Defective collagen synthesis, α-actin deficiency, and autonomic dysfunction are potential explanations for abnormal motility in Ehlers-Danlos syndrome.[41,42] SIBO may be common in CRPS because Goebel et al.[25] demonstrated that increased intestinal permeability was common in CRPS. A recent case report using long-term cephalosporin to keep CRPS in remission supports the idea that manipulation of the microbiome may play a role in CRPS therapy.[43] Thus, inflammation from SIBO caused by Ehlers-Danlos syndrome may contribute to CPRS activation. Finally, the severity of CRPS may be enhanced in patients with Ehlers-Danlos syndrome owing to central hypersensitivity.[44]

In our patient, LDN was administered to attenuate microglia activation by blocking Toll-like receptors 2 and 4.[11,20] In addition, LDN causes rebound met-enkephelin production, which then regulates systemic inflammation by regulating T- and B-cell lymphocyte response, and cytokine production, which may be important in CRPS.[11] This is now the third reported case in which LDN has demonstrated improvement in CRPS symptoms.[20] Subsequently, 1 of the authors has

used this therapy frequently in his practice and has observed therapeutic benefit in patients with CRPS. Administration of LDN as off-label use for pain control is experimental.

The limitations of this report include that CRPS symptoms might have gone into spontaneous remission although most patients experience symptoms for many years.[6,7] The unremitting nature of this patient's symptoms and the rapid response to each course of therapy argue against this concern. Multimodality therapy was administered so it is unknown how much each contributed to remission of CRPS symptoms. However, a multimodality approach by pain management physicians is commonplace in CRPS.[1]

Physicians may not be familiar with the SIBO link to IBS, and thus, gastrointestinal symptoms may be dismissed as unrelated problems in the patient with CRPS. OSA may go unrecognized because sleep disturbance is common in CRPS and is often blamed on pain. An epidemiological study of the prevalence of Ehlers-Danlos syndrome, SIBO, and OSA is required to further understand the roles that these conditions may play in CRPS. It is possible that undiagnosed Ehlers-Danlos syndrome in patients with CRPS could also explain some cases of familial CRPS. We theorize that recognition and treatment of underlying causes of inflammation are likely to be important future modalities in CRPS. ■

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