LETTER TO THE EDITOR

The Beneficial Effect of Topical Glycopyrrolate in a Patient with Neuropathic Lower Extremity Pain

Dear Editor,

The postoperative course of lower extremity (LE) soft tissue orthopedic procedures to treat congenital spasticity disorders may be complicated by nerve injury and development of a chronic neuropathic pain syndrome [1]. In some patients, pain resolution may be unachievable despite multimodal treatment. Here, we report a patient who developed disabling LE neuropathic pain after bilateral hamstring lengthening. The clinical presentation over a 10-year period after the procedure was remarkable for varying degrees of pain and pain-related disability that persisted despite a multifaceted pain management program that a remarkable clinical response to topical application 2% glycopyrrolate, a quaternary ammonium that blocks cholinergic muscarinic receptors, was observed.

Briefly, a 19-year-old female presented to the pain clinic with a history of spastic diplegic cerebral palsy with an overlying right spastic hemiplegia, and recurrent, intense, burning foot pain of 3-year duration following bilateral hamstring lengthening. The pain was localized to the dorsum of both feet, with “sparking” and pain migration to the medial and lateral borders, consistent with the sensory distribution of the peroneal and tibial nerves. The soles were hypoalgesic. Pain intensity varied from 3–8 on a numeric rating scale (10 = worst imaginable). Social stresses and dampness were pain precipitants. Exposure to cold was associated with LE motting, toe cramping, and swelling of her feet. The patient was otherwise in good health, attending college or working while living at home. Hematological and autoimmune disorders had been ruled out, and the family history was noncontributory. The initial physical examination revealed stiffness in the patient’s LE requiring crutches for antalgic gait ambulation. Perfusion, skin color, and temperature were normal, but gentle stroking across the dorsum of the right foot with an alcohol-soaked pad elicited painful needle-like sensations, and light touch to the left foot was experienced as pins and needles radiating medially and laterally. No evidence of spinal cord compression or tethering was seen on spine magnetic resonance images. Diagnostic electromyography, nerve conduction studies, and/or quantitative sensory testing were declined.

A multifaceted pain management program was instituted. Medications included amitriptyline, naproxen, 5% lidocaine patches, and topical capsaicin. Clonidine was associated with unacceptable levels of sedation. Atypical anticonvulsant medications (gabapentin, topiramate) were helpful, but doses sufficient to provide substantial analgesia also incurred unacceptable levels of sedation, poor memory, and interference with the patient’s responsibilities at work. A trial of opioids was declined, as were regional anesthesia and inpatient admission for a trial of intravenously administered vasoactive or sodium channel blocking drugs. Supportive psychotherapy was helpful, but an effort to supplement therapy with a selective serotonin reuptake inhibitor was abandoned because of increased pain due to medication-associated myoclonus. Additional pain management interventions included careful attention to orthopedic and rehabilitation issues, LE bracing, seating and mobility aids, acupuncture, TENS, physical therapy, nutritional support, and patient education. These, in combination with medications as tolerated, brought the patient’s level of pain to 3–4/10. She was employed and managed her commute to work on public transportation, despite pain and the challenges of wheelchair mobility.

During subsequent years of follow-up, our patient reported that LE sweating was a reliable predictor of soon-to-increase painful “sparking” and burning pain. A trial of topical 2% glycopyrrolate cream was instituted, based on reports of its use in Frey syndrome [2]. During an episode where both feet were painful and sweating, 2% glycopyrrolate (compounded by a community pharmacist) was applied to the most painful foot, and capsaicin 0.25% to the other. Topiramate, TENS, and acupuncture were withheld. The patient found that treatment with 2% glycopyrrolate better alleviated the neuropathic symptoms compared with capsaicin. Given this response, 2% glycopyrrolate was applied 3–4 times per day. Pain steadily decreased; ambulation and sensation in her soles improved. After approximately 9 months, the LE pain resolved completely and all medications, including 2% glycopyrrolate, were discontinued. She went on to tolerate hip and LE botulinum toxin type A injections without recurrent pain, resulting in a marked improvement in gait and stability with increased ambulation. The patient remains essentially pain free and off all medications (>3 years), leading an active and independent adult life as of this writing.

Our patient had hyperhidrosis in both feet in addition to pain and alldynia. Hyperhidrosis has been described in several neuropathic pain conditions, including diabetic autonomic neuropathy, auriculotemporal nerve damage (Frey syndrome), and postherpetic neuralgia. The incidence of hyperhidrosis in patient cohorts with...
neuropathic pain syndromes presenting to the pain clinic ranges from 20% to 47% [3–5].

Acetylcholine (ACh) acting at eccrine sweat glands is a major effector in hyperhidrosis conditions. Eccrine glands are densely distributed in the soles of human feet, innervated by ACh-expressing postganglionic sympathetic fibers from the T10-L2 spinal level. In addition to ACh, these same periglandular nerves express adenosine triphosphate, catecholamines, and neuropeptides associated with neuropathic pain symptomatology, including calcitonin gene-related peptide (CGRP). CGRP amplifies ACh-induced sudomotor function and sweating, and is itself associated with central sensitization and acute complex regional pain syndrome symptomatology [6,7]. Further, ACh mediates cholinergic signaling at metabotropic, G protein-coupled muscarinic receptors (mAChRs). Five subtypes of mAChRs have been identified (M1-M5), and accumulating evidence suggests that most have a role in mediating peripheral and spinal cholinergic control of nociception and antinociception [8,9].

Given the resolution of hyperhidrosis and alleviation of pain without systemic anticholinergic side effects, we speculate that the antinociceptive effect of topical glycopyrrolate was related to local ACh antagonism at one or more mAChRs, and that this in turn downregulated local tissue expression of pain-associated neuropeptides. We cannot fully exclude the possibility of a placebo effect, or a change in our patient’s natural pain history, but would suggest that these are unlikely given the clinical course and sustained improvement with glycopyrrolate treatment.

In conclusion, we present this case to suggest that hyperhidrosis may be an index symptom for an underlying pathobiological driver of neuropathic pain in patients with painful sweating. Future translational studies and clinical trials to determine the neurobiological effects and potential therapeutic benefit of targeting mAChRs in neuropathic pain may be warranted.

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References


