Therapeutic Success with Local Botulinum Toxin in Erythromelalgia

To the Editor

Erythromelalgia is a rare clinical syndrome characterized by the triad of intense burning pain, marked erythema, and increased skin temperature (1,2). Patients describe a severe tingling or neuropathy-like pain (2) that usually affects the extremities: feet more frequently than hands (1,2) but also ears and face (3). Warming, exercise, and dependence on legs are worsening factors while cooling and feet elevation are relief factors (3). It has often an intermittent course and the typical constellation of symptoms are only apparent during the flares (1,2).

The disease can be mild or have a quick beginning, start spreading, and become disabling within months (2). Nonetheless even the mild cases may lead to sleep interference and limit daily activities (1). Erythromelalgia patients have higher morbidity and mortality rates when compared with the general population (2).

It is classified as either primary (begins spontaneously at any age) or secondary (associated with other diseases) (1). Primary erythromelalgia is categorized in familial (autosomal dominant) and sporadic types and these can be further subdivided into juvenile and adult forms depending on the onset before or after 20 years old (3). Its diagnosis remains in clinical grounds: a typical history with a normal physical examination in the intercrisis period and exclusion of differential diagnosis (4).

The management of primary erythromelalgia is complex and a multidisciplinary approach is preferred (4). Many therapeutic approaches are possible. However, in most cases, evidence comes from anecdotal reports or small case series. Some examples of therapeutic approaches are a) nonmedical therapies (biofeedback and hypnosis) (5); b) topical (capsaicin) or infusion therapies (lidocaine) (6); c) oral medications (beta-blockers) (7), nonsteroidal anti-inflammatory drugs (NSAIDs) (8), antidepressant drugs (9), aspirin (in secondary erythromelalgia) (1), gabapentin (10) and misoprostol (8); and d) invasive procedures (sympathectomy, sympathetic nerve block, and epidural infusion of bupivacaine and opiates) (1,10). Due to the different patterns of response to the multiple approaches, a careful trial and error strategy may be used to provide the most benefit (1).

A 31-year-old woman presented to our pain clinic with a 6 year history of paroxysmal burning pain episodes of her left hand. The patient mentioned that during the episodes the fingers were hot, red, and mildly swollen. Occasionally the same episodes affected her right hand and left foot. The episodes occurred infrequently, but along the years both its intensity and frequency increased. They lasted a few minutes and were deflagrated by hot environments and alleviated in cold atmospheres. During her first visit, she denied relevant personal history, including trauma or symptoms of orthostatic hypotension, gastrointestinal problems or perspiration abnormalities, or relevant familiar history. No alterations were noticed at the physical and neurological examination. We asked her to bring some photographic evidence of the episodes.

The diagnosis of erythromelalgia was established based on clinical evidence and after exclusion of secondary causes of the disease: myeloproliferative and autoimmune diseases. The laboratory (complete blood count, biochemistry, and autoimmunity testing), image (computed tomography [CT] and magnetic resonance [MR] angiography), and electromyographic studies were normal.

Many therapeutic approaches were applied: acetylsalicylic acid, selective serotonin reuptake inhibitors, and anti-epileptics. The patient had not noticed relief with any of these drugs. After a proper written informed consent, she started in 3-monthly type A botulinum toxin local injections. She immediately noticed a significant reduction of the episode numbers and major relief of symptoms during the remaining episodes. The reported side-effects were mild decrease in finger flexion in the first few days after the injection that was compatible with the performance of daily tasks. Due to personal reasons the patient stopped the treatment during 12 months and an increase in the frequency and intensity of symptoms was observed. The reapplication of type A botulinum toxin was accompanied by a de novo relief of the symptoms and reduced frequency. If the administration was delayed, the symptoms relapsed with growing intensity.

The therapy with botulinum toxin type A provided

relief of the patient's symptoms: either by diminishing the intensity of the pain and associated features or by reducing the number of episodes.

Neuropathic pain is caused by damage or dysfunction within the central or peripheral nervous system. Botulinum toxin type A has demonstrated relief of pain in conditions associated with muscular activity but also may be effective in the treatment of neuropathic pain as reported in a double-blind crossover trial of intradermal botulinum toxin type A for diabetic neuropathic pain (11).

The primary mechanism of action of botulinum toxin is related to its capacity of inhibiting the release of acetylcholine from cholinergic nerve terminals. However, this effect does not explain its analgesic activity (12). Intense investigations have tried to explain the role of botulinum toxin type A injection in the treatment of neuropathic pain: reduced afferent input to the central nervous system by inhibition of glutamate, substance P and calcitonin-gene related peptide (13) reduced peripheral sensitization, and consequently possibly reduced central sensitization (14). We speculate that the therapeutic success of this technique can be compared to the principles that underlie invasive sympathectomies: a) increased cutaneous and muscle blood flow with improved oxygenation and b) interruption of sympathetic-nociceptive coupling by a direct neurolytic action on nociceptive fibers (15).

We have no experimental data that support the success of the application of this technique in erythromelalgia patients. New studies, either animal models or randomized, double-blind, placebo-controlled studies, could help us better understand the correct underlying mechanisms. In between, we propose that this minimally invasive technique may be used when no other drug options remain available and before trying more invasive and definitive techniques in an adequately informed patient.

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