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MANAGING ERYTHROMELALGIA-ASSOCIATED PAIN WITH SUZETRIGINE: A CASE REPORT

Don Hoang, MD, Jennifer Hubbell, DNP, and Thomas Verbeek, MMed

Background: Erythromelalgia is a rare, debilitating chronic condition characterized by erythema, warmth, and recurrent burning pain typically in the feet. Despite numerous treatment options, management of erythromelalgia can be challenging. Sodium channel blockers are offered as treatment options for erythromelalgia; however, they are often nonselective, limiting their utility. Suzetrigine is a novel, selective Nav1.8 sodium channel inhibitor that appears to have promising antinociceptive potential.

Case Report: Our clinical vignette describes the case of a 23-year-old woman with worsening burning pain in her bilateral feet and ankles, diagnosed as erythromelalgia. Various interventions were trialed without adequate relief, including nonpharmacological management, aspirin, lumbar sympathetic block, and various systemic medications. Suzetrigine was ultimately tried with significant pain relief, making this the first described case of suzetrigine alleviating erythromelalgia-associated pain.

Conclusions: Overall, our highlights suzetrigine's potentially wide applicability in various pain conditions, although additional clinical trials are still required to clarify the full extent.

Key words: Erythromelalgia, suzetrigine, Nav1.8, nociception, case report

BACKGROUND

Erythromelalgia is a rare disease characterized by burning pain, warmth, and erythema, typically in the feet, occasionally in the hands, and rarely the neck, face, or genitals (1,2). Symptoms usually start as pruritus before progressing to burning, lasting minutes to days, with normal-appearing skin in between episodes (2,3). Symptoms can be triggered by exercise and heat, but can also occur spontaneously (3). There is no cure or ideal treatment (1,2,4). Sodium channel blockers are often used; however, most of these agents are nonselective, limiting their utility. Suzetrigine is a novel, selective inhibitor of Nav1.8 sodium channels, which are expressed in peripheral nociceptive neurons, and offers promising antinociceptive potential (5,6). Our clinical vignette describes the treatment course of a 23-year-old woman with idiopathic erythromelalgia. The authors believe this to be the first reported case of erythromelalgia-associated pain being treated with suzetrigine. Written consent was obtained from the patient in this report to include information protected by the Health Insurance Portability and Accountability Act.

CASE PRESENTATION

A 23-year-old woman with a history significant for anxiety/depression (on clonazepam), lower extremity edema (on furosemide), and a family history of rheumatoid arthritis presented to the Emergency Department with a 4-month-long history of progressively worsening aching, burning pain in bilateral feet and ankles. Her symptoms started as left big toe pain before spreading to her left foot and then both feet and ankles. The pain was associated with bilateral feet swelling and was worst at night. She had tried acetaminophen,

From: Department of Anesthesiology and Perioperative Medicine, Penn State College of Medicine, Hershey, PA

Corresponding Author: Thomas Verbeek, MMed, E-mail: tverbeek@pennstatehealth.psu.edu
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naproxen, tramadol, gabapentin, pregabalin, prednisone, oxycodone-acetaminophen, and intravenous morphine without pain relief. She had also tried, but did not tolerate ketamine (due to hallucinations) and topical medications (due to worsened pain). The patient denied any significant foot injury or history of blood clots. Radiographic and magnetic resonance imaging of her feet were unrevealing. Orthopedics and Rheumatology were previously consulted, expressing concern for complex regional pain syndrome.

On presentation, she was tachycardic, tachypneic, and hypertensive. She complained of 10/10 pain on the Numeric Rating Scale (NRS-11), a 10-point scale where 0 represents "no pain" and 10 represents "worst possible pain imaginable." Exam demonstrated bilateral lower extremity erythema, warmth, and edema, as well as trophic changes to the nails of the bilateral feet. Bilateral lower extremity peripheral pulses were intact. She demonstrated no focal neurological deficits with intact sensation. Laboratory investigations were notable for mild thrombocytosis of 377,000 platelets per μL (normal range: 150,000-350,000 platelets/μL), elevated total bilirubin of 1.8 mg per dL (normal range: < 1.2 mg/dL), mild hyponatremia of 135 mmol per L (normal range: 136-145 mmol/L), elevated anion gap of 19 mmol/L (normal range: 5-14 mmol/L), and mild hypercalcemia of 10.4 mg/dL (normal range: 8.4-10.2 mg/dL). Bilateral lower extremity venous duplex demonstrated no obvious abnormalities.

She was admitted to Internal Medicine the following day (day 1) for pain control, on acetaminophen 1 g every 6 hours, pregabalin 75 mg twice daily, intravenous ketorolac 30 mg every 6 hours as needed, intravenous hydromorphone 0.4 or 0.6 mg every 4 hours as needed for moderate or severe pain, as well as clonazepam 0.5 mg twice daily and hydroxyzine 25 mg every 6 hours as needed for anxiety. Neurology had a low suspicion for primary large fiber neuropathy, recommending against nerve conduction studies, but recommending rheumatological workup, including C-reactive protein (CRP), erythrocyte sediment rate (ESR), antinuclear antibody (ANA) with reflex, and antineutrophil cytoplasmic antibodies, which, along with rheumatoid factor, were all unremarkable. The chronic pain service was consulted, recommending increasing pregabalin to 100 mg 3 times daily as well as duloxetine 60 mg nightly.

On day 2, she reported slightly improved pain with duloxetine, pregabalin, hydromorphone, and ice. However, with mildly elevated alanine aminotransferase (ALT) of 55 units/L (normal range: < 33 units/L) and aspartate aminotransferase (AST) of 81 units/L (normal range: < 32 units/L), chronic pain recommended reducing acetaminophen to 1 g every 8 hours.

On day 3, her ALT and AST improved to 47 units/L and 36 units/L, respectively; however, she was noted to have a new leukocytosis of 12,890 white blood cells (WBC) per μL (normal range: 4.0-10.4 WBC/μL), elevated vitamin B12 of > 1,800 pg per mL (normal range: 211-946 pg/mL), and low folic acid of 6.8 ng per mL (normal range: > 7.2 ng/mL). Rheumatology diagnosed erythromelalgia. They recommended trialing aspirin 81 mg daily. Complement levels (C3 and C4), serum protein electrophoresis with immunofixation, and urine protein electrophoresis were all unremarkable. Chronic pain again recommended increasing pregabalin to 100 mg 3 times daily, and the ketorolac was stopped.

On day 4, she noted mild pain relief with aspirin, although denying any relief on day 5. Soaking her feet in cold water provided the most relief. Rheumatology recommended trialing intravenous methylprednisolone 60 mg daily, with possible mild improvement on day 6.

On day 7, she again reported intolerable pain.

Chronic pain recommended intravenous hydromorphone patient-controlled analgesia (PCA): 0.2 mg every 6 minutes, oral hydromorphone 4 mg every 6 hours , and memantine 5 mg twice daily.

On day 8, she reported some improvement with the PCA, although, given persistent pain, chronic pain increased pregabalin to 150 mg 3 times daily. Rheumatology recommended testing for anti-Sjogren's syndrome (SS)-A and anti-SS-B antibodies, which were unremarkable, and potentially involving hematology for myeloproliferative disease workup.

By day 10, she reported uncontrolled pain and requested an sodium voltage-gated channel alpha subunit 9 (SCN9A) gene test, which was unavailable. Chronic pain recommended tizanidine 2 mg 3 times daily and discussed performing a lumbar sympathetic block.

On day 13, a left-sided sympathetic block at the third lumbar vertebra was performed with 5 mL of 1% lidocaine, followed by 10 mL of 0.25% bupivacaine without complications. Pain relief was mild and short lived.

On day 17, the acute pain service offered an epidural injection, which she would ultimately forgo. On day 18, chronic pain recommended trialing suzetrigine with a loading dose of 100 mg followed by 50 mg twice daily for 14 days, which was initiated on day 19. Starting day 20, she reported considerable pain relief,

and she transitioned from hydromorphone PCA to oral oxycodone. On day 21, the patient was discharged with instructions to finish the 14-day course of suzetrigine 50 mg twice daily in addition to acetaminophen 500 mg every 8 hours, aspirin 81 mg daily, duloxetine 20 mg twice daily, pregabalin 150 mg 3 times daily, and a 7-day supply of oxycodone 7.5 mg every 8 hours as needed. No adverse effects were documented after initiating suzetrigine; however, 4 mg of as-needed ondansetron was recorded as administered on day 21. She was scheduled to follow-up with chronic pain in the clinic, but was lost to follow-up.

DISCUSSION

Erythromelalgia typically falls under 2 categories: primary and secondary (4). Primary erythromelalgia is idiopathic, typically associated with inherited disease, while secondary erythromelalgia is caused by an underlying condition or medication (4). Diagnosis is clinical, without need for testing (7). Tests, such as complete blood count, ANA, ESR, or CRP, may help distinguish between primary and secondary erythromelalgia. Given erythromelalgia's association with small and large fiber neuropathy, electromyography and nerve conduction studies may be considered. Also consider thermoregulatory sweat testing and quantitative sudomotor axon reflex test for small fiber neuropathy (3). Skin biopsies are nonspecific, occasionally showing decreased epidermal nerve fiber density (1).

Inherited erythromelalgia is often associated with a gain-of-function variant of the SCN9A gene, which encodes neuronal Nav1.7 sodium channels, located in the sympathetic ganglia and nociceptive neurons (1). This lowers the action potential threshold, causing sodium channel hyperexcitability and nociceptive neuron firing at subthreshold stimuli, leading to increased pain (2,8). Not all cases of primary erythromelalgia are associated with SCN9A variants (1). Other genetic variants implicated include genes encoding other sodium channels (e.g., Nav1.8, Nav1.9, sodium voltage-gated channel beta subunit 1), transient receptor potential channels (e.g., transient receptor potential ankyrin 1 and transient receptor potential vanilloid 1), and other pain targets (e.g., lysine-deficient protein kinase 1 and nerve growth factor receptor) (7,9). Secondary erythromelalgia is associated with multiple conditions, most notably myeloproliferative disorders and, to a lesser extent, autoimmune disorders (1). Symptoms are believed to be related to tissue hypoxia from increased arteriovenous shunting, causing imbalance in thermoregulation and nutritive perfusion (2).

Erythromelalgia is managed symptomatically with lifestyle changes, avoiding triggers, elevating the extremity, and cooling the affected area, while avoiding tissue damage and ulceration (1,2). For secondary erythromelalgia, the underlying etiology should be addressed. Aspirin (or alternative nonsteroidal anti-inflammatory drugs like anagrelide) can be trialed, especially in cases of underlying myeloproliferative disorders (2). Topical therapies, such as lidocaine and compounded amitriptyline-ketamine, can be tried for pain, and compounded midodrine for erythema (1,2). Systemic medications, such as gabapentin, pregabalin, venlafaxine, sodium channel blockers (e.g., lidocaine, mexiletine, and carbamazepine), selective serotonin reuptake inhibitors (e.g, sertraline), and amitriptyline, can be considered (1,2). Epidural infusions of bupivacaine/ropivacaine, transcranial magnetic stimulation, botulinum toxin injections, and thoracic or lumbar sympathectomy could also be considered (2).

As demonstrated by our case, erythromelalgia can be challenging to manage, and, although numerous potential treatment options exist, none appear to reliably work (2). Suzetrigine was ultimately trialed with quick and significant pain relief, as demonstrated by trends in the NRS-11 (Fig. 1) and trends in the total daily administered morphine milligram equivalents (Fig. 2).

Suzetrigine is a novel, oral medication indicated for moderate to severe acute pain in adults (5,6). It is a selective inhibitor of Nav1.8, a sodium channel expressed in peripheral nociceptive neurons, which blocks nociceptive pain signaling peripherally without any assumed central activity (5,6). Like Nav1.7, Nav1.8 also controls neuronal excitability, particularly in C-fibers. Inhibiting Nav1.8 should help reduce pain sensitivity (8). The extent of suzetrigine's utility, however, is still largely uncertain, with ongoing clinical trials (6).

Reported adverse effects of suzetrigine include pruritus, muscle spasms, rash, nausea/vomiting, elevated creatine phosphokinase, and decreased estimated glomerular filtration rate, as well as postprocedural hematoma, hypotension, arrhythmia, syncope, and somnolence (10). Not much is currently known about the long-term safety; it may be worth monitoring for cardiac arrhythmias given the association between loss-of-function mutations of Nav1.8 and potentially lethal cardiac conditions, such as Brugada syndrome (8).

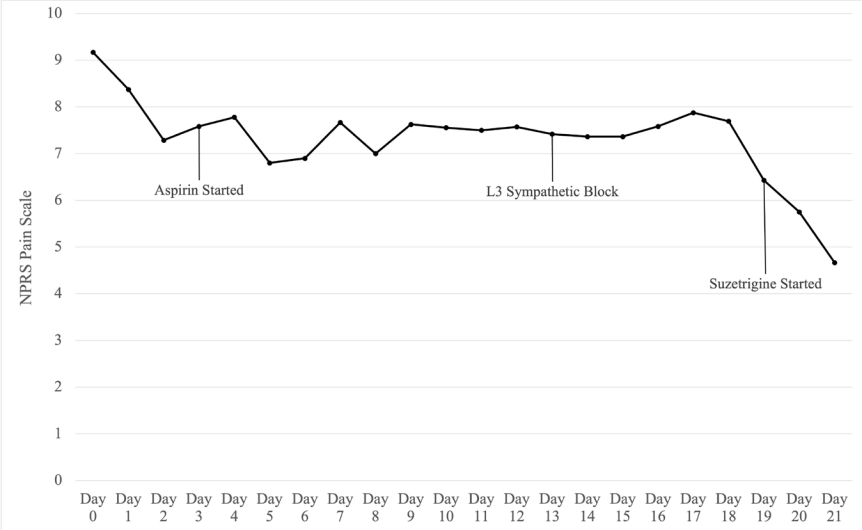

Fig. 1. Daily averaged NRS-11 reported pain rating each hospitalization day. NRS-11, Numeric Rating Scale.

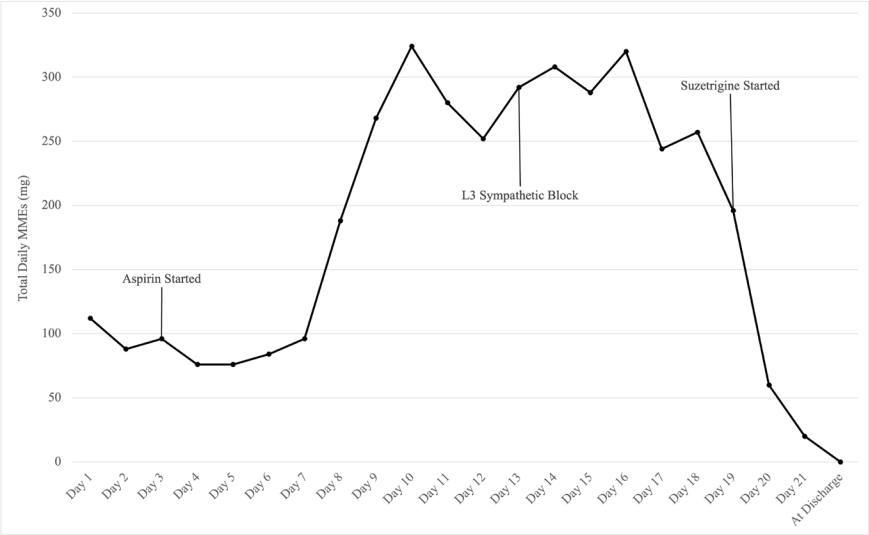

Fig. 2. Total daily administered MMEs each hospitalization day and at discharge. MMEs, morphine milligram equivalents.

Suzetrigine appears efficacious in treating erythromelalgia-associated pain without obvious adverse effects. This represents the first description of suzetrigine being used in erythromelalgia for the short-term treatment of pain.

A limitation of this discussion is that the patient was lost to follow-up following discharge from the hospital. Consequently, nothing is known about the longitudinal impact of suzetrigine on our patient's symptoms. Furthermore, although the patient's pain significantly improved after receiving suzetrigine, this relief cannot be definitively attributed to the drug. It may have resulted from other factors, such as the aspirin, a placebo effect, or the natural course of the disease.

CONCLUSIONS

Erythromelalgia is a condition that can be debilitating yet difficult to manage. Numerous treatment options are described, but no single treatment option reliably manages symptoms. Suzetrigine, an oral selective inhibitor of Nav1.8 sodium channels, was tried in our case with great results, suggesting its potential utility in erythromelalgia. There is a need for additional clinical trials, as the extent of suzetrigine's utility is still uncertain.

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