ANNALS OF HEADACHE MEDICINE®

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ANNALS OF HEADACHE MEDICINE JOURNAL

Botulinum Toxin: Treatment for Refractory Chronic Migraine and Red Ear Syndrome

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Keywords: Migraine, Aura, Red Ear Syndrome, Botox

Article Information

DOI: 10.30756/ahmj.2022.09.03

Article Type: Case Report
Issue: 09.03
Manuscript ID: 2022007

Received: Nov 2, 2022
Revised: Jan 10, 2023
Accepted: Jan 13, 2023
Published: Jan 24, 2023

Recommended Citation:
Callan GM, Tolebeyan AS. Botulinum Toxin: Treatment for Refractory Chronic Migraine and Red Ear Syndrome. *Ann Head Med.* 2022;09:03. DOI: 10.30756/ahmj.2022.09.03

Abstract

Objectives: The objective of this case report is to discuss botulinum toxin as a treatment for Red Ear Syndrome (RES) and refractory chronic migraine, as well as provide a brief overview of possible RES etiologies.

Background: Because RES presents with several conditions, its pathophysiology and treatment options are difficult to define. Given their similar clinical presentations, RES may be an auricular subtype of erythromelalgia. Additionally, RES presents consistently with chronic migraine. Botulinum toxin has been proven an effective medication for erythromelalgia and refractory migraine, and it may be just as useful for RES.

Results: This paper reports one case of a patient who presented with chronic migraine with aura and unilateral RES. This patient failed several treatment options, and the most recent regimen only reduced the intensity of migraine attacks. With the addition of botulinum toxin, both chronic migraine and RES symptoms were mitigated.

Conclusion: While a definitive treatment for RES has not been determined, a promising option for patients with concomitant chronic migraine may be botulinum toxin.

Introduction

Red Ear Syndrome (RES) is an unusual experience described as painful, burning sensations and redness of the ear and surrounding skin. While several more cases have been recounted since its characterization by Lance in 1996, RES pathophysiology and

treatment are still debated. Several conditions have presented with RES, including trigeminal neuralgia, trigeminal autonomic cephalalgia, thalamic syndrome, cervical spine disorders, systemic lupus erythematosus, vasculitis, and temporomandibular joint (TMJ) dysfunction, but seems most consistently to appear in patients with chronic migraine; RES may also be a subtype of erythromelalgia, a comparable erythema and pain of the hands and feet.[1, 2] Because its underlying mechanism is uncertain, RES remains resistant to most treatment options which consist of routine medications used for migraine: NSAIDs (indomethacin), tricyclic antidepressants (amitriptyline), calcium channel blockers (verapamil), beta-blockers (propranolol), antiepileptic drugs (gabapentin), cervical nerve blocks, and botulinum toxin.[2-4]

At the neuromuscular junction, the botulinum toxin is known to cleave SNARE proteins, preventing acetylcholine release and muscle contraction. However, its mechanism for chronic migraine must be more than reduced muscle tension, as its use is ineffective for tension-type headaches.[5] Studies suggest that botulinum toxin acts in several ways: inhibiting calcitonin-gene related peptide (CGRP) and substance P release peripherally and centrally due to retrograde axonal transport; reducing surface expression of nociceptive receptors; decreasing the production of inflammatory cytokines; and, stimulating mu-opioid receptors.[5, 6] Overall, these actions subsequently minimize vasodilation and pain. In our case, botulinum toxin A was used as a treatment for RES and chronic migraine.

Case Report

A 67-year-old female with a past medical history of occipital neuralgia status post multiple ablations, possible Ehlers-Danlos Syndrome, rheumatoid arthritis, Raynaud's disease, facial basal cell carcinoma, gastroesophageal reflux disease, and nasal septal ulcer, presented in clinic with chronic migraine with aura and unilateral RES.

Previous failed treatments for migraine include amitriptyline, gabapentin, dihydroergotamine, acupuncture, ibuprofen, naproxen, and CBD cream. At this time, her prophylactic treatment included nadolol and galcanezumab, while abortive treatment consisted of sumatriptan. Galcanezumab, a CGRP ligand monoclonal antibody, reduced her headache intensity but did not reduce the frequency from 20 headaches per month. Unrelated to her headache, she reported redness of her right ear several times a week, lasting 1-2 hours. Botulinum toxin A 155 units every twelve weeks was added as a treatment for RES and migraines in addition to her prophylactic galcanezumab and nadolol. Botulinum toxin A was administered based on the PREEMPT protocol [7]. On the right temple, treatment was adjusted to inject five units of toxin near the pterion, ten units behind the ear, and five above the TMJ.

With the addition of botulinum toxin A treatment to her regimen, both her RES and migraine symptoms were mitigated about two weeks following the second round. Her headache frequency had decreased to 4-6 per month from the baseline of 20. Additionally, her RES improved significantly with a reduction in frequency and duration to about 12 episodes lasting 30 minutes in three months.

Discussion

One basic proposal for RES pathophysiology revolves around decreased sympathetic activity and increased parasympathetic activity. The trigeminal nerve innervates the middle temporal and posterior auricular arteries which supply the ear. A branch of the trigeminal nerve, the auriculotemporal nerve, innervates the anterior superior ear and TMJ. Lastly, the earlobe is innervated by C2 and C3 nerve roots branches.

Nerve signals release calcitonin gene-related peptide (CGRP), substance P, and nitric oxide, which lead to blood vessel dilation, erythema, and pain.[2, 8, 9]

Clinically, RES commonly occurs in association with chronic migraine; therefore, it has been proposed that RES may be produced by trigeminovascular activation and vasodilation during a migraine.[2, 9] RES could be related to erythromelalgia; although its pathology is still being studied, it is thought the primary trigger may be hypoxia-induced neuropathy as well as arteriovenous shunting due to atypical distribution of blood vessels.[2, 10, 11] Erythromelalgia has also been linked to several hematologic disorders where thrombosis or intimal and smooth muscle proliferation may be key contributing factors for attacks.[11] Interestingly, botulinum toxin has been shown to effectively treat refractory erythromelalgia, supporting the idea that RES may be an auricular subtype since both respond to these injections.[12, 13]

Conclusion

No definitive treatment for RES has been determined because of its different clinical presentations and numerous associated conditions. However, botulinum toxin A may be the most effective treatment in RES patients who present with chronic migraine. Furthermore, the success of this treatment may support the classification of RES as a subtype of erythromelalgia and add to the basic understanding of its possible pathophysiology.

Declarations/Disclosures

Consent/Permission/Ethics Approval: A single case with no identifiable data. There are no potentially identifiable human images or data presented in the manuscript. None of the patient's information included is identifiable to any specific individual.

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, author declares the following:
Payment/services info: Author has declared that no financial support was received from any organization for the submitted work.
Financial relationships: Author have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.
Other relationships: Author have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. D'Amico A, Galati C, Manzo ML, Reina F, Nocera GM, Raieli V. Red ear syndrome in children: Review of literature and report of three cases. *Int J Pediatr Otorhinolaryngol*. Mar 2021;142:110615. PubMed PMID: 33440309. doi:10.1016/j.ijporl.2021.110615
2. Lambru G, Miller S, Matharu MS. The red ear syndrome. *J Headache Pain*. Oct 4 2013;14(1):83. PubMed PMID: 24093332; PubMed Central PMCID: PMCPMC3850925. doi:10.1186/1129-2377-14-83
3. Boulton P, Purdy RA, Bosch EP, Dodick DW. Primary and secondary red ear syndrome: implications for treatment. *Cephalalgia*. Feb 2007;27(2):107-10. PubMed PMID: 17257229. doi:10.1111/j.1468-2982.2007.01270.x
4. Castellanos-Gonzalez M, De Manueles F, Martos MG, Rodriguez MAS. Successful treatment of red ear syndrome with botulinum toxin type A. *Indian J Dermatol Venereol Leprol*. Jan-Feb 2019;85(1):107-108. PubMed PMID: 30487346. doi:10.4103/ijdvl.IJDVL_111_18
5. Do TP, Hvedstrup J, Schytz HW. Botulinum toxin: A review of the mode of action in migraine. *Acta Neurol Scand*. May 2018;137(5):442-451. PubMed PMID: 29405250. doi:10.1111/ane.12906
6. Ramachandran R, Yaksh TL. Therapeutic use of botulinum toxin in migraine: mechanisms of action. *Br J Pharmacol*. Sep 2014;171(18):4177-92. PubMed PMID: 24819339; PubMed Central PMCID: PMCPMC4241086. doi:10.1111/bph.12763
7. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-

controlled phase of the PREEMPT 1 trial. *Cephalalgia*. Jul 2010;30(7):793-803. PubMed PMID: 20647170. doi:10.1177/0333102410364676

8. Raieli V, Compagno A, D'Amelio M. Red Ear Syndrome. *Curr Pain Headache Rep*. Mar 2016;20(3):19. PubMed PMID: 26879877. doi:10.1007/s11916-016-0547-y
9. Raieli V, Monastero R, Santangelo G, Eliseo GL, Eliseo M, Camarda R. Red ear syndrome and migraine: report of eight cases. *Headache*. Feb 2002;42(2):147-51. PubMed PMID: 12005292. doi:10.1046/j.1526-4610.2002.02033.x
10. de Amorim IL, Kauppila LA, Martins IP. Red Ear: Syndrome or Symptom? *Headache*. Jun 2018;58(6):885-891. PubMed PMID: 29802637. doi:10.1111/head.13333
11. Mann N, King T, Murphy R. Review of primary and secondary erythromelalgia. *Clin Exp Dermatol*. Jul 2019;44(5):477-482. PubMed PMID: 30609105. doi:10.1111/ced.13891
12. Gerwin RD. Botulinum Toxin as Successful Treatment of Refractory Erythromelalgia Pain. *Pain Med*. Jun 1 2019;20(6):1251-1253. PubMed PMID: 30605501. doi:10.1093/pm/pny271
13. Lin KH, Wang SJ, Fuh JL, Chen SP. Effectiveness of botulinum toxin A in treatment of refractory erythromelalgia. *J Chin Med Assoc*. May 2013;76(5):296-8. PubMed PMID: 23683264. doi:10.1016/j.jcma.2013.01.003