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Treatment Of Trigeminal Neuralgia With Botulinum Toxin Type A – Possible Association With Hashimoto's Thyroiditis And Hashimoto's Encephalopathy: Case Report

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Abstract
Trigeminal neuralgia (TN) is a condition that causes severe neuropathic pain, impairing quality of life. Most cases are caused by compression of the trigeminal nerve, resulting in demyelination. The annual incidence is 4 to 13 cases per 100,000 people, making it a rare disease. Hashimoto's thyroiditis and Hashimoto's encephalopathy are interrelated, affecting the thyroid and nervous system, respectively. There is a possible link between trigeminal neuralgia and these autoimmune conditions. This case report presents a 37-year-old female patient with acute bilateral pain since January 2025. She had already undergone treatment with Pregabalin and Musculare, both without success. Due to the intense pain, she tried Toragesic and later used Tramadol Hydrochloride. Despite the medication, the pain attacks continued, leading her to seek emergency care several times. Treatment with NABOTA® botulinum toxin was performed using the suprazygomatic technique to block the maxillary nerve. The approach proved effective, resulting in a 100% improvement in pain attacks. The patient had no complications and was able to completely reduce her use of conventional medications within four months. The case highlights the possible connection between trigeminal neuralgia and the aforementioned autoimmune diseases.

Keywords: *Trigeminal neuralgia, Botulinum toxin, Hashimoto's thyroiditis, and Hashimoto's encephalopathy.*

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I. Introduction

Trigeminal neuralgia (TN) is a disease that causes severe neuropathic pain, negatively impacting individuals' lives and affecting physical, emotional, and social aspects. Acute orofacial pain, which occurs in episodes and is comparable to an electric shock, typical of TN, impairs daily routines and is accompanied by a notable increase in anxiety, depression, and problems with sleep quality in patients. The comprehensive effect of TN requires an integrative approach and understanding for its treatment, involving different health professionals, including dental surgeons (oral and maxillofacial surgeons, specialists in orofacial harmonization), and physicians. However, the variety of therapeutic options emphasizes the need for a unified, evidence-based approach, especially given recent advances in our understanding of the symptoms, causes, pathophysiology, categorization, and treatment options for TN.[1,2]

Most cases of trigeminal neuralgia result from pressure on the trigeminal nerve, leading to demyelination of the compressed region of the nerve. The relationship between demyelination and the symptoms of trigeminal neuralgia is unclear. It has been suggested that the production of ectopic impulses caused by demyelinated lesions triggers epiphyllic conduction, which is described as electrical conduction between adjacent neurons occurring through extracellular spaces without the use of synapses or neurotransmitters. The effective connection between fibers related to pain production and those that transmit gentle touch may be the cause of shock-like pains in the facial trigger area when mild tactile stimulation occurs.[3,4]

From an epidemiological point of view, TN is the result of a complex combination of risk factors ranging from heredity to environmental elements. It is considered a rare disease, with an annual incidence of 4 to 13 cases per 100,000 people, often unilateral. The prevalence in the general population is less than 0.1%. The condition is more common in women, and its incidence increases with age, being more frequent in people over 50 years of age.[2,5,6]

Hashimoto's thyroiditis and Hashimoto's encephalopathy are two distinct diseases, although they are interrelated, affecting the thyroid gland and the central nervous system, respectively. Hashimoto's thyroiditis is an autoimmune condition that causes chronic inflammation of the thyroid and often results in hypothyroidism. On the other hand, Hashimoto's Encephalopathy (HE), also known as steroid-responsive autoimmune thyroiditis-associated encephalopathy (SREAT), is a rare neurological condition that can manifest in individuals with Hashimoto's Thyroiditis, without being directly linked to thyroid hormone levels.[7,8]

Since it was first reported in 1966 by Brain, EH has become significant in the differential diagnosis between encephalopathies of unknown causes. With an estimated prevalence of 2.1 per 100,000 cases, the ratio of women to men is 4 to 1.[9]

Connection between the two conditions: Hashimoto's thyroiditis is commonly identified in people with HD, but it can also be found in individuals with normally functioning thyroids. The detection of elevated levels of thyroid antibodies plays a crucial role in the diagnosis of both conditions, but the precise function of these antibodies in the onset of HD is not yet fully understood. The treatment of Hashimoto's thyroiditis aims to regulate thyroid activity, while the focus of HD treatment is to reduce inflammation in the central nervous system.[7,8,9]

Trigeminal neuralgia is not often observed in cases of Hashimoto's thyroiditis or Hashimoto's encephalopathy. However, in some exceptional situations, there are reports of trigeminal neuralgia in individuals suffering from Hashimoto's thyroiditis or Hashimoto's encephalopathy, which may be attributed to overlapping autoimmune or inflammatory mechanisms.[7,8,9]

The importance of this subject lies in the urgency of understanding the connections between these circumstances, especially with regard to the possibility of similar immune mechanisms, such as the detection of autoantibodies or general inflammation, reporting a clinical case, and offering a treatment protocol with type A botulinum toxin for TN.

II. Case Report And Literature Review

Patient LPTG, female, 37 years old. She attended the Orofacial Harmonization Specialization clinic at Polo Ieda, São Lourenço – Minas Gerais – Brazil. She requested a clinical evaluation for orofacial pain (trigeminalgia). She reported acute, bilateral pain since January 2025. Figure 1.

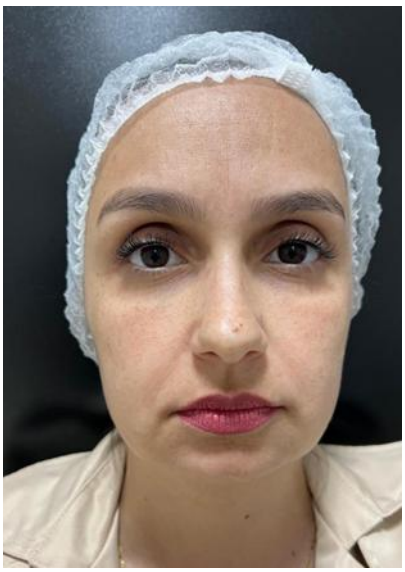


Figure 1. LPTG patient.

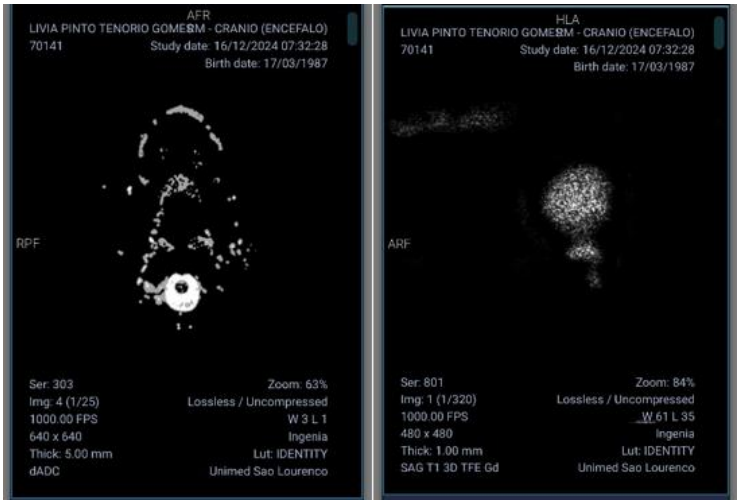
At the initial consultation, he reported previous treatments with 150 mg of pregabalin per day, in two daily doses of 75 mg; combined with 20 mg of Musculare (cyclobenzaprine hydrochloride) three times daily, a centrally acting muscle relaxant that helps with muscle spasms associated with trigeminal neuralgia and, as a secondary action, chronic pain and hyperexcitability, with a dosage of 10 mg every 8 hours for 3 weeks. Both were unsuccessful. Due to severe facial pain, he tried Toragesic 10 mg (tromethamine ketorolac), a nonsteroidal anti-inflammatory drug with analgesic properties, administered sublingually. Finally, he used tramadol hydrochloride. The usual single dose is 1-2 mg of tramadol hydrochloride per kilogram of body weight. The lowest analgesically effective dose should generally be selected. Daily doses of 8 mg of tramadol hydrochloride per kg of body weight. Also unsuccessful.

The current treatment is Gabapentin 300 mg every 8 hours, which acts on the mechanism of neuronal activity modulation. In trigeminal neuralgia, it helps stabilize the hyperexcitability of the trigeminal nerve, reducing the frequency and intensity of paroxysmal pain episodes.

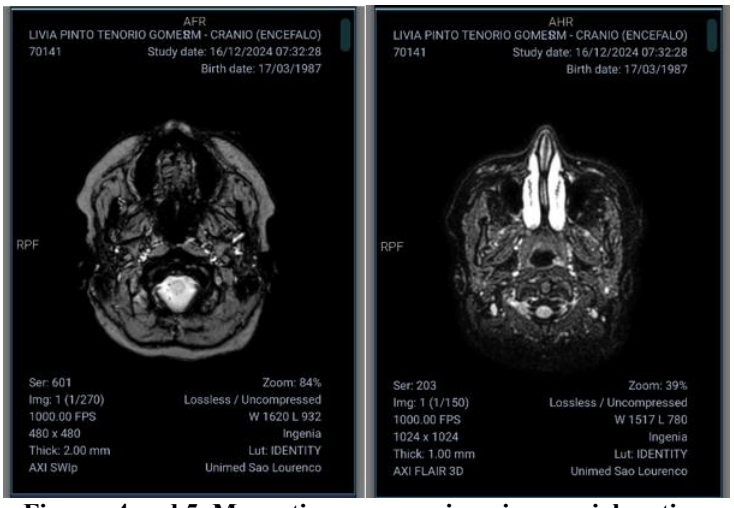
However, episodes of pain became frequent, even with medication. The patient sought emergency hospital care 3 to 4 times for intravenous administration of Tamadol Hydrochloride 100 mg/ml associated with Decadron 4 mg/ml. These episodes and the worsening pain led the patient to seek our care.

Magnetic resonance imaging to evaluate trigeminal neuralgia was performed by EPI/SE, FSE, and GE, with weightings in

Diffusion, T1, T2, T2*/SWI, FLAIR, M3D/FSPGR, with multiplanar acquisitions, with and without intravenous infusion of paramagnetic contrast. Figures 2,3,4 e 5



Figures 2 and 3. Magnetic resonance imaging – axial section.



Figures 4 and 5. Magnetic resonance imaging – axial section.

The analysis showed: Brain parenchyma with normal morphology and signal. Ventricular system with normal morphology and dimensions. Basal cisterns, brain fissures, and cortical sulci with normal appearance for the age group. Trigeminal nerves with preserved trajectory and thickness, without significant vascular-nerve contacts and/or neural displacements. Basal cisterns, cerebral fissures, and cortical sulci appear normal for the age group. Trigeminal nerves preserved in path and thickness, without significant vasculoneural contacts and/or neural displacements. Usual flow void of the carotid and vertebrobasilar systems, based on analysis of conventional sequences. No signs of acute ischemic events, extra-axial collections, and/or intracranial hemorrhages. The administration of paramagnetic contrast agent did not reveal any foci of abnormal impregnation.

The trigeminal nerve is divided into three main branches: ophthalmic (V1), maxillary (V2), and mandibular (V3). The anatomical regions that receive innervation from each of these branches are: Ophthalmic (V1): responsible for innervation of the eye, upper eyelid, and forehead. Maxillary (V2): innervates the lower eyelid, cheek, nostril, upper lip, and upper gum. Mandibular (V3): covers the lower lip, lower gum, jaw, and muscles involved in chewing. Trigeminal neuralgia is most often caused by compression of the trigeminal nerve root, located a few millimeters from its entry into the pons. In 80% to 90% of these cases, root compression occurs due to a nearby artery or vein; the superior cerebellar artery is associated with 75% to 80% of these cases. In addition, other blood vessels that can cause this compression include the petrosal vein and the cerebellar or vertebral arteries located in the anterior and inferior parts. Trigeminal nerve compression can also result from space-occupying lesions, such as meningiomas, acoustic neuromas, epidermoid cysts, arteriovenous malformations, or saccular aneurysms. In addition, multiple sclerosis is a risk factor for the onset of trigeminal neuralgia, being the underlying cause in about 2% to 4% of symptomatic patients, due to demyelination of the trigeminal.[4,10]

Brain magnetic resonance imaging (MRI) is the gold standard test for ruling out secondary causes of trigeminal neuralgia (TN). If MRI is contraindicated, cranial computed tomography, CT cerebral angiography, and trigeminal evoked potentials and/or neurophysiological recordings of trigeminal reflexes are recommended. In addition to ruling out secondary TN, neuroimaging plays a crucial role in subclassifying symptoms in classic and idiopathic TN. This allows cases of classic TN to be considered for trigeminal microvascular decompression when indicated. To identify the existence of a trigeminal neurovascular conflict, the type of vascular structure (artery, vein, or both) and the level of compression, detailed brain MRI sequences of the trigeminal nerve are required. The protocol should employ a combination of three high-resolution sequences, including a fast 3D cisternal image, using steady-state acquisition, steady-state constructive interference, or perfect sampling with contrasts optimized for the application. This should be done using different inversion angle evolution sequences, along with time-of-flight magnetic resonance angiography and 3D T1-weighted gadolinium sequences.[10,11]

The tomographic features of Hashimoto's encephalopathy (HE) are often nonspecific or normal, making diagnosis by imaging challenging. In most cases, CT is normal or shows nonspecific changes, such as mild brain atrophy or subtle hypodense areas, which are not unique to HE.[12]

For the reported case, axial tomographic sections were performed with volumetric acquisition in a multislice CT scanner, without the administration of intravenous iodinated contrast medium. It showed brain parenchyma with normal morphology and attenuation; brain sulci and fissures with normal appearance; ventricular system with normal morphology and dimensions; bone structures with preserved tomographic appearance, without intracranial hemorrhages detectable by the method.

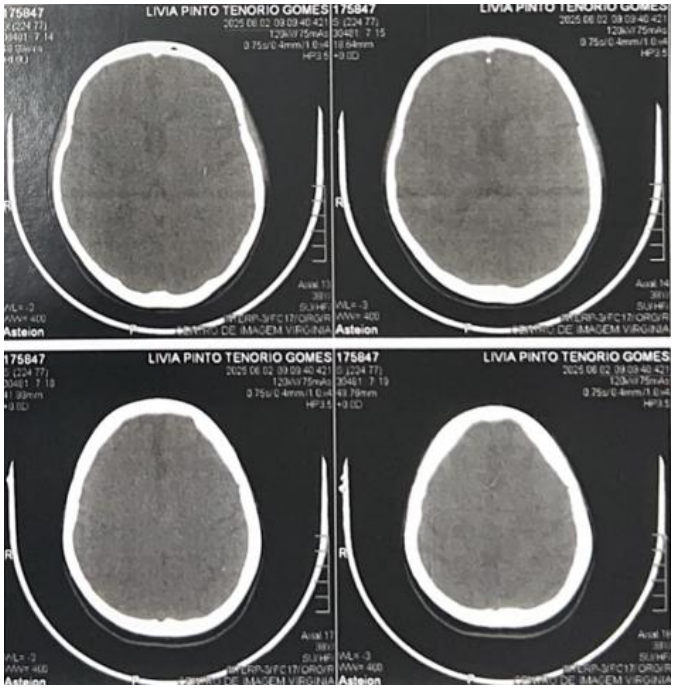


Figure 6. Computed tomography scan of the skull – axial section.

For diagnoses to be accurate, it is necessary to consider the phenotypic variants of the disease, whether typical or atypical, in addition to the symptoms, which are associated with different etiologies, such as primary, secondary, or idiopathic neuralgia. Furthermore, it is necessary to investigate the characteristics of pain to identify pathophysiological mechanisms, which may be central or peripheral. These issues are important both to guide future research and to define the type of treatment, which may be surgical or pharmacological.[13]

Hashimoto's encephalopathy (HE), also known as steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), is a rare condition characterized by abnormal brain dysfunction, including variable neurological and psychiatric symptoms, associated with elevated titers of antithyroid antibodies, particularly anti-thyroid peroxidase antibodies (anti-TPO).[14]

Thyroid peroxidase (TPO) is a key enzyme in the thyroid gland, responsible for iodide oxidation and the synthesis of thyroid hormones (T3 and T4), located in thyroid follicular cells.[15]

Anti-TPO antibodies are autoantibodies that bind specifically to TPO, inhibiting its activity and promoting autoimmune inflammation in the thyroid, as in Hashimoto's thyroiditis. In HS, this relationship extends to the central nervous system (CNS), where anti-TPO antibodies act as diagnostic markers, although their direct pathogenic role remains controversial.[14,15]

The pathogenesis of HS is multifactorial and not fully understood, but involves autoimmune mechanisms. Anti-TPO antibodies, which target TPO in the thyroid, may indicate a cross-immune response or a broader inflammatory process in the CNS, possibly due to autoimmune vasculitis, immune complex deposition, or endothelial inflammation.[14]

In patients with HS, anti-TPO antibodies are elevated in approximately 85-100% of cases, but they may function as an epiphenomenon or marker of general autoimmunity rather than as direct causes of neuronal damage.[16,17]

In the case presented, the patient showed the following results: Thyroperoxidase, Anti-TPO 236.3 IU/mL and Thyroglobulin, ANTI Antibodies 287.8 IU/mL.

Thyroid peroxidase (TPO), also known as thyroid peroxidase, is an enzyme essential for the synthesis of thyroid hormones in the thyroid gland. Anti-TPO antibodies are autoantibodies that attack this enzyme and are key markers of autoimmune thyroid diseases, such as Hashimoto's thyroiditis, which often leads to hypothyroidism. Trigeminal neuralgia, in turn, is a chronic painful condition that affects the trigeminal nerve, characterized by intense episodes of unilateral and/or bilateral facial pain, similar to electric shocks, and may have vascular, inflammatory, or autoimmune causes. Although there is no established direct and universal relationship between thyroid peroxidase, anti-TPO antibodies, and trigeminal neuralgia, evidence suggests indirect associations through autoimmune mechanisms and hypothyroidism. In particular, Hashimoto's encephalopathy (HE), a rare autoimmune condition associated with high titers of anti-TPO antibodies, can manifest with atypical neurological symptoms, including headache similar to trigeminal neuralgia.[18]

Furthermore, hypothyroidism itself, often resulting from the action of anti-TPO antibodies, has been associated with an increased risk of trigeminal neuralgia in genetic studies.[18]

Our main objective was to treat episodes of facial pain or corroborate treatment with botulinum toxin injections into the maxillary branch of the facial nerve (V2).

We administered NABOTA® botulinum toxin, 50 IU on each side, diluted at a ratio of 100 IU to 0.9 ml of sterile 0.9% saline solution. To do this, we followed the suprazygomatic technique, an advanced technique used to block the maxillary nerve (V2), a branch of the trigeminal nerve, in the pterygopalatine fossa (Figure 6). This approach is used in dental procedures, maxillofacial surgeries, or for facial pain relief, such as in trigeminal neuralgia, when intraoral anesthesia is inadequate or unfeasible (e.g., trismus, oral infections, or the need for broader blockage). The technique aims to anesthetize the maxillary nerve before its branching, provides analgesia in large areas of the maxilla, including upper teeth, gums, palate, cheek, upper lip, and nasal mucosa.

It is worth highlighting the relevant anatomy of the region. The maxillary nerve (V2) emerges from the skull through the foramen rotundum and enters the pterygopalatine fossa, an anatomical region located posterior to the maxilla and anterior to the pterygoid process of the sphenoid bone. In the pterygopalatine fossa, the maxillary nerve branches into: infraorbital nerve, which innervates the upper lip, nostril, cheek, and upper anterior teeth/premolars; posterior superior alveolar nerve, which innervates the upper molars and adjacent gingiva; greater and lesser palatine nerves, which innervate the hard and soft palate; zygomatic nerve, innervates the skin of the zygomatic region and temple; pterygopalatine branches, innervate the mucosa of the maxillary sinus and nasopharynx; the pterygopalatine fossa is accessed externally through the pterygomaxillary fissure, located between the maxilla and the pterygoid process. The suprazygomatic approach uses the zygomatic arch and sigmoid notch as the main anatomical landmarks.[20] (Figures 7 and 8)

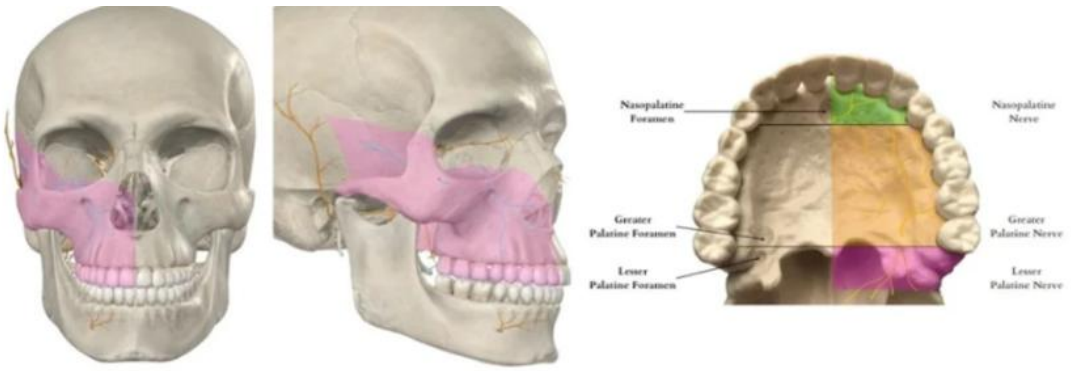


Figure 7. Expected sensory coverage.[20]

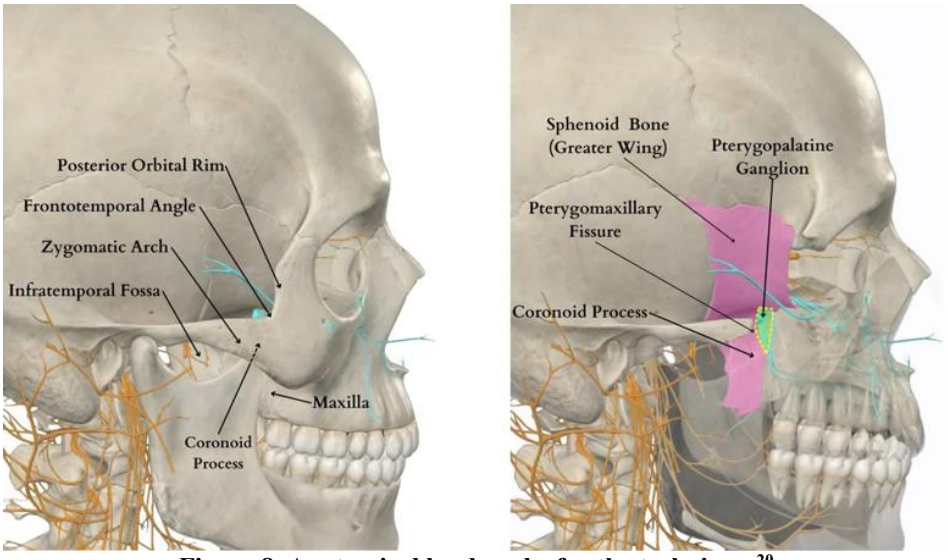


Figure 8. Anatomical landmarks for the technique.[20]

The suprazygomatic technique was performed with the aim of depositing botulinum toxin type A in the pterygopalatine fossa, "blocking" the maxillary nerve in its main trunk.[20]

The patient was positioned in the supine position, with her head slightly tilted backward, facilitating access to the zygomatic (suprazygomatic) region.

Rigorous skin asepsis was performed on the right and left sides of the face to prevent infection. After diluting the botulinum toxin, as described above, we transferred 100 IU to an empty, sterilized glass anesthetic tube and proceeded with the application using a carpule syringe and a long needle (25-27G, 3-4 cm) to reach the necessary depth.

Anesthetic buttons were made with 2% lidocaine with vasoconstrictor (epinephrine 1:100,000) to provide comfort and reduce local bleeding.

The needle was inserted into the skin above the zygomatic arch, at the frontozygomatic angle (formed by the intersection of the posterior orbital rim and the upper edge of the zygomatic arch).20 The direction was medial, inferior, and posterior, at an angle of approximately 45° in the sagittal plane and 10-15° in the horizontal plane. The insertion depth was approximately 4-5 cm, until reaching the pterygopalatine fossa (Figures 9 and 10). The operator may feel a change in resistance when passing through denser tissues. Aspiration was performed. One hundred units of botulinum toxin type A (NABOTA®), 50 IU on each side, totaling 0.45 ml on each side (since 100 IU was diluted in 0.9 ml of sterile saline), injected slowly to minimize discomfort and the risk of unwanted diffusion. (Figures 11 and 12)

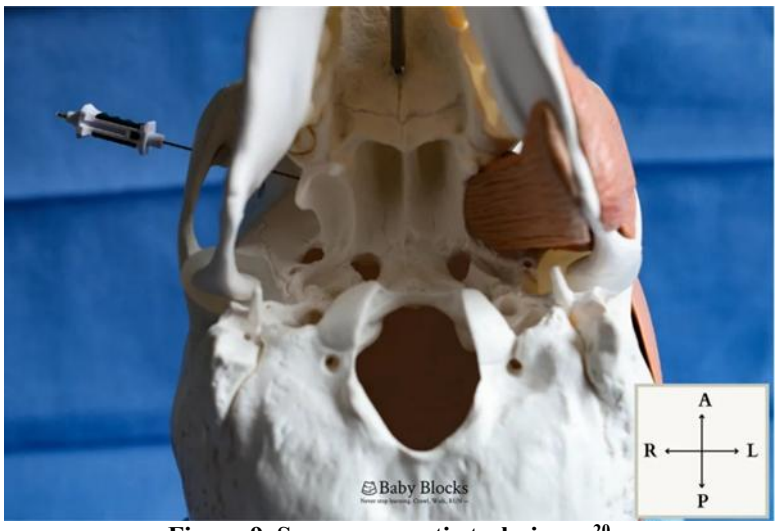


Figure 9. Suprazygomatic technique. [20]

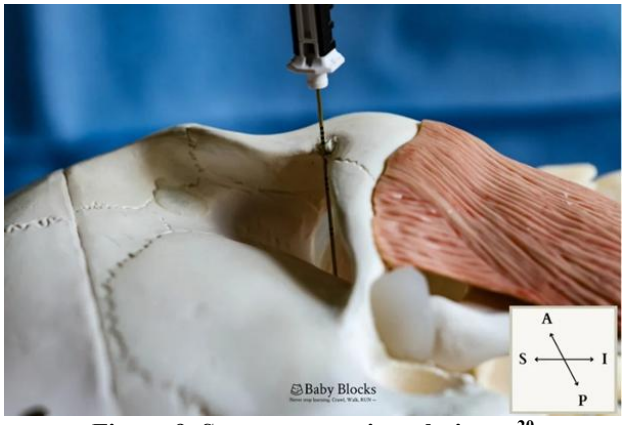


Figure 9. Suprazygomatic technique. [20]

Figure 11. Application of the toxin according to the technique described. (right side)

Figure 12. Application of the toxin according to the technique described. (left side)

The objective was to diffuse botulinum toxin in the region to block the transmission of nociceptive stimuli.

The patient was observed for 5-10 minutes to confirm the onset of diffusion and monitor for possible complications, particularly hematoma.

NABOTA® (Daewoong's botulinum toxin type A; Daewoong Pharmaceutical, Seoul, Korea) is a new formulation of botulinum toxin type A derived from wild-type Clostridium botulinum Hall A. NABOTA is produced by strictly controlled anaerobic fermentation and high-efficiency purification using size exclusion high-performance liquid chromatography with a single peak at 900 kDa (>98%).[21,22]

In 2005, onabotulinumtoxin A (BoNT/A) was reported to be effective for cases of trigeminal neuralgia that did not respond to other therapies. The therapeutic effect of BoNT/A on TN was first mentioned after a chance discovery by Wang and Jankovic.[23,24,25]

Regarding the neurobiological mechanisms responsible for the antinociceptive activity of BoNT/A, after being injected into the subcutaneous tissue, BoNT/A is taken up by endocytosis in the nerve terminals of C fibers and travels by retrograde axonal transport through the trigeminal ganglion to the spinal trigeminal nucleus. One of the main antinociceptive effects of BoNT/A is likely related to its ability to block the transmission of nociceptive stimuli to the centers that modulate nociception.[25,26,27]

BoNT/A negatively modulates nociceptive neurotransmitters. Its action can be preganglionic, on CGRP, substance P, and glutamate, or postganglionic, at synaptic terminals, blocking the release of norepinephrine (NE) and adenosine triphosphate (ATP). A third mechanism may involve internal and external sensory adaptation. In external neural adaptation, BoNT/A reduces the secretion of neuroeffector substances from mast cells, blood vessel endothelium, and sensory nerve tissue.[25,28,29,30,31]

One of the key factors that may explain the antinociceptive action of BoNT/A in combating trigeminal neuralgia is its ability to regulate internal sensory adaptation, which occurs through the control of vesicular traffic, directly impacting the ion channels of the transient receptor potential (TRP). TRPs function as integrators of different stimuli and signaling pathways. Dysfunction of these channels can lead to thermal hyperalgesia and allodynia in pathological pain contexts, such as trigeminal neuropathy. Among these receptors, those that have the potential to be used in the treatment of trigeminal neuralgia include TRPV1, TRPV2, TRPV4, TRPM3, TRPM8, and TRPA1.[32,33]

After the application, we adjusted the patient's returns at 30, 60, 90, and 120 days. Thirty-five days after the application, the patient reported no more pain, and we began weaning her off the medications. At 90 days, she was no longer using any oral or intravenous medication. At the last consultation, 120 days later, she had no episodes of pain and was not taking any oral or intravenous medication. The patient is still under control.

The differential diagnosis of TN is clinical, based on detailed history and examination. Although often considered a simple diagnosis, its differential diagnosis can be challenging, given the considerable overlap with other neuropathic and neuralgiform headaches and orofacial pain disorders. Dental causes include dental caries, pulpitis, tooth sensitivity, periodontal disease, periocoronitis, tooth fractures, and alveolar osteitis.36 Other causes such as sinus disorders are also reported. In rare cases, sialolithiasis can lead to complications that directly affect the lingual nerve by compression, resulting in trigeminal neuropathy, characterized by episodic hemilingual numbness, submandibular swelling, and sialorrhea, without the traditional paroxysmal attacks of TN, but with significant chronic neuropathic afferents.[37]

Temporomandibular disorders (TMD), also known as temporomandibular joint (TMJ) dysfunction, encompass a spectrum of conditions that affect the temporomandibular joint, the masticatory muscles, and associated structures, resulting in orofacial pain, limited jaw movement, joint noises (such as clicks or pops), and headaches. TMDs are multifactorial, involving factors such as stress, trauma, inadequate dental occlusion, and parafunctional habits (e.g., bruxism), affecting approximately 5-12% of the population, with a higher prevalence in young women. Trigeminal neuralgia (TN), on the other hand, is a chronic neuropathy characterized by sudden and intense attacks of unilateral facial pain, in the form of electric shocks, distributed along the branches of the trigeminal nerve (V1: ophthalmic; V2: maxillary; V3: mandibular). The primary cause is vascular compression at the nerve root, but secondary forms include lesions or inflammation. TN is rare, with an incidence of 4-28 cases per 100,000 inhabitants/year.[37,38]

The relationship between TMD and trigeminal neuralgia lies mainly in the overlap of facial pain symptoms, which often leads to diagnostic confusion. Both can cause severe pain in the preauricular, mandibular, or maxillary region, exacerbated by jaw movements, chewing, or touch. In TMD, pain is typically musculoskeletal, continuous or intermittent, associated with dysfunction (e.g., mouth opening limitation <40 mm, mandibular deviations) and local signs such as tenderness on palpation of the masseter or pterygoid muscles. In contrast, TN presents with paroxysmal, short-lasting pain (seconds to minutes), triggered by non-nociceptive stimuli (e.g., brushing teeth, facial wind), without obvious mechanical dysfunction and with asymptomatic periods between attacks. The literature emphasizes that TMDs are one of the main differential conditions for NT, especially in the atypical variant of NT (constant pain with paroxysmal components), where the distinction can be challenging.[37,38,39]

Regarding association mechanisms, there is no evidence of direct causality between TMD and primary TN, but indirect interactions occur; peripheral sensitization: chronic inflammation in TMD can irritate sensory branches of the trigeminal nerve (e.g., auriculotemporal nerve), leading to neuropathic pain that mimics secondary TN. This is more common in myofascial TMD, where muscle hyperalgesia amplifies nociceptive signals; common factors: conditions such as stress and anxiety predispose both TMD and exacerbation of TN, possibly via central sensitization mechanisms (e.g., wind-up phenomenon in the dorsal horn of the spinal cord); rare complications: in severe cases of TMD (e.g., disc displacement with reduction), mechanical compression may affect the trigeminal nerve, resulting in trigeminal neuropathy (TNO), which differs from TN in that it includes numbness or paresthesia, but with the potential for excruciating pain; misdiagnosis and iatrogenesis: dental procedures for TMD (e.g., occlusal adjustments) can injure branches of the trigeminal nerve, triggering or aggravating TN. Epidemiologically, there is no significant increase in TN in patients with TMD, but co-occurrence is reported in up to 10-15% of cases of chronic orofacial pain, highlighting the need to rule out TMD before diagnosing TN. [37,38,39,40]

Various neuropathic causes have been reported, among the most relevant being glossopharyngeal neuralgia, intermediate nerve neuralgia, and postherpetic neuralgia.[37]

Postherpetic neuralgia (PHN) is a common painful complication of herpes zoster, also known as shingles, caused by the varicella-zoster virus (VZV), the same virus responsible for chickenpox. After a primary chickenpox infection, the virus can remain dormant in the sensory ganglia and reactivate years later, leading to shingles. PHN occurs when pain persists or reappears after the acute episode of rash and skin lesions, typically defined as neuropathic pain lasting more than 3 months after the resolution of vesicular eruptions. PHN mainly affects individuals over 50 years of age, with incidence increasing with age due to immunosenescence (decline in cellular immunity). It is estimated that 10-18% of patients with herpes zoster develop PHN, being more prevalent in the elderly (up to 30% in those over 80 years of age) and in immunosuppressed individuals. Risk factors include: advanced age, severe pain during the acute episode of zoster, extent of skin lesions, involvement of certain dermatomes (e.g., thoracic or ophthalmic), and delay in antiviral treatment (such as acyclovir, valacyclovir, or famciclovir).[41,42]

NPH results from persistent neuropathic damage to sensory nerve fibers. During herpes zoster, VZV causes ganglionic inflammation, neuronal necrosis, and peripheral and central sensitization. This leads to hyperalgesia (increased pain from painful stimuli), allodynia (pain from non-painful stimuli), and chronic spontaneous pain. [41,42,43]

In an analytical study conducted in the neurosurgery department of Yantai Yuhuangding Hospital, Yantai, Shandong, China, from January to April 2024, Mendelian randomization (MR) was used to determine the causal relationship between hypothyroidism and trigeminal neuralgia (TN). Fifty single nucleotide polymorphisms (SNPs) related to hypothyroidism were retrieved as instrumental variables (IVs) from genome-wide association studies (GWAS). The MR analysis was conducted using summary statistics from GWAS in European individuals. The inverse variance weighted (IVW) method was the main tool for finding causality. Other RM methods corroborated the IVW results and helped confirm the causality results. Additional methods strengthened the findings. Finally, multiple sensitivity studies were conducted to assess stability, heterogeneity, and horizontal pleiotropy. The IVW method demonstrated a strong link between hypothyroidism and NT ($p = 0.009$). MR-Egger regression revealed that directional pleiotropy was unlikely to bias the results ($p = 0.351$). Evidence of a causal relationship between hypothyroidism and NT was also found using the weighted median ($p = 0.008$) and weighted mode ($p = 0.016$) approaches. Although the simple model showed a null causal effect, it showed a trend similar to that of several other methods. The results of the MR study corroborate the possibility that hypothyroidism and the risk of NT are directly related.[44]

Encephalopathy associated with autoimmune thyroid disease, currently known as Hashimoto's encephalopathy, but also defined as corticosteroid-responsive encephalopathy associated with autoimmune thyroiditis, is a relatively rare condition observed in a small percentage of patients with autoimmune thyroid disease. It consists of a subacute, recurrent-remitting, steroid-responsive encephalopathy characterized by proliferative neurological and neuropsychiatric symptoms, diffuse electroencephalographic abnormalities, and increased titers of antithyroid antibodies in serum and/or cerebrospinal fluid. Most cases presenting this neurological complication are affected by Hashimoto's thyroiditis or, less frequently, by other autoimmune thyroid diseases, mainly Graves' disease.[45,46,47]

The pathogenesis of this encephalopathy is still unknown and widely debated, due to its extremely varied clinical presentation, possibly related to different etiological and pathophysiological mechanisms, as confirmed by the two clinical cases reported in this article. However, an autoimmune etiology is very likely, given the well-established favorable response to corticosteroid administration. Both vasculitis and autoimmunity directed against common thyroid brain antigens represent the most likely etiological pathways.[45,46,47]

Hashimoto's encephalopathy (HE) is an uncommon and clinically varied condition that is related to the presence of thyroid autoantibodies. It is increasingly recognized that this condition can be a significant and

treatable cause of autoimmune encephalopathy. In the context of HE with seizures, thyroid-related antibodies such as antithyroid peroxidase (TPO), antithyroglobulin (TG), and antithyrotropin receptor (TR) antibodies have been identified. Although the presence of these antibodies is essential to confirm the diagnosis of HE, their role in the origin of the disease is not entirely clear. It is possible that these antibodies are not direct factors in the pathophysiological processes of EH, but rather characteristics associated with this condition. Seizures occur in about two-thirds of individuals diagnosed with EH, and conventional anticonvulsant treatments often fail to provide relief. Some patients do not achieve a satisfactory response with any antiepileptic medication. Immunotherapy treatment has been shown to be effective in controlling seizures. Changes identified in electroencephalograms and imaging tests are not unique to HE and can be seen in other forms of encephalopathy. However, when Hashimoto's encephalopathy is diagnosed and treated appropriately, the prognosis for most patients is generally favorable.[48]

Patients suffering from trigeminal neuralgia (TN) may experience adverse effects resulting from the use of psychoactive substances, restrictions on neurosurgical interventions, or decreased effectiveness of these therapies. Botulinum neurotoxin type A (BTN/A) has been shown to be beneficial in relieving TN, although this conclusion has generated controversy. A narrative and qualitative study of the existing literature is presented. Approximately 90% of patients treated with BTA reported improvement, a percentage that exceeds what would be expected from the placebo effect related to BTA in other headaches. Furthermore, NTB/A has been associated with a low rate of side effects, which are usually transient. Although most studies consist of case reports, clinical series, and open trials, recent controlled and randomized investigations reaffirm the efficacy of NTB/A in NT. This evidence, combined with a deeper understanding of the pain relief mechanisms provided by NTB/A and its effectiveness in other painful conditions, consolidates NTB/A as a viable therapeutic alternative for NT.[27,49]

For patients who do not respond well to conventional pharmacotherapy for the treatment of trigeminal neuralgia, there is growing clinical evidence indicating that botulinum toxin type A injections administered into the trigeminal ganglion can provide pain relief lasting from weeks to months. An alternative involves administering these injections into the Meckel's cave, where a needle is inserted through the pterygopalatine fossa, with the aid of fluoroscopy to guide and ensure the correct position of the needle. However, there is evidence that botulinum toxin can cross nerve synapses, making direct injection into the trigeminal ganglion unnecessary. We describe two cases of patients with confirmed diagnosis of trigeminal neuralgia who received botulinum toxin type A injections in the mental foramen area, resulting in pain relief for six months or more. The application in the mental foramen proved to be significantly simpler than injections performed directly into the trigeminal ganglion, and the results observed in both patients treated with this method were similar to what would be expected from conventional fluoroscopy-guided injections. Although further investigation is needed, these reports indicate that a less invasive approach may be sufficient for the management of pain associated with trigeminal neuralgia.[27,49,50]

Botulinum toxin type A, which is a Food and Drug Administration (FDA)-approved treatment for chronic migraine, has been used off-label by neurologists as a safe alternative for treating trigeminal neuralgia (TN). Several smaller-scale studies have evaluated the efficacy and clinical safety of onabotulinumtoxin A, revealing that it may represent a safe and effective option for these patients, especially those who cannot tolerate medications or who are not candidates for neurological surgery. In addition to promoting a decrease in pain intensity and frequency of attacks, there is also data supporting an improvement in quality of life indicators after onabotulinumtoxin A injections for TN compared to placebo.[51]

III. Conclusion

In conclusion, the case report demonstrated that the injection technique using NABOTA® brand type A botulinum toxin was highly effective, especially in patients who did not respond to conventional drug treatment.

The correlation between trigeminal neuralgia, Hashimoto's thyroiditis, and Hashimoto's encephalopathy is discussed in the literature, and the case presented suggests a strong relationship.

Our principle was not to treat the two autoimmune diseases, but rather to seek an alternative for the alternative and/or corroborative treatment of trigeminal neuralgia.

After the application of botulinum toxin type A, using the technique described, the patient did not experience complications such as bruising, paralysis, paresthesia, and/or facial ptosis. She reported a 100% improvement in pain episodes, without hospital medication interventions, and over the course of four months, we promoted the complete weaning of traditional medications.

The patient is undergoing monthly follow-up. We are evaluating the need to adjust the dose and the intervals between application sessions, given the durability of the desired effects achieved with the first application.

Neuromodulation of trigeminal neuralgia with the application of botulinum toxin A proved to be effective in this specific case, but traditional therapies are the first-line choices and further studies are suggested.

Trigeminal neuralgia interferes with various aspects of patients' lives. From this perspective, early diagnosis is important, paying attention to the patient's clinical history, differential diagnoses, and associated comorbidities. Treatment should address the biological aspect of the disease and the patient's psychological state, with the aim of reducing pain and providing a better quality of life.

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