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FACIAL FLUSHING (HARLEQUIN SYNDROME) FOLLOWING RADIOFREQUENCY ABLATION OF THE TRIGEMINAL GANGLION: A CASE REPORT

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Background: Harlequin syndrome (HS) is a rare clinical manifestation characterized by unilateral sweating and flushing of the face, neck, upper chest, and/or arm, which results from a dysfunction of the autonomic nervous system. Symptoms may worsen with heat, stress, strenuous exercise, or emotional reactions. The syndrome is also associated with traumatic or vascular injuries, tumors, or complications from medical procedures, such as radiofrequency ablation (RFA), surgery, intravenous cannulation, among others.

Case Report: A 41-year-old woman with trigeminal neuralgia of the right maxillary and mandibular branches underwent RFA treatment. While the pain resolved completely following the procedure, the patient developed hemifacial flushing and mild sweating (HS). The facial flushing was successfully treated using botulinum neurotoxin type A injections (100 units), with an 80% improvement. A brain magnetic resonance imaging was ordered, which revealed no significant abnormalities that could account for the patient's clinical signs and symptoms.

Conclusions: This case underscores the importance of a multidisciplinary follow-up approach for the identification and management of autonomic nervous system complications after ablative procedures of the trigeminal ganglion.

Key words: Harlequin syndrome, ablation, radiofrequency, trigeminal neuralgia, botulinum neurotoxin type A

BACKGROUND

Trigeminal neuralgia (TN) is a facial pain syndrome caused by an injury or disease of the trigeminal nerve (V). The condition, which may involve one or several branches of the nerve, is characterized by severe, recurrent, unilateral episodes of facial pain. These brief paroxysms, which can last between one second and two minutes, are oftentimes likened to electric shocks.

TN can have a prevalence of 0.16% to 0.3% and a yearly incidence of 4-19 cases per 100,000 persons. It mainly affects women (3:2) and the likelihood of suffering from the condition may increase with age (1,2).

The trigeminal sensory system is said to be responsible for conveying sensory information to the head and facial region, mainly through peripheral structures, like the trigeminal ganglia and the V, as well as central structures, including the trigeminal brainstem sensory nuclear complex.

The V divides into 3 branches: ophthalmic (V1), maxillary (V2), and mandibular (V3). The V1 and V2 branches

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are mainly sensory, while the V3 branch is mixed, with motor fibers innervating the jaw muscles (3).

Radiofrequency ablation (RFA) of the trigeminal ganglion is a minimally invasive interventional technique used in the treatment of refractory facial pain of trigeminal origin (4).

According to some studies (5,6), the use of RFA is favored given its advantages over other procedures, which include an efficacy of over 90% in terms of pain relief, as well as less tissue trauma, which results in a faster recovery.

While the procedure is generally safe and effective, several complications may arise, as referenced in reports by different authors. Note, however, that none of these meta-analyses include Harlequin syndrome (HS) as a complication of RFA, which makes its study all the more interesting (7,8).

This rare autonomic disorder presents as flushing and sweating of mainly the face, neck, or upper chest. Some have suggested it may be due to a sympathetic dysfunction of the vasomotor and secretory fibers that innervate these areas (9).

This case report describes the facial flushing and sweating secondary to HS observed in a patient with TN following RFA of the trigeminal ganglion. The patient's clinical course, as well as the implemented therapeutic strategies, are discussed. Likewise, a review of the relevant literature is presented to promote a more thorough comprehension of this rare postprocedural complication and its management.

Study Description

Following approval of 96.230.1.3.2.1.2/395/2024, granted by the ethics committee of the Centro Médico Nacional 20 de Noviembre, a member of the Mexican Institute of Social Security and Services for Government Employees hospital network, and with the prior signed informed consent from the patient, we present the case of a woman who was evaluated at the hospital's Pain Management Department. At that time, she exhibited clinical criteria for TN, as outlined by the International Headache Society (10). The patient was treated using trigeminal ganglion RFA and subsequently developed this complication, which has not been reported in the literature.

CASE PRESENTATION

A 41-year-old woman had been diagnosed with TN of the right V2 and V3 branches since 2017. She was free of general or central nervous system comorbidities and had a surgical history of right trigeminal microvascular decompression, performed at the Neurosurgery Service in 2018. The procedure took place without any complications and provided full pain relief for 4 years.

In 2022, the patient reported recurrence of pain, which increased gradually and affected the region innervated by the right V2 and V3 branches. The pain presented as a piercing sensation, accompanied by intermittent paroxysms of severe pain (electric shock-like). It worsened with temperature changes, as well as V3 movements, and interfered with daily activities. At the time of assessment, the patient rated her pain as 8-10/10 on the Numeric Rating Scale (NRS-11).

The neurosurgery team resumed conservative treatment with neuromodulators (200 mg oral carbamazepine, 3 times a day; 75 mg oral pregabalin, 2 times a day) and opioids (including 50 mg tramadol solution drops for oral administration, 3 times a day as a rescue therapy), but no adequate pain relief was achieved. Additionally, the patient experienced side effects, such as drowsiness and constipation.

In view of the above, a consultation with our service was requested. Considering the patient's clinical history, her poor response to conservative pharmacological treatment, the nature and intensity of the pain, as well as the presence of side effects, the option to perform a fluoroscopy-guided RFA of the right trigeminal ganglion was discussed with the patient. The risks and possible complications were explained to her and she agreed to the procedure.

The interventional procedure was scheduled for late April 2024. The patient was brought to the fluoroscopy room, placed supine with the neck hyperextended, and under intravenous (IV) sedation using 50 µg of fentanyl and 1 mg of midazolam. Likewise, noninvasive monitoring (basic anesthetic monitoring) was instituted. The foramen ovale was first localized utilizing fluoroscopic guidance in a posteroanterior radiological view. The C-arm was tilted cranially until a submental radiological view was obtained. The C-arm was then rotated into a contralateral oblique radiological view by 15° to 20° until the foramen ovale was visualized medially to the coronoid process and above the line that forms the petrous part of the temporal bone (11). Once the entry point was radiologically localized in a coaxial view, the cheek skin and the subcutaneous tissue 2.5 cm lateral to the commissura labialis (corner of the mouth) were infiltrated with a local anesthetic (8 mL 1% lidocaine)

for the procedure. A 10-cm, 22-G RFA needle with a 10-mm bent active tip was subsequently introduced under fluoroscopy guidance and advanced past the base of the foramen ovale. Then a local anesthetic (.5 mL of 1% lidocaine) was administered. Once we gained access to the foramen ovale, a lateral fluoroscopic view was obtained to visualize the depth of the needle tip, which was advanced until the clivus bone was reached. Proper positioning of the needle tip was confirmed applying 0.5 V/2 Hz motor and 0.7 V/50 Hz sensory stimulation on the right V2 and V3 branches (Fig. 1).

Once the site of the needle tip was confirmed, RFA was performed using two 75-second cycles at 80°C on each affected trigeminal branch. Before removing the needle, we administered 2 mg (0.5 mL volume) of non-particulate dexamethasone. The procedure was deemed completed, with no complications observed at that time.

The patient returned for assessment 5 days after the procedure, reporting full pain relief. She had hypoesthesia of the V2 and V3 branches. Additionally, right (ipsilateral) hemifacial flushing and mild sweating had developed. Therefore, a brain magnetic resonance imaging (MRI) was ordered to rule out any possible injuries.

The patient returned 2 weeks later for assessment. While she reported proper pain control (1/10 on the NRS-11), the right hemifacial flushing and sweating continued (Fig. 2).

The brain MRI revealed no significant abnormalities that could account for the clinical signs and symptoms.

Based on the patient's clinical course and on the nature of the facial flushing, she was diagnosed with post-procedural HS. Application of botulinum neurotoxin type A (BoNT/A) injections around the red areas was recommended as a treatment, and the patient agreed.

We proceeded to apply 100 injection units into 15 injection sites, distributed around the right V2 and V3 branches. No complications were noted.

The patient was reassessed 2 weeks after the procedure. She reported full trigeminal pain relief, so the medication was withdrawn. Likewise, there was a significant clinical improvement of the facial flushing and sweating, with a mild worsening of the flushing occurring only in hot weather, according to the patient (Fig. 3).

DISCUSSION

HS is a rare disease described by Lance et al (12) in 1988. The authors demonstrated HS is an autonomic nervous system disorder, specifically affecting the preganglionic sympathetic pathways.

The main symptoms include sudden unilateral flushing and sweating of the face, neck, upper chest, and/

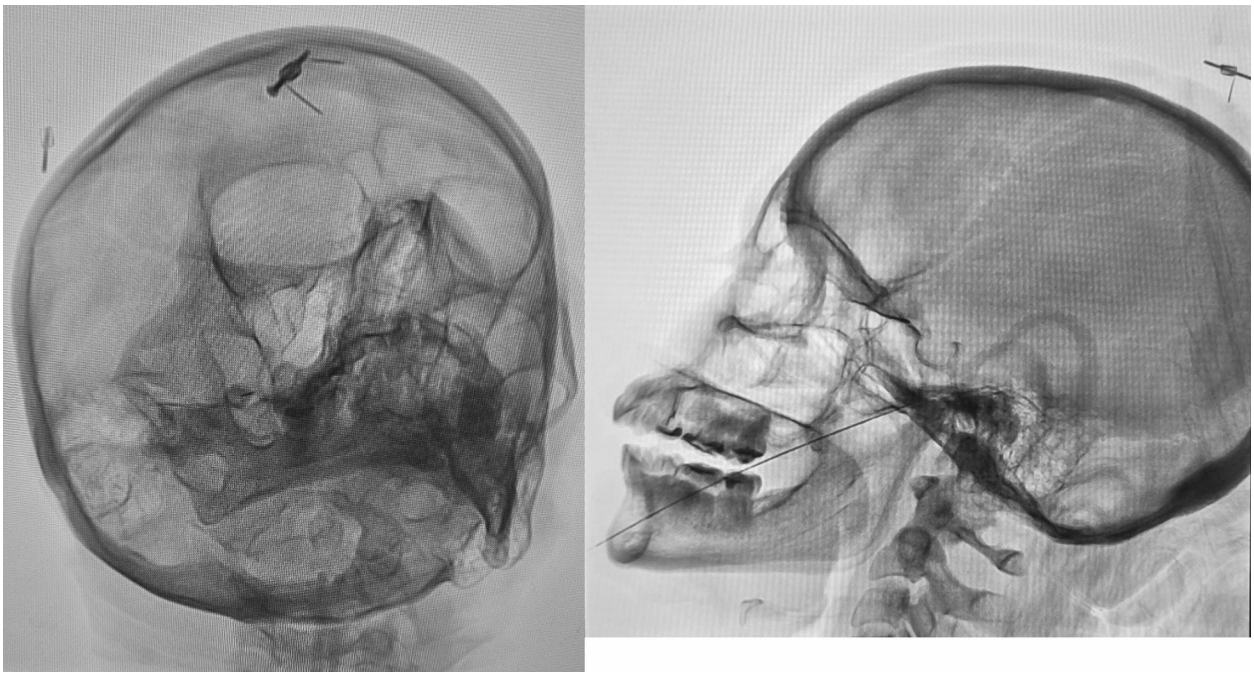

Fig. 1. Fluoroscopic posteroanterior view (PA) and lateral view, showing cannula placement for RFA.

or arm, as well as contralateral anhidrosis, which may worsen in response to heat, stress, strenuous exercise, emotional reactions, or spicy foods.

According to the literature (13-17), 54.6% of cases are idiopathic, while 44.5% are associated with traumatic or vascular injuries, tumors, or complications from medical and anesthetic procedures, surgery, or IV cannulation, among others. After reviewing the medical literature, we did not find any evidence suggesting a direct relationship between vascular decompression and HS.

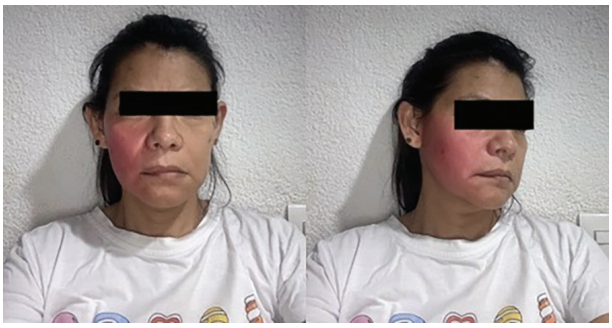

Fig. 2. Clinical follow-up demonstrating right hemifacial flushing following RFA.

A study conducted by Bremner et al (18) on 39 patients with HS revealed other pathologies may directly or indirectly trigger the development of the disorder. These include multiple system atrophy, Guillain-Barré syndrome, idiopathic dysautonomia, diabetes mellitus, lupus erythematosus, TN, or vasovagal attacks (18).

Regarding percutaneous interventional procedures of the trigeminal ganglion, the heat generated by the RF, together with the neuralgia itself, may disrupt the function of both sympathetic and parasympathetic nerve fibers, which may have contributed to the development of this syndrome in our patient. Knowing the anatomy of the V is very important, as that may help to identify the cause leading to the development of this dysautonomia.

The V is a mixed nerve, although sensory fibers are predominant. It supplies sensory innervation to the hemiface and motor innervation to the V3 region. Facial

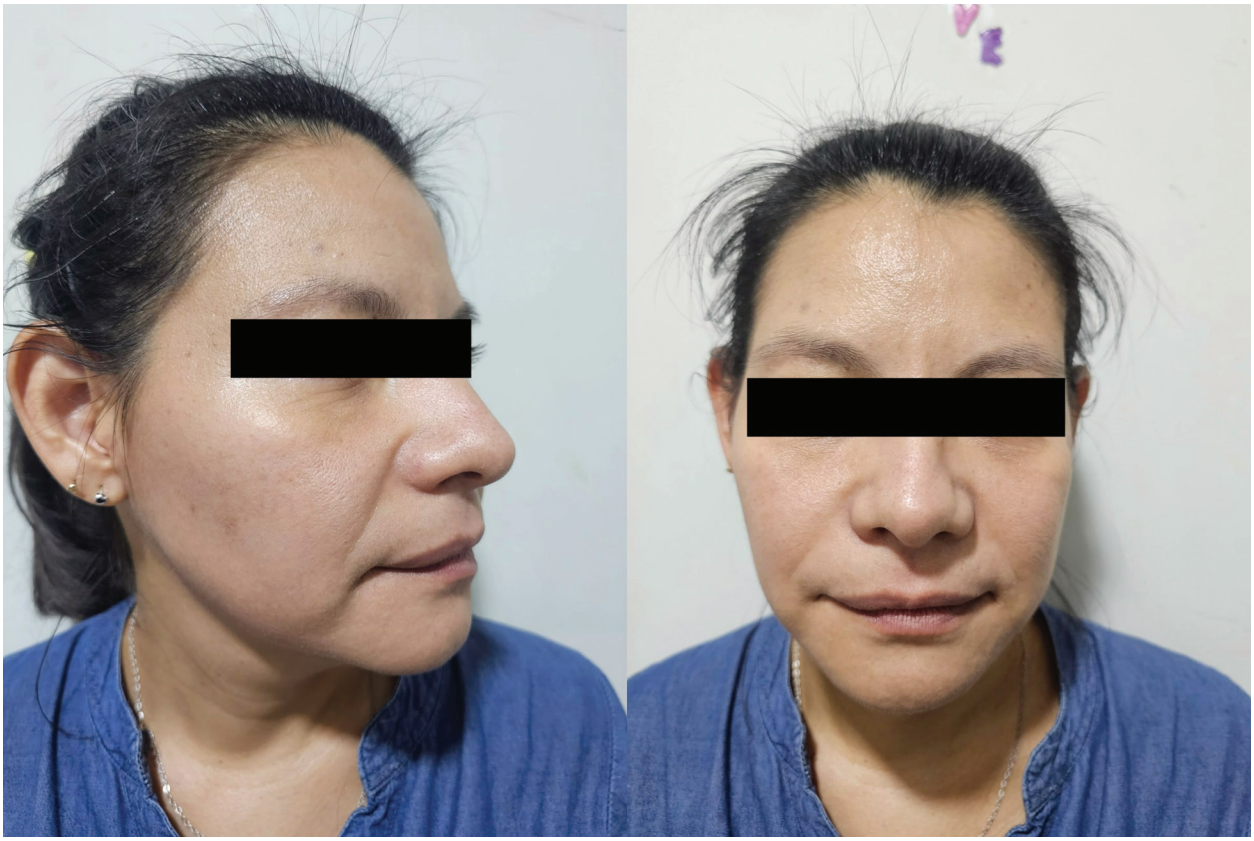

Fig. 3. Two-week follow-up after BoNT/A injection showing improved facial flushing and sweating.

vasodilation is known to be caused by the inhibition of preganglionic sympathetic neurons that exit the spinal cord at T2/T3 and terminate in the superior cervical ganglion. The postganglionic fibers are distributed to the forehead via the internal carotid plexus and to the rest of the face via branches of the external carotid artery. The deep petrosal nerve and the greater petrosal nerve also play a role.

Based on the anatomy, one of the possible causes of the HS case described in this report may be the activation of postganglionic parasympathetic nerve fibers, which synapse with the sphenopalatine ganglion, producing a vasodilation response in the affected areas.

It is worth noting that the V2 gives off 2 sensory branches to the sphenopalatine ganglion and that most of the soluble phosphate glass fibers perform parasympathetic nervous system functions. These originate from the facial nerve as follows: the preganglionic fibers of the greater petrosal nerve synapse both with postganglionic parasympathetic fibers that cause vasodilation probably by release of vasoactive intestinal polypeptide and nitric oxide, and with secretory efferent fibers, whose action is mediated via a trigeminal facial reflex.

Both the sympathetic and the parasympathetic efferent fibers transmit information via the infraorbital, superior alveolar, and nasopalatine, as well as greater and lesser palatine nerves (18,19).

Drummond et al (20) conducted a study on 16 patients who underwent thermocoagulation of the trigeminal ganglion and were monitored to determine the cause of facial flushing utilizing thermography. The possible causes, as reported by the authors, included stimulation of vasodilator pathways, antidromic release of chemical transmitters, such as substance P or calcitonin gene-related peptide, among other vasoactive substances in the V, as well as stimulation of other nerves, including the superficial petrosal nerve, for example (20).

According to several studies (21-23), the main complications following RFA of the trigeminal ganglion include hypoesthesia, dysesthesia, painful anesthesia, masticatory muscle weakness, facial sweating, corneal damage, otalgia, hypoacusis, vascular injuries, and cardiovascular complications, among others. Note, however, that none of these studies references HS as a complication from the procedure.

A correct diagnosis of HS is essential to decide on proper treatment. Therefore, in this case, a detailed clinical history was taken and a thorough physical examination conducted in order to rule out the presence of diseases that could relate to the development of HS. Likewise, we ordered complementary imaging studies, including MRI of the brain and spine, to rule out the presence of tumors, infarctions, or other conditions (24).

Our patient's MRI revealed no injuries, which confirmed the facial flushing and sweating did not associate with significant structural damage, but rather with a postprocedural autonomic dysfunction likely caused by the temperature used, the lesion duration in the RFA cycles, or the nerve dysfunction due to the TN itself.

While some authors report spontaneous remission of the flushing and sweating over the short term (25), the use of treatment alternatives, such as stellate ganglion blocks, in patients whose symptoms do not remit spontaneously, has also been described (26).

The use of BoNT/A was shown to be an effective strategy for the reduction of HS-related facial flushing and sweating (27).

It is worth noting that in most patients with HS, no treatment is necessary. However, considering the physical and emotional discomfort the patient was experiencing as a result of the facial flushing and sweating, BoNT/A injections were chosen over other previously mentioned interventional procedures, in view of the effectiveness, lower risk of complications, and longer duration of the former.

The significant clinical improvement of the facial flushing and sweating after the application of BoNT/A injections to our patient suggests the treatment may play a valuable therapeutic role in the management of this dysautonomia. Future conduct of long-term studies in a wider population is under consideration, as that would provide better medical evidence concerning this treatment.

Based on this case report, it is important to consider that while RFA may be a safe and effective treatment against trigeminal pain, patient observation before, during, and after the procedure is essential not only for the assessment of pain relief but also for the early identification and management of possible autonomic complications, as in our patient's case.

CONCLUSIONS

In conclusion, HS is an unusual disorder that should be considered a possible complication of trigeminal ganglion RFA. Postprocedural supervision, together with the corresponding thorough evaluation, is re-

quired to determine the most appropriate therapeutic approach for affected patients. Early detection and proper management of autonomic complications may significantly impact the patients' clinical outcomes and majorly improve their quality of life.

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