Review Article

Tenth case of bilateral hemifacial spasm treated by microvascular decompression: Review of the pathophysiology

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Abstract

**Background:** Bilateral hemifacial spasm (BHFS) is a rare neurological syndrome whose diagnosis depends on excluding other facial dyskinesias. We present a case of BHFS along with a literature review.

**Methods:** A 64-year-old white, hypertensive male reported involuntary left hemiface contractions in 2001 (aged 50). In 2007, right hemifacial symptoms appeared, without spasm remission during sleep. Botulinum toxin type A application produced partial temporary improvement. Left microvascular decompression (MVD) was performed in August 2013, followed by right MVD in May 2014, with excellent results. Follow-up in March 2016 showed complete cessation of spasms without medication.

**Results:** The literature confirms nine BHFS cases bilaterally treated by MVD, a definitive surgical option with minimal complications. Regarding HFS pathophysiology, ectopic firing and ephaptic transmissions originate in the root exit zone (REZ) of the facial nerve, due to neurovascular compression (NVC), orthodromically stimulate facial muscles and antidromically stimulate the facial nerve nucleus; this hyperexcitation continuously stimulates the facial muscles. These activated muscles can trigger somatosensory afferent skin nerve impulses and neuromuscular spindles from the trigeminal nerve, which, after transiting the Gasser ganglion and trigeminal nucleus, reach the somatosensory medial posterior ventral nucleus of the contralateral thalamus as well as the somatosensory cortical area of the face. Once activated, this area can stimulate the motor and supplementary motor areas (extrapyramidal and basal ganglia system), activating the motoneurons of the facial nerve nucleus and peripherally stimulating the facial muscles.

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INTRODUCTION

Hemifacial spasm (HFS) is a common, involuntary, intermittent movement disorder induced in most cases by neurovascular compression (NVC) in the root exit zone (REZ) of the ipsilateral facial nerve in the brainstem. Bilateral involvement of the face is a very rare event, ranging from 0.6 to 5% of cases of facial spasm. To our knowledge, this is the tenth case of bilateral HFS (BHFS) treated by microvascular decompression (MVD) to be described. A comprehensive review of the literature follows the case report.

MATERIALS AND METHODS/CASE MATERIAL

Case report

A 64-year-old, white, hypertensive male reported the onset of involuntary contractions of the left orbicularis muscle in 2001 (aged 50), which progressed to contractions of all the muscles in this hemiface. In 2007, symptoms also appeared in the right orbicularis muscle and again progressed to all muscles in this hemiface. The patient reported no remission of spasms in either hemiface during sleep. Carbamazepine was prescribed (200 mg BID) with slight improvement in the symptoms initially, followed by relapses. Next, he was submitted to applications of botulinum toxin type A (BTX-A), which produced partial temporary improvement.

The course of the disease included bilateral progressive hearing loss. In September 2012, he was submitted to audiometry, which showed mild to moderate sensorineural loss (descending audiometric curve) in both ears. Magnetic resonance imaging (MRI) was performed in October 2012 and showed that the left vertebral artery followed a tortuous and elongated path, compressing and dislocating ipsilateral cranial nerves VII and VIII, compatible with neurovascular conflict, and discrete tortuosity of the right posterior inferior cerebellar artery (PICA), touching the brainstem along the REZ of the VII-VIII nerve complex on the right side.

The patient was submitted to left MVD in August 2013 because the symptoms were more pronounced in this hemiface. He evolved with complete cessation of spasms in the left hemiface, presenting moderate postoperative peripheral facial paresis with progressive and full improvement in December, though the left hypoacusis remained. In May 2014, he was submitted to right MVD, again presenting moderate postoperative peripheral facial paresis, with full recovery in 3 weeks. All right HFS ceased, but the previous right hypoacusis remained.

He remained free from facial spasms until August 2014, when he began to experience mild relapse in the right hemiface, with two to three fleeting spasms of the orbicularis muscle per hour and no episodes during sleep, which had previously been an important complaint. His health status remained the same during 19 months of follow-up. In March 2016, he returned for evaluation showing cessation of spasms without medication. The hearing deficits did not improve.

RESULTS AND DISCUSSION

Epidemiology

The annual incidence of HFS is 0.81 per 100,000 in women and 0.74 per 100,000 in men. The average prevalence is 11 per 100,000 in the general population. Women develop the disease in 14.5 per 100,000 individuals and men in 7.4 per 100,000 individuals, thus female: male distribution is 2:1. Prevalence increases with age, affecting 37.9 per 100,000 inhabitants in those over 70 years old.

A systematic review of 5,685 cases of HFS submitted to MVD showed 69% were female and 31% were male. Patient mean age at surgery was 54 (45–58) years old. The mean duration of symptoms was 6.5 (4.2–10.7) years.

Among 6,029 patients with HFS submitted to MVD, 66.82% were female and 33.18% were male. Patient mean age at surgery was 54 (45–58) years old. The mean duration of symptoms was 6.5 (4.2–10.7) years.

Cases of bilateral hemifacial spasm in the literature

To our knowledge, only 102 cases of BHFS have been reported [Table 2] and of these, only 10 cases were submitted to bilateral MVD, including our case.

In cases of BHFS, following a highly variable latency period of approximately 33–100 months, the spasms, which initially begin in one hemiface, progress to the contralateral side. In our case, the interval was 6 years (72 months). The patient then goes on to present involuntary painless asymmetric asynchronous facial

Conclusions: We believe that bilateral MVD is the best approach in cases of BHFS.

Key Words: Bilateral hemifacial spasm, botulinum toxin, microvascular decompression
### Table 1: Epidemiology of patients with HFS

| Authors and year (location) | Number of HFS/MVD | Females/Male (%) | Left/right sides (%) | Mean age/years | Mean duration of symptoms until treatment/years |
|-----------------------------|-------------------|------------------|----------------------|----------------|-----------------------------------------------|
| Huang et al., 1992 (Taipei, Taiwan) | 310 | 46/54 | 54.2/45.8 | 53.4 | - |
| Barker et al., 1995 (Pittsburgh, USA) | 648 | 65/35 | 60/40 | 52 | 8 |
| Zhang et al., 1995 (Guangzhou, China) | 300 | 56.3/43.7 | 44.7/55.3 | - | 6 |
| Payner and Tew, 1996 (Cincinnati, USA) | 34 | 55.9/44.1 | 52.9/47.1 | 52 | 6.8 |
| Ishikawa et al., 2001 (Saitama, Japan) | 175 | 62.9/37.1 | 57.7/42.5 | 53 | 6.8 |
| Samii et al., 2002 (Hannover, Germany) | 143 | 62.3/37.8 | 56.6/43.4 | 54.5 | 6 |
| Li, 2005 (Taipei, Taiwan) | 545 | - | 59.8/40.2 | - | 5.4 |
| Yuan et al., 2005 (Beijing, China) | 1,200 | 59.6/40.4 | 45.3/54.7 | - | ? |
| Han et al., 2009 (Sungnam, Korea) | 77.3/22.7 | 49.5 (3.4 <30 yrs) | - | 7 |
| Hyun et al., 2010 (Seoul, Korea) | 1,174 | 71.1/28.9 | 50.2/49.8 | 48.8 | 5.6 |
| Thirumala et al., 2011 (Pittsburgh, USA) | 293 | 64.8/35.2 | 56/44 | 52.25 | - |
| Rosenstengel et al., 2012 (Greifswald, Germany) | 110 | 62.7/37.3 | 64.45/34.55 | - | 8.1 |
| Total or percentage (%) | 6,574 | 66.82/33.18 | 52.43/47.57 | - | Variations from 5.4 to 8.1 years: mean 6.7 years |
| Miller and Miller, 2012 (North Carolina, USA) Systematic Review | 5,685 | 69/31 | - | 54 | 6.5 |
| Tan et al., 2004 (Singapore) BTX-A | 80 | 67.5/32.5 | - | 56.3 | 4.3 |

### Table 2 (Part I): The 102 cases of bilateral HFS

| Authors and year (location) | Age at onset (Years) | Sex | % BHS | Etiology | Comorbidity | Side of onset | Duration/years | Latency (between R and L sides) | Neuroimaging diagnosis | Therapy | Result | Follow-up |
|-----------------------------|--------------------|-----|--------|----------|-------------|--------------|---------------|-----------------|-----------------|----------|--------|----------|
| Ehni and Woltman, 1945 (USA) | n/a | 68 | 41 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Gardner and Dohn, 1966 (USA) | 62 | n/a | 1M | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Eckman, Kramer and Altrocchi, 1971 (USA) | n/a | 5F, 1M | 1M | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Møller and Møller, 1985 (USA) | 5F | n/a | 0.7 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Holds et al.*, 1990 (USA) | 1F | n/a | 0.7 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Niemeyer Filho, Bezerra and Mufarrej, 1990 (Brazil) | 1F | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Van de Biezenbos et al., 1992 (Netherlands) | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Rosso et al., 1994 (Brazil) | 62 | n/a | 0.7 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a |

- Concomitance case, n/a: not available, AD: Antidepressant, AED: Antiepileptic drug, AICA: Anterior inferior cerebellar artery, MRI: Magnetic resonance imaging, BA: Basilar artery, BHS: Bilateral hemifacial spasm, BP: Bell's paralysis, BTX: Botulinum toxin injections, BZD: Benzodiazepine, CBZ: Carbamazepine, C-dopa: Carbidopamine, CNZ: Clonazepam, CsT: Conservative treatment, CT: Computed tomographic, F: Female, HBP: Hypertension blood pressure, HI: Hearing impairment, M: Male, MI: Marked improvement, MS: Multiple sclerosis, MTP: Methylprednisolone, MVD: Microvascular decompression, PICA: Posterior inferior cerebellar artery, SA: Small arteries, SAV: Small arteries and veins, TN: Trigeminal neuralgia, TXP: Trihexyphenidyl, VA: Vertebral artery, ~: Mean
contractions of short duration. Previous reports and as observed here, the hemiface affected second usually presents with less intense spasms. Studies involving MRI and magnetic resonance angiogram (MRA) of the brain show that, on the hemiface most affected, NVC was more intense.

In series studying HFS, there is a low incidence of BHFS ranging from 0.0% to 5.7% of cases. In our analysis, the mean age of onset of symptoms in BHFS was 58.9 years old, with wide variation between 13 years and 88 years old. The predominance between the sexes in 63 cases, for which data were available, was 76% female and 24% male. Symptoms began in the right hemiface in 36% of these cases and on the left in 64%.

**Etiology of hemifacial spasm**

In a 2012 review of 5,685 cases of HFS submitted to MVD, the NVC frequencies most observed were: 37% by AICA (anterior inferior cerebellar artery), 30% by PICA, and 23% by multiple vessels. Lee et al. (2016) studied 2,040 patients submitted to MVD and reported the frequencies of NVC were: 54.5% by AICA; 27.1% by PICA; and 17.1% by multiple vessels.

It is worth noting that the largest series of HFS cases submitted to MVD are Asian, with the exception of the series studied by Jannetta’s research group, a US reference in MVD. On the other hand, an Asian cohort did not show higher prevalence of HFS in relation to other ethnic groups.

Dou et al. (2014) suggested that reduced space in the posterior fossa could be involved in the genesis of HFS. This type of anatomical feature increases the likelihood of neurovascular conflict due to space restriction in this region.

Secondary causes of HFS are described as 0.0–0.6% of cases in published series, and include the lesions of the cerebellopontine angle, schwannoma, meningioma, epidermoid tumor, lipoma, and arachnoid cyst; and processes in the brain stem, demyelinating diseases, gliomas, cavernomas, arteriovenous malformations, and strokes. Cases of HFS secondary to Paget’s disease have also been described.

Familial HFS due to probable autosomal transmission with low penetrance has been reported. However, a study of HFS in a family showed that hypertension was the most important factor involved in the genesis of late-onset spasms.
The causes of HFS vary, but they are all consequences of changes in motor neuron conduction in the nucleus of the facial nerves by peripheral or central deafferentation and may include cortical and subcortical influences.

Pathophysiology: Historical perspective and current concepts

In 1890, Gilbert, Cadiot, and Roger (apud Meige, 1907) described the case of a dog that presented spasms in an external ear considered similar to facial spasms in humans. Successive resections of the cortex, striatum, and cerebellum were performed with no improvement. However, following unilateral destruction of the facial nerve nucleus, the spasms ceased.

In 1898, Habel et al. described the case of a woman with HFS who did not improve after an ischemic stroke with ipsilateral hemiplegia. They suggested that the cause of the facial spasm was associated with changes in the facial nucleus or peripherally in the nerve, rather than at the cortical level. A similar case was later described in 1943, in which HFS also did not improve with the onset of ipsilateral hemiplegia subsequent to an ischemic stroke.

In 1909, Hunt proposed that the spasm was due to an afferent system resulting from irritation of the facial nerve. A hypothesis was proposed that the origin of the spasm could be cortical, but this was contested by Russell (1910) who suggested that spasm discharges originated in the pons of the facial nerve nucleus. Babinski (apud Gordon, 1912) expressed the view that the cause was probably peripheral irritation of the facial nerve. Wilson (1940) suggested that facial nerve stimulation alone rarely produces spasms, but that nerve

Table 2 (Part III): The 102 cases of bilateral HFS

| Authors and year (location) | Felício et al., 2007 and 2008 (Brazil) | Han et al., 2009 (Korea) | Yang et al., 2009 (Korea) | Kiziltan et al., 2010 (Turkey) | Lopez-Castellanos and Lopez-Contreras, 2015 (El Salvador) | Dou et al., 2015 and 2016 (China) | Martins et al., 2016 (Brazil) |
|-----------------------------|--------------------------------------|-------------------------|--------------------------|-------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Age at onset (years)        | 60.7 (average)                       | 50.3 (average)          | n/a                      | n/a                           | 70.3 (average)                  | 49                              | 50                              |
| Sex                         | 5F, 5M                               | 7F                      | 27 ?                     | 3 ?                           | 5F; 1M                          | 8F; 2M                          | 1M                              |
| % BHS                       | 2.6                                  | 0.4                     | 2.3                      | 1.5                           | 2.1                             | 0.7                             | n/a                             |
| Etiology                    | Vascular                             | Vascular                | n/a                      | n/a                           | 3 L, 3 R                        | 6L, 4R                          | L                               |
| Comorbidity                 | Most of African descendent - 1 TN, 1BP4HBP | n/a                    | n/a                      | n/a                           | 12.3                            | 7.8                             | 13                              |
| Side of onset               | 5 L, 5 R                             | 5 L, 2 R                 | n/a                      | n/a                           | 8 yrs                           | 3.8                             | 6 yrs                           |
| Duration/years (mean)       | 6.6 (mean)                           | 8.6 (mean)              | n/a                      | n/a                           |                                 |                                 |                                 |
| Latency (between R and L sides) (mean) | 2.8 yrs | 6.1 yrs | n/a | n/a | 8 yrs | 3.8 | 6 yrs |
| Neuroimaging diagnosis      | 1 MRI: vertebrobasilar tortuosity, 4 MRI: normal, 4 CT: normal | 1 dolichoectatic: L: 1 PICA, 4 AICA, 1 normal R: 2 PICA, 3 AICA, 1 normal | n/a | n/a | 6 normal | n/a | L VA tortuosity and R PICA |
| Therapy                     | 2 BZD, 4 AED, 3 AD, 8 BTX             | L: 5 MVD R: 3 MVD       | n/a                      | 5 BTX, 1 refused treatment    | 5 MVD unilateral and 5 MVD bilateral | CBZ, BTX, MVD (R and L) |
| Result                      | n/a                                  | n/a                     | n/a                      | 5 slight severity post BTX    | 1MVD unilateral 4 MVD unilateral (3 bilateral cure and 1 contralateral partial improvement) and 5 MVD bilateral (5 bilateral cure) |
| Follow-up                   | 100 mos                              | n/a                     | n/a                      | n/a                           | n/a                             | n/a                             | 5-92 mos                        | 17 mos |

n/a: Not available, AD: Antidepressant, AED: Antiepileptic drug, AICA: Anterior inferior cerebellar artery, MRI: Magnetic resonance imaging, BA: Basilar artery, BHS: Bilateral hemifacial spasm, BP: Bell's paralysis, BTX: Botulinum toxin injections, BZD: Benzodiazepine, CBZ: Carbamazepine, C-dopa: Carbidopamine, CNZ: Clonazepam, CT: Conservative treatment, CT: Computed tomographic, F: Female, HBP: Hypertension blood pressure, HI: Hearing impairment, M: male, MI: Marked improvement, MS: Multiple sclerosis, MTP: Methylprednisolone, MVD: Microvascular decompression, PICA: Posterior inferior cerebellar artery, SA: Small arteries, SAV: Small arteries and veins, TN: Trigeminal neuralgia, TXP: Trihexyphenidyl, VA: Vertebral artery. ~: Mean
irritation might result in antidromic conduction to the nucleus, resulting in abnormal activity that could cause spasms.

The spread of action potentials in two adjacent unmyelinated axons has been demonstrated in experimental studies, by Katz and Schmitt (1940),[40] and later by Arvantaki (1942),[2] who proposed that the term “ephapse.” Granit et al. (1944),[29] demonstrated that “ephapses” occurred in the sciatic nerve of a cat after mechanical compression, which disappeared following its release. Generation of ectopic action potentials concomitant with ephaptic conduction has also been demonstrated in spinal motoneurons in dystrophic mice when stimulated antidromically.[51] These ephaptic characteristics are similar to facial spasms, due to NVC in the REZ, where the transition from oligodendroglia to Schwann cells occurs.[46,90] Reversibility of abnormal synkinesis after MVD occurs, often within 10 days, in 81% of the patients who had not been submitted to previous peripheral facial nerve block procedures. They correspond to the reversibility of ephapse. The spasm itself might be a phenomenon analogous to the ephaptic excitation and hyperexcitation demonstrated in dystrophic mouse spinal nerve roots.[46]

In 1962, Gardner and Sava,[25] and later Gardner and Dohn (1966),[24] reported that myelin lesions due to NVC can cause “cross talk” or the spread of action potentials to adjacent axons (transaxonal short-circuit theory).

Gardner and Dohn (1966)[24] reported that, in four cases of HFS refractory to MVD, section of the intermediate nerve was performed with complete cessation of spasms and without motor alteration of the facial muscles. They suggested that NVC could set up a peripheral reverberating circuit between afferent (proprioceptive) and efferent fibers at the site of compression.

The main cause of HFS is NVC in the REZ, which is more vulnerable because this area is devoid of epineurium and Schwann cells because it is only covered by arachnoid cells.[69] These characteristics enable minimal compression to result in anatomical changes. Histopathological study of the REZ of facial nerve of patients with HFS showed fibers with complete and partial demyelination, with demyelinated axons in contact with each other. Normal and abnormal fibers showing proliferative hypermyelination with features of microneuromas have been reported.[82]

De Ridder et al.[10] suggested that NVC can occur in any cranial nerve segment within the central nervous system (CNS), not only in REZ or DREZ (dorsal REZ). They reported that all cranial nerves, except I and II, are composed of a CNS segment and a peripheral nervous system segment. The central segment has a structure similar to that of white brain matter, it consists of parallel traveling nerve fibers, lacks funicular structure, and is less vascularized. The density of the peripheral segment is greater than the central segment, consisting of undulating nerve fibers, which creates a firmer and more elastic structure that is more resistant to compression. Sensory nerves are usually larger than conduction nerves, consequently the central segments of the latter are smaller, providing fewer possibilities for compression.[10]

This view was supported by Sindou et al. (2002),[90] who showed that 54.3% of 579 cases of NVC, using MVD to treat trigeminal neuralgia, were in the middle portion of the root. A study by Zhong et al. (2012),[108] involving 1,327 cases of HFS submitted to MVD, showed that 93% of NVC occurred in the REZ, 7% occurred in the medial portion of the facial nerve, and none of the cases presented distal compression by the internal auditory meatus.

Studies involving intraoperative electromyography (EMG) indicated the presence of abnormal muscle responses (AMR) in the facial muscles, such as the lateral spread response (LSR), which were attributed to demyelination/axonal injury of the facial nerve, causing ephaptic transmissions and ectopic excitations, leading to hyperexcitability of facial nucleus motoneurons.[69]

Experimental studies in rats have demonstrated that facial motoneurons are involved in HFS after facial nerve demyelination. It has been suggested that when a branch of the facial nerve is stimulated, the stimuli are transmitted in axons in both directions, antidromically and orthodromically. They argued that, to induce facial hyperactivity, the phenomena of facial nerve demyelination and vascular compression are both required.[51]

Research has shown that the severity of facial nerve NVC is associated with spasm intensity.[88] This fact has been reported previously and thus supports the neurovascular cause.[82]

The hypothesis of the peripheral origin of facial spasm suggests that ectopic firing and peripheral ephaptic transmissions that originate in their REZ due to NVC and demyelination cause hyperexcitability of the facial nerve nucleus, leading to spasms.[50,90,70] Experimental research has shown that local demyelination induced by the nerve injury enables ectopic insertion of Na+ channels, causing hyperexcitable nerve fibers at this level.[70] Demyelination facilitates close contact between bare axons, promoting direct electrical communication between individual nerve fibers.[67]

The hypothesis of the nuclear origin suggests that some form of reorganization of the synapses occurs in the facial nerve nucleus, leading to motor neuron hyperexcitability due to demyelination caused by NVC.[19,44,66,85,98,99] Neurophysiological studies show a high frequency of
discharges recorded in muscles innervated by facial nerve axons, whereas the interference pattern is related to facial motor neuron activity or its supranuclear control. This activity is more frequently seen in cases showing longer symptom duration and could be related to the onset of facial motor neuron hyperexcitability due to antidromic impulses that results in spontaneous activation.\(^{[47]}\)

Thus, neither the nuclear nor the peripheral hypotheses can be rejected. A study involving EMG in a case of BHFS, with asynchronous contractions in each hemiface and treated unilaterally, showed complete resolution of ipsilateral spasms and the persistence of spasms on the contralateral side. This finding suggest independent trigger mechanisms in both hemifaces, more likely due to bilateral nerve zone irritation by aberrant vessels than hyperexcitability of a facial nerve nucleus spreading to the contralateral side.\(^{[60]}\) Similarly, another electrophysiological study demonstrated asynchrony, asymmetry and differences in the patterns of spasm activity in each hemiface in cases of BHFS.\(^{[47]}\) Most cases of bilateral BHFS not improve bilaterally following unilateral MVD, as observed in our case. These observations suggest that there is no interrelationship between the facial nerve nuclei. Following treatment with BTX-A in patients with HFS, decreases in the synkinetic response of the blink reflex and AMR were observed, suggesting that skin or muscle afferent volleys via the trigeminal nerve enhance the excitability of facial nerve motor neurons in HFS.\(^{[71]}\) Spasm-induced somatosensory input from the skin may activate the somatosensory afferent pathway and basal ganglia-thalamo-cortical motor circuits.\(^{[60]}\) Activation of the thalamus is probably due to projections arising from muscle spindles, as demonstrated in an experimental study on rats.\(^{[42]}\) Brain circuitry may be altered in patients with HFS, as Tan et al. (2004)\(^{[92]}\) have suggested.

A thought-provoking study\(^{[15]}\) showed that once the offending artery was intraoperatively removed from the nerve, the AMR wave diminished immediately and most muscle spasms improved following MVD treatment for HFS. This cannot be easily explained by the combined peripheral and nuclear hypotheses, since insufficient time had passed for histological repairs in the area of NVC. Thus, Dou et al. (2015)\(^{[15]}\) proposed a new explanation for the pathogenesis of spasms in which the offending artery played a more important role than the mere effect of mechanical compression in the pathogenesis of the HFS. They suggested that attrition at the neurovascular interface is the essence of HFS etiology and that the substance of the disease is emersion of ectopic action potentials from the demyelinated facial nerve fibers, which are trigged by sympathetic endings from the offending artery wall. In support of this hypothesis, they repeated the Kuroki and Møller (1994)\(^{[51]}\) experiments in mice, in which the superficial temporal artery was place in contact with the facial nerve where it exits in stylumastoid foramen. After 4 weeks, EMG monitoring was performed on the faces of affected mice that showed AMR waves very similar to those monitored during MVDs in HFS. Electron microscopy showed lesions in the epineurium and the tunica adventitia of the vessel. The presence of AMRs was only observed in the rats that also presented both lesions under microscopic observation. When the vessels were cut and separated from contact with the facial nerve, the AMRs disappeared, as occurs during MVD. The arteries are covered by adventitia, which contains the vasa vasorum and the autonomic nerve endings that release neurotransmitters. These neurotransmitters act in neuromuscular junctions and control vessel expansion and contraction. Once the cervical sympathetic ganglia ipsilateral to the NVC were removed, the AMRs disappeared.\(^{[31]}\) These findings indicate that an effective participation of the sympathetic innervation occurs in the pathogenesis of HFS, possibly through the release of norepinephrine. The authors suggested that while the adventitia is wearing out, particularly during moments when sympathetic impulses occur, neurotransmitters released from sympathhetic endings may spillover from the breakage and spread to nerve VII fibers in close contact with the offending arteries. Thus, after removing the compressor artery and in the absence of AMRs, they dripped norepinephrine on the nerve where the compression occurred and the AMRs reappeared. They concluded that sympathetic innervation was involved, via neurotransmitters, in the pathogenesis of HFS. They also speculated regarding the possibility of Na\(^{+}\) channel involvement in the genesis of action potentials generated in facial nerve axons and concluded the study by stating that more work is required to substantiate the “sympathetic hypothesis.”\(^{[15]}\) It is important to highlight that this hypothesis does not explain cases of HFS secondary to cysts, to extrinsic and intrinsic brainstem, cerebellum, and fourth ventricle tumors, and particularly in demyelinating and ischemic diseases.

A study involving positron emission tomography (PET scan) in patients with HFS compared with asymptomatic controls showed bilateral glucose hypermetabolism in the somatosensory thalamus [corresponding to the ventral posteromedial (VPM) nucleus, related to the sensory somatotopic part of the face] in patients with HFS, in both active and suppressive states. It is worth noting that the upper part of the face receives motor afferents from ipsilateral and contralateral facial nerves. The spasms were significantly reduced following suppression with BTX-A, according to the Jankovic disability rating scale. Thalamic hypermetabolism was attributed to various causes, such as skin afferents and neuromuscular spindles, antidromic conduction of the facial nerve and secondary changes in the CNS.\(^{[38]}\)

It has been reported that in patients with unilateral writer’s cramp, functional MRI (f-MRI) showed increased
activity in both putamens, the caudate nuclei, the internal globus pallidus, and the thalamus during tactile stimulation of the right index finger. During dystonias, the basal ganglia-thalamo-cortical motor circuit can occasionally be bilaterally activated by hemilateral stimuli. Blepharospasm and HFS seem to show similar pathophysiology, which explains the bilateral activation of the thalamus by a unilateral stimulus. It has been suggested that after BTX-A application in HFS, sensory afferents of the neuromuscular spindles via the trigeminal nerve to the thalamus can diminish, which would partially explain the small reduction inthalamic hypermetabolism on a PET scan. It is possible that other sensory afferents via nerve VII remain. Hypermetabolism in the cerebellum was also observed, which could be due to facial muscle activity. No hypermetabolism was observed in the primary (M1) motor area. Sensitive afferents arising from the intermediate nerve conducted to the spinal nucleus of the trigeminal nerve could also remain, which drive to the sensory thalamus and then to the cortical somesthetic area.

As mentioned above, Gardner and Dohn (1966) described four patients with HFS who showed no improvement following MVD, who were then submitted to intermediate nerve section, with complete cessation of the spasms. Thus, sensory fibers of the intermediate nerve come from the outer ear, part of the external auditory meatus, and outside of the eardrum. Central extensions of ganglion cells geniculated to the peripheral sensitivities enter the brain stem through the nerve and drive to the spinal nucleus of the trigeminal nerve. Peripheral extensions of sensory neurons located in the gasserian ganglion and the mesencephalic trigeminal nucleus receive peripheral impulses from the face sensitivity of the face and, together with the sensory fibers of the intermediate nerve, drive to the sensory trigeminal nucleus. After connecting with secondary neurons in the brainstem (except neurons of the mesencephalic nucleus of the trigeminal nerve, which contains primary neurons like the gasserian ganglion), most of the fibers cross the midline driving to the VPM nucleus of the thalamus and after connecting to these neurons, reach sensory cortical areas, which are connected with motor areas that in turn are modulated by the basal ganglia, thalamus, and cerebellum. It is possible that the intermediate nerve, also compressed in the DREZ by the vessel, is involved in the genesis of HFS.

There are connections between the trigeminal nerve and the facial nerve, which can be demonstrated by the blinking reflex in response to stimulus in the cornea. Research has shown the activation of primary and supplementary motor areas by evoked potentials during voluntary eyelid movement, but this has yet to be verified for involuntary movements. The study of transcranial magnetic stimulation (TMS) showed cortical influence on HFS, which, through cortical mechanisms, such as postexcitatory inhibition of motoneurons after excitation of the corticonuclear tract, may activate the corticonuclear inhibitory system controlled by intracortical mechanisms modulated by basal and thalamus ganglia. The facial motoneurons respond easily to trigeminal stimulation, they presumably receive only mild or short-lasting excitation of the corticobulbar inhibitory descending projections.

Considering the data outlined here, we argue that the most probable explanation is ectopic firing and ephaptic transmissions, originating in the REZ of the facial nerve due to NVC, orthodromically stimulate the facial muscles and antidromically stimulate the facial nerve nucleus, while the latter, in its hyperexcited state, also intermittently stimulates the facial muscles. These activated muscles trigger the somatosensory afferent impulses of the skin and neuromuscular spindles of the face conducted by the trigeminal nerve, which after passing through the gasserian ganglion and trigeminal nuclei, reach the contralateral VPM somatosensory thalamic nucleus, which then drive to the cortical somesthetic area of the face.

Once activated, this area stimulates the primary and supplementary motor areas through the extrapyramidal system, while the basal ganglia retrogradely activate the motor neurons of the facial nerve nucleus, which peripherally stimulates the facial muscles. In addition, the intermediate nerve, which is anatomically aligned with the facial nerve, likely participates in this pathophysiology. Its impulses orthodromically drive to the spinal trigeminal nucleus and ascend to the basal ganglia-thalamocortical circuits, whereby descending feedback activates the facial nerve nucleus, expressed peripherally through spasms [Figure 1, Adapted from Afifi and Bergman and Obeso, Rodriguez and DeLong].

It is worth emphasizing that the patient cannot suppress the spasms voluntarily and that they persist during sleep and anesthesia, a fact verified in this case, clearly indicating the influence of the extrapyramidal system and the basal ganglia.

Patients with central facial paralysis, who cannot voluntarily move the muscles of the lower face, show involuntarily movement through reflexes, in response to emotional stimuli from the basal ganglia to the facial nerve nuclei. Clinical observations have shown that emotional factors, such as stress, influence the precipitation or exacerbation of HFS. This suggests the influence of the cognitive/associative and limbic systems on the basal ganglia and the extrapyramidal system in HFS [Figure 1, Adapted from Afifi and Bergman].
Obeso, Rodriguez and DeLong\cite{74} Further investigation should clarify these suppositions.

**Clinical presentation**

Although HFS is not life-threatening, it can cause major disruptions to daily life activities such as driving and working, causing withdrawal from socializing and even depressive disorders.\cite{63,93} The natural history of the disease begins with irregular twitching and clonic and tonic contractions in the lower part of the orbicular oculi muscle, until it encompasses the entire muscle. It progresses to the lower part of the same hemiface and can manifest in the platysma muscle.\cite{15-17,19,34,47,63,84,94,97,100,104}

Contractions may progress, with predominance of the tonic component over the clonic.\cite{57,94,97} Atypical HFS is characterized by onset in the orbicularis oris muscle and buccinator, which may ascend to the orbicular oculi muscle.\cite{6,64,87,97} Spasms worsen with stress and fatigue, they cannot be suppressed voluntarily, and they persist during sleep or anesthesia.

The spasms begin in adult life, around 45 years of age, and prior history of peripheral facial paralysis or traumatic nerve injury is not uncommon.\cite{6,16,24,28,34,46,68,80,97} In a large series, motor nerve dysfunction was verified in 57% of cases.\cite{6} Synkinesis has been reported in 70% of cases with HFS.\cite{47} Mild facial motor deficit has also been observed, with 10.3% of patients affected in an Asian series of 310 cases.\cite{34} Voluntary movements of the face and speech can worsen spasms.\cite{24,28,102} Some patients complain of “clicks” in the ipsilateral ear due to contraction of the stapedius muscle, and auditory deficit may be observed.\cite{117,124,134,146,68,80,97}

The ipsilateral facial paralysis preceded 1.9% of 106 cases of HFS studied by Ehni and Woltman (1945).\cite{17} 15.3% of 131 cases studied by Lopez-Castellanos and Lopez-Contreras (2015),\cite{16} and 2% of 648 cases studied by Barker, et al. (1995).\cite{6} One report describes a case of bilateral synchronous HFS following bilateral Bell’s palsy.\cite{103} In a North American series of 293 HFS cases, 22.8% had moderate to severe facial motor deficits (≥III House and Brackmann), principally among those submitted to BTX-A.\cite{97} In our case, Bell’s palsy did not occur before the onset of the spasms.

Previous auditory deficit is also not uncommon in HFS patients submitted to MVD. Huang et al. (1992)\cite{34} verified auditory deficit in 4.8% of 310 cases, while Thirumala et al. (2011)\cite{97} reported it in 12.3% of 293 cases. In a series of 143 HFS cases submitted to MVD, 41% presented abnormalities in the middle ear acoustic reflex in the preoperative period, suggesting that NVC can affect both the acoustic and facial nerves. In the same series, 2.8% of cases presented significant postoperative auditory deficits.\cite{6} In a series of 34 patients with HFS submitted to MVD, 17.6% presented auditory deficits ipsilateral to the HFS, and 2.9% had severe dizziness.\cite{77} Our patient presented mild to moderate bilateral auditory deficits.

**Differential diagnosis**

A diagnosis of BHFS requires considerable care, since it can be mistaken for other facial dyskinesias:

- **Blepharospasm** consists of symmetrical, synchronous, and bilateral contractions of the orbicularis oculi muscle, and may be associated with contractions of the frontal muscles and the corrugator and procerus muscles, resulting in characteristic depression of the eyebrows (Charcot’s sign).\cite{12} There is no evidence of the Babinski-2 sign, present in the HFS, which is characterized by unilateral contraction of the frontal muscles, causing eyebrow elevation, with simultaneous contraction of the ipsilateral orbicularis oculi muscle, resulting in eyelid closure.\cite{12,96,104}
- **Facial tics** usually begin in childhood, though their

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**Figure 1: Simplified scheme of motor, sensory, cognitive/associative and limbic systems**

Note: The diagram illustrates the complex interplay between motor, sensory, cognitive/associative, and limbic systems, highlighting key neural pathways and their interactions in the context of HFS.
characteristics can change, they can be controlled voluntarily and they do not improve with rest. Besides the facial nerve, other nerve groups may be involved, a finding observed in younger patients. The movements are abrupt and multifocal. They are associated with motor, phonic, gestural tics, or other signs and symptoms of Tourette’s syndrome

- Facial myokymia is characterized by unilateral and temporary contraction of the orbicularis oculi muscle, usually associated with periods of physical or emotional stress, fatigue, or excessive caffeine consumption
- Synkinesis following facial nerve paralysis leads to the activation of several muscles innervated by the facial nerve and it typically occurs in the context of voluntary movement
- Oromandibular dystonia is usually bilateral and affects other muscular groups not innervated by the facial nerve, such as the pterygoid, masseter, and temporalis muscles
- Hemimasticatory spasm affects the musculature involved with the trigeminal nerve with painful contraction of the medial pterygoid, masseter, and temporalis muscles
- Psychogenic facial spasm does not present a specific pattern of contractions, intensity, and frequency. It can involve muscles not related to the facial nerve and can be modified by distraction
- Drug-induced late-onset dyskinesias, mainly by neuroleptics, manifest as stereotypical orofacial, lingual and limb movements, and akathisia
- Focal seizures characterized by rapid clonic contractions that can be observed in an EEG or an EEG video

The long latency period that occurs between the onset of HFS and contralateral involvement is symptomatic and assists in the differential diagnosis of BHFS and other movement disorders. EMG studies may assist in the diagnosis of HFS

**Comorbidities**
Arterial hypertension (AH) is the main HFS-related comorbidity, occurring in 24% of cases in a series of 648 patients, and 18.9% in another series of 587 patients. Besides AH, the increase in patient age was related to hyperactive dysfunction syndrome (HDS), when an increase in the atherosclerotic process occurs together with AH, which leads to vessel stretching and tortuosity. This can result in compression of the DREZ or REZ of the nerves. AH generally precedes HFS

Gardner and Dohn (1966) described a case of BHFS secondary to Paget’s disease with basilar impression. BHFS associated with blepharospasm and associated with cervical dystonia have both been reported

**Complementary examinations**
MRA and MRI are important for evaluating neurovascular conflicts, observed in 15% of HFS cases, or the presence of an expansive lesion at the cerebellopontine angle. A lack of visible neurovascular conflict is often due to limitations in the imaging method. The studies comparing specific sequences of MRI imaging acquisition improved surgical planning for patients with NVC. There was a diagnostic correspondence in the evaluation of 1.5 T with T2 fast spin echo and intraoperative findings. Garcia et al. demonstrated that there is a higher resolution and greater sensitivity with 3D-CISS and 3D-TOF MRA at 3 T compared with 1.5 T in patients with NVC. The high-resolution STIR MRI sequence can be considered a good method for simultaneous evaluation of vessels and cranial nerves, even without contrast. EMG is characterized by discharge patterns of spasm activities that can occur as single isolated, clustered, and tonic spasms. Isolated discharges are more prevalent in patients with HFS with shorter disease duration, though over time, tonic spasms tend to prevail. In patients with BHFS, the spasms are asynchronous and asymmetric and the patterns of spasms activities are different. Audiometry should be performed to ensure pre- and postoperative comparisons.

**Treatment**
To treat HFS, oral medication, BTX-A, and MVD have all been described. Treatment with oral medications is generally considered unsatisfactory. The most commonly prescribed drugs are carbamazepine, phenytoin, clonazepam, baclofen, and gabapentin. Acupuncture was prescribed for 85 patients in a series of 310 cases and for 65 patients in another series of 545 cases with HFS, but showed no therapeutic benefits. BTX-A applications are a practical therapy that has low morbidity and good clinical response. In general, BTX-A is injected into the affected muscles, resulting in presynaptic blockade of the motor plate that provides a good therapeutic response. The patient remains free from symptoms for 3–4 months, after which it must be reapplied. The most frequent complications associated with this treatment are peripheral facial paralysis, diplopia, and palpebral ptosis. However, after prolonged use, the efficacy of the neurotoxin can diminish or fail, resulting in an unsatisfactory response.

This treatment is the first option in patients with high anesthetic risk, who present milder or refractory symptoms or in those who present HFS relapse following MVD. In cases of BHFS after unilateral MVD, in which hearing loss is a complication, the use of contralateral BTX-A is an excellent option to avoid the risk of bilateral hearing loss, which has high morbidity. Wang and Jankovic (1998) published the first case of a patient with painful tic convulsif (HFS + trigeminal neuralgia) who showed improvement in both symptoms following BTX-A application. A similar case was published in
BHFS and unilateral painful tic convulsive has also been described, in which the spasms and ipsilateral trigeminal neuralgia improved following the application of BTX-A.\footnote{2002} The best long-term therapeutic response for HFS due to NVC is endoscope\footnote{[5,58]} or microsurgery-assisted MVD.\footnote{[6,34,49,54,60,63,72,107,109]} MVD is the only option for curing HFS.\footnote{[49,63,109]} Improvement in the spasms can occur immediately following MVD or may take several months.\footnote{[25]}

Intraoperative EMG monitoring has shown the immediate disappearance of AMR or LSR recorded from a muscle innervated by the superior branch of facial nerve when the inferior branch was stimulated, or conversely, during MVD. This phenomenon is probably due to ephaptic transmission at the lesion site or in combination with motor nucleus hyperactivity.\footnote{[63]} It has been suggested that the disappearance of LSR is a good predictor for obtaining an optimal result,\footnote{[17,65,97,108]} and two large studies involving thousands of patients show that AMR vanished after MVD in 93.9\% of HFS cases.\footnote{[107,108]} Some authors recommend intraoperative EMG, since this form of monitoring is very useful when manipulating the facial nerve, to avoid deficits.\footnote{[57,65,97,108,309]}

One study reported that direct stimulation of the offending artery during surgery in cases of HFS produces a wave analogous to AMR, denominated the “Z-L response,” which disappeared immediately after decompression. Monitoring the Z-L response is useful when an AMR is not recorded prior to decompression or if it persists after all vascular compressions are properly treated. It can help determine the real culprit when multiple offending vessels exist.\footnote{[109]}

The duration until complete cure of HFS after MVD was studied in 175 Japanese patients, who were assigned to two postoperative groups: Group I (n = 88), in which the residual spasms resumed on day 4, after a period of silence, and diminished gradually until complete resolution in 28 days, on average; and group II (n = 87), in which the spasms ceased immediately after surgery. In group I, 10 (11\%) patients did not present a period of silence. Complete resolution of the spasms took more than a year in six (7\%) group I patients, with two patients presenting long delays, one of 22 months and another of 27 months. Facial paresis is common in the postoperative period, however, no case of permanent facial paralysis was observed. The authors concluded that approximately 50\% of patients show persistent postoperative spasms after a 4-day period of silence, with complete resolution occurring in 25\% of cases in 1 week, 50\% in 1 month, and 90\% within 8 months postsurgery. If the spasms do recur after 4 days and there is no facial paresis, recurrence is more likely and the patient may be considered for surgical re-exploration.\footnote{[38]}

Persistence of motor neuron hyperactivity of the facial nerve nucleus was demonstrated in the postoperative period by electrophysiology studies, which explains the persistence of spasms for a certain period.\footnote{[40]} Microanatomical changes, such as demyelination, myelin sheath vacuolization, and partial axonal degeneration, caused by NVC were also demonstrated by microscopy. Electrophysiological changes, such as changes in F waves and AMR that are indicative of neuronal excitability, have also been described.\footnote{[91,69,71,82]}

The mechanism of spasm improvement depends on two factors. The primary mechanism is due to the interruption of ectopic excitation and the efficient transmission that occurs following REZ decompression, leading to the abrupt disappearance of the spasms, in most cases. The secondary mechanism is due to remyelination of the affected segment, with the disappearance of LSR, and perhaps the gradual decrease of neuronal hyperexcitability in the facial nucleus, which could explain delayed improvement.\footnote{[22,38,40,69,71,97]}

The persistence of spasms in the immediate postoperative period varies widely in the literature: 50.3\% (Ishikawa et al., 2001),\footnote{[38]} 34\% (Marneffe et al., 2003),\footnote{[39]} 12\% (Huang et al.),\footnote{[49]} 5.8\% (Kim et al.).\footnote{[48]} Most residual spasms improve in up to a year.\footnote{[22,38,4,59]}

Intraoperative brainstem auditory evoked potential (BAEP) monitoring helps prevent auditory deficit.\footnote{[17,60,34,97]}

In 2012, a systematic review of 5,685 HFS cases submitted to MVD verified complete cessation of spasms in 91.1\% of the cases. The mean follow-up was 2.9 years. Spasms recurred in 2.4\% of patients and 1.2\% were submitted to a second MVD. Transient complications included 9.5\% facial deficit, 3.2\% auditory deficit, and 1.4\% cerebrospinal fluid fistula. Permanent complications included 2.3\% auditory deficit, 0.9\% facial paralysis, 0.06\% stroke, and 0.02\% death. Curiously, the second author of this article had HFS for 5 years, which was cured with MVD.\footnote{[61]}

Treatment of HFS by MVD is curative in approximately 90\% of cases in the long term and is therefore the best definitive treatment. Improvement immediately following surgery was observed in 76.7\% of cases, on average, with the majority of delayed improvements resolving within a year. Partial improvement varied from 1.3\% to 9\% and the total failure of MVD ranged from 2.6\% to 9\%. Cases of recurrence ranged from 1\% to 3.2\% in follow-up ranging from 1 year to 18 years. Permanent hearing loss ranged from 1.1\% to 2.9\% and permanent facial deficit ranged from 0.7\% to 2.9\% of cases. There was only one case (0.01\%) of mortality due to infection in 8,096 cases of HFS submitted to MVD [Table 3].
Special secondary cases of HFS can be treated with other techniques such as embolization, when treating arteriovenous malformations, gamma knife surgery, or microsurgery. All of these methods are effective.\[31,34,48\]

In cases of HFS associated with Paget’s disease, the use of alendronate sodium may be favorable.\[21\]

**CONCLUSIONS**

BHFS is a rare neurological syndrome. Diagnosis is a challenge that depends on excluding other facial dyskinesias. We present the tenth case of BHFS, which was resolved with bilateral surgery. Microvascular decompression is a definitive, long-term surgical option with low complications.

In cases of BHFS, we believe that the best approach is bilateral MVD. If hearing loss occurs following a unilateral surgery, the use of contralateral BTX-A is the best option to avoid the risk of bilateral hearing loss, a complication of considerable morbidity. Use of BTX-A prior to other treatments should be considered in patients with a high anesthetic risk, when the symptoms in one hemiface are mild, to avoid surgery on that side, or at the patient’s discretion.

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**Table 3 (Part I): Results and complications (%) of MVD treatment of HFS**

| Authors and year (location) | Number of MVD | Immediate cure | Delayed cure | Partial improvement | Full recovery | Did not improve | Recurrence | Permanent facial weakness | Permanent auditory damage | Follow-up/ years | Notes |
|-----------------------------|---------------|----------------|--------------|---------------------|--------------|----------------|------------|--------------------------|------------------------|----------------|-------|
| Niemeyer Filho, Bezerra and Mufarrej, 1990 (Rio de Janeiro, Brazil) | 53 | 81.1 | 18.9 | - | 91 | - | - | - | - | - | - |
| Huang et al., 1992 (Taipei, Taiwan) | 310 | 88 | 5.2 | - | 93.2 | 1 | - | - | - | - | - |
| Barker et al., 1995 (Pittsburgh, USA) | 648 | 86 | - | 7 | 84 | 9 | 2 | 0.9 | 2.6 | 10 | - |
| Zhang et al., 1995 (Guangzhou, China) | 300 | - | - | 1.3 | 92 | 3.4 | 3 | Up to 5 yrs | 1 | 2.0 | 1.0 tinnitus | - | 3% controlled infection 0.3 death by infection |
| Payner and Tew, 1996 (Cincinnati, USA) | 34 | - | - | 9 | 85 | 6 | - | 2.9 | 2.9 | 6.2 | - |
| Rothon, 1996* (USA) | 72 | - | - | 7 | 87 | 6 | Majority <1 yr | 1.4 | 2.8 | 1-18 | In: comments |
| Ishikawa et al., 2001 (Saitama, Japan) | 175 | 49.7 | * | - | - | - | - | - | - | - | - |
| Samii et al., 2002 (Hannover, Germany) | 143 | 59 | - | - | 90.6 | - | - | - | - | 9.6 | - |
| Li, 2005 (Taipei, Taiwan) | 545 | 87.9 | After 3 mos: 91.4 | - | 93.4 | - | - | - | - | - | 1 case took 2 yrs to improve |

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Mean, *comments
The described case was successfully submitted to bilateral MVD after attempting to treat the patient with oral medications and BTX-A, which ended in relapses.

Disclosure
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