EDITORIAL

Considering a neurovascular compression etiology**Anthony M. Kaufmann, MD, MSc, FRCSC**

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PETER J. Jannetta proposed the neurovascular compression (NVC) theory in 1967.⁵ He, together with his mentor Robert W. Rand, had been developing a technique of selective partial sensory rhizotomy for the treatment of trigeminal neuralgia (TN) and building on the pioneering works of Dandy, Gardner, and others.⁶ With the assistance of John F. Alksne, the first of these operations was performed through a subtemporal-trans-tentorial approach and with the novel use of an operating microscope. As exposure was gained, Jannetta revealed the superior cerebellar artery impinging on the proximal trigeminal nerve root and quietly exclaimed, “That’s the cause of trigeminal neuralgia.” Similar observations were evident in the next four such rhizotomy surgeries, although Jannetta found no similar compression in a series of cadaveric dissections. Later that same year in the neurosurgery clinic, Jannetta was assessing a gentleman with hemifacial spasm (HFS) and had an epiphany: this was another cranial nerve hyperexcitability condition analogous to TN and was also likely caused by pulsatile compression upon the proximal cranial nerve root. He explained this to the patient who then consented to what would become Jannetta’s first microvascular decompression (MVD) surgery. Together with his co-surgeon Paul H. Crandall, he identified and alleviated NVC of the facial nerve root exit and achieved a cure of the HFS. Two months later Jannetta and Rand performed their first MVD for TN with equal success. The neurosurgery community, however, was slow to accept this new cure for an old disease. Jannetta persevered despite the naysayers, the critics, and those who questioned his credibility. He gradually presented a body of surgical and clinical follow-up evidence that convinced a critical mass of adopters that MVD was an effective treatment, and neurosurgeons worldwide began to replicate his excellent results.

Over the course of decades, NVC has become established as the cause of nearly all cases of classic or typical TN, HFS, and glossopharyngeal neuralgia (GPN) when

strict diagnostic criteria are applied. These conditions are also amenable to high rates of cure by the atraumatic alleviation of culprit vascular compression via Jannetta’s MVD procedure. However, the NVC theory has also been invoked by some as a potential cause of other conditions such as non-episodic facial pain (e.g., type 2 TN), Bell’s palsy, tinnitus, vertigo, hypertension, and diabetes. Evidence of an association between these conditions and culprit vascular compression is less robust, and MVD surgery has not been generally accepted as effective in their treatment. There remains an appropriately great burden of proof when proposing an NVC etiology, just as Jannetta faced 50 years ago.

In the current article, Dr. Honey et al. posit that NVC is a responsible etiology for some selected cases of laryngospasm, a condition that they have termed “hemi-laryngopharyngeal spasm,” or HELPS.⁴ Their three patients, as well as a patient in a previously reported single case,³ all suffered from episodic stridor, choking, and coughing that sometimes led to loss of consciousness. All had some degree of temporary symptom improvement with unilateral laryngeal botulinum toxin (Botox) injections. The authors suggest that culprit vascular compression upon vagus nerve rootlets was evident in each case and that symptoms were relieved with MVD. They also provide a thoughtful discussion regarding the possible mechanism underlying the proposed pathophysiology and conclude that MVD may be considered as a possible treatment in selected patients with HELPS.

But there are several factors to consider before accepting this proposed NVC etiology and microsurgical treatment. First, the clinical manifestations of the proposed HELPS condition should be more clearly delineated. The exclusion of most common causes such as gastroesophageal reflux and psychological issues must be detailed beyond a failure to respond to standard treatments. While the reported patients had some clinical improvement with unilateral Botox injections, there was no confirmation that

the laryngospasm was restricted to one side. This unilaterality should be confirmed with laryngoscopy, ultrasound, and electromyography studies as bilateral hyperactivity of the laryngeal muscles would not support an NVC etiology. Also, the loss of consciousness the patients suffered should be thoroughly characterized, particularly as unilateral involvement would be unlikely to cause airway obstruction. Was there hypoxia due to airway compromise? Was there cardiovascular hypotension or bradydysrhythmias, as rarely seen in GPN? Was there a vasovagal syncope related to the severe anxiety described in all of their patients? Finally, relating to clinical manifestations, it is noteworthy that no patients with HELPS had pain symptoms of GPN and that the clinical manifestations of GPN do not include laryngospasm. If NVC of cranial nerve IX and X rootlets were an underlying etiology of HELPS, then one should expect a clinical overlap with GPN.

Second, compression of the vagus nerve by the implicated posterior inferior cerebellar artery (PICA) was not as impressive as typically seen in patients with GPN, in whom the culprit vessel usually impinges dramatically upon cranial nerves IX and X at their root entry/exit zone, often causing distortion of the brainstem and proximal nerve.⁷ The PICA has a natural course of its lateral medullary segment between the cranial nerve X rootlets and invariably contacts the nerve. A simple and ubiquitous juxtaposition of the artery and nerve are not sufficient evidence to invoke the NVC etiology. It remains to be determined whether vagus nerve NVC is more prevalent in patients with HELPS than in control patients (or on the opposite side). This could be assessed in a blinded review of high-resolution MRI, as has been effectively done for typical TN, HFS, and GPN.

Finally, a curative effect of MVD surgery would strongly support the NVC theory. This has certainly been well established for conditions of classic or typical TN, HFS, and GPN. In each of these conditions, a cure can be achieved in the vast majority of patients with an atraumatic alleviation of vascular compression of the respective root entry/exit zone without the need to induce any degree of nerve injury. However, it should be noted that microsurgical injury to these respective nerves in itself may alleviate the hyperactivity symptoms, as originally demonstrated by Dandy¹ and Gardner.² In the series presented by Honey et al., all patients unfortunately suffered a symptomatic vagus nerve injury as a complication of MVD surgery. While these clinical symptoms improved, there was no documentation with laryngoscopy or other studies that vagus nerve function had normalized. Therefore, it remains to be proven whether an atraumatic MVD of the vagus nerve roots could be curative of HELPS or whether the laryngospasm was instead improved with a surgically induced nerve injury analogous to other denervation procedures. An important implication of this differentiation of the treatment effect may be the introduction of less invasive vagal rhizotomy techniques such as Gamma Knife radiosurgery, as has already been successfully utilized in the treatment of TN and GPN.

Laryngospasm poses a complex clinical challenge, with several potential underlying causes and variable responses to treatments. The authors are to be congratulated in

their efforts to assess a possible NVC etiology not previously considered for a subset of patients with this condition. However, there is a great burden of proof to establish evidence of cause and cure, just as there was 50 years ago when Jannetta first presented his NVC theory and MVD surgery. I trust Dr. Honey and colleagues will continue studies into this possible cause of HELPS and provide us with a definitive set of findings and recommendations in the future. While I am currently not convinced that laryngospasms are caused by vagal NVC, history has shown that such skepticism may sometimes be overturned by diligent clinical and scientific efforts.

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Disclosures

The author reports no conflict of interest.

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Response

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We thank Dr. Kaufmann for his thoughtful critique of our paper. His editorial highlights concerns with 1) confirming the diagnosis of HELPS, 2) the etiology of loss of

consciousness in this condition, 3) the possible overlap of HELPS with GPN, 4) the incidence of vascular compression of the vagus nerve, and 5) whether our MVDs were atraumatic or worked by inadvertent rhizotomy, and if the latter, whether a vagal rhizotomy could be an equally effective but less invasive option for these patients.

First, the diagnosis of HELPS will require a definitive test. We have retrospectively compared a number of these tests with the surgical outcome in nine patients and plan to present the results later this year in an otolaryngology journal. The diagnosis of this condition will most likely be made initially by an otolaryngologist and not by a neurologist or neurosurgeon. Laryngoscopy is not a sensitive enough test because the condition is intermittent. None of our patients have yet consented to allow us to try to provoke an episode during laryngoscopy—although one patient did have interictal, ipsilateral vocal fold twitches captured on video laryngoscopy that may turn out to be a pathognomonic sign (neither of our laryngologists had ever seen anything similar before). Laryngeal electromyography (EMG) will not likely be helpful because the condition is intermittent. In between episodes, the EMG activity will be normal, as in other intermittent conditions such as paradoxical vocal fold motion. During an episode, it is unlikely that the patient will be calm enough to allow a needle to be inserted through their neck. The MRI demonstration of a vessel juxtaposed to the vagus nerve rootlets will be a necessary but insufficient test because of expected poor specificity. We believe the unilateral response to Botox will be the definitive test. The choking episodes (ipsilateral pharyngeal and/or laryngeal contractions) but not the coughing are dampened in response to ipsilateral Botox in the vocal fold in a manner similar to that in HFS. Contralateral Botox, however, appears to be ineffective (similarly to HFS). All other known causes of episodic laryngeal contractions respond symmetrically to Botox regardless of the side.

Second, the etiology of loss of consciousness that can occur with HELPS remains unclear. No patient had a Holter monitor at the time, and descriptions of the episodes are ambiguous. Most describe “a fading out” rather than an abrupt loss of consciousness as can be occasionally seen with vago-glossopharyngeal neuralgia.

Third, the proximity of cranial nerves IX and X suggests that HELPS should also sometimes co-occur with GPN. Two of our patients (unpublished) had concurrent HELPS and GPN, and their cases will be submitted for publication shortly. Interestingly, several large cohort studies of GPN have described rare patients with additional symptoms of coughing, throat tightness, and difficulty breathing.^{1,3}

Fourth, we have recently completed an analysis of a large group (n = 100) of high-resolution MRI studies to determine the incidence of vascular contact with the vagus nerve. As with the trigeminal and facial nerves, incidental asymptomatic vascular contact and even distortion of the vagus nerve can occur. The results of this analysis have

just been submitted to the *American Journal of Neurology*. We believe all patients with HELPS must have ipsilateral vascular contact with the vagus nerve, but many asymptomatic patients will also have a vascular contact. The presence of a vascular contact will therefore be a *sine qua non*, although this test will likely turn out to be necessary but not sufficient to confirm HELPS.

Fifth, we are recalling all our postoperative patients to examine their vocal cords with laryngoscopy. The first patient² has video-confirmed normal vocal cord function suggesting that the MVD was atraumatic. Examination in the remaining patients is pending. Rhizotomy of the vagus nerve is possible but difficult and could be accompanied by intolerable side effects. The senior author has performed percutaneous rhizotomy of the glossopharyngeal nerve and can report that it is logarithmically more difficult than that of the trigeminal nerve. Our center has no experience with the Gamma Knife.

A patient with intermittent choking and coughing and a vessel distorting their vagus nerve is not enough to prompt neurosurgery but does warrant investigation. These patients are suffering, often under the false diagnosis of a psychogenic etiology, and need our help. A beneficial response to Botox in the vocal fold ipsilateral but not contralateral to the compressing vessel should justify MVD by experienced hands. We caution our colleagues that this surgery is more demanding than that for TN (the trigeminal nerve can withstand more manipulation) or HFS because the slightest deficit of the vagus nerve is clinically significant, whereas mild facial numbness is soon ignored and temporary facial weakness is well tolerated.

Ultimately, the proof that HELPS is a definable medical condition with a neurosurgical cure will require others to confirm its existence. We appreciate Dr. Kaufmann's skepticism and critical demands. His editorial has prompted us to re-examine all our postoperative patients to confirm their laryngeal function. The discovery of this medical condition occurred because of a collaboration between a laryngologist interested in vocal disorders and a neurosurgeon comfortable with MVD. We believe that any center interested in correctly diagnosing and safely treating these patients will require a similar partnership.

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