Editorial

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Sphenopalatine (pterygopalatine) ganglion stimulation and cluster headache: New hope for ye who enter here

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Cluster headache is a devastating primary headache disorder (1) that in its chronic form presents as if approached and consumed by three beasts. Medically intractable chronic cluster headache (2) is among the most challenging of ailments headache specialists can be called on to treat. While we have seen important advances in understanding the disorder with brain imaging (3,4), and the conduct of randomized controlled trials in the last decade (5,6), many patients still suffer far too much. Research in the field is at best pathetically funded; as an example the writer is unaware of any dedicated projects involving the United States National Institutes of Health or United Kingdom (UK) Medical Research Council. Yet at some 0.1% of the population (7,8), cluster headache is as common as multiple sclerosis in the UK (9). Developments are welcome, and this issue of the *Journal* offers a new twist based on our understanding of the pathophysiology of the condition (10)—the involvement of the cranial parasympathetic outflow through the sphenopalatine ganglion (11).

Cluster headache is one of the trigeminal autonomic cephalalgias (TACs) (12). These syndromes have the signature features of lateralization of the phenotype: pain, cranial autonomic features (13), features typically associated with migraine, such as photophobia (14), and very distinct responses to treatment, such as the response in paroxysmal hemicrania (15) and hemicrania continua (16) to indomethacin (17,18). When clinicians consider the phenotype, and as the collection group term TAC implies, cranial autonomic features, viz. conjunctival injection, lacrimation, nasal congestion or rhinorrhea, eyelid edema, forehead or facial sweating or flushing, a sense of aural fullness or miosis or ptosis, come readily to mind. One or more is usually found in any patient and, importantly, we have a very good grasp of the anatomy and physiology of these symptoms.

To begin with a note of clarification, one of the key structures in the expression of cranial autonomic symptoms is the sphenopalatine (SPG) (19), sometimes called pterygopalatine (20), ganglion. The latter term seems to have invaded the literature as the SPG sits in the pterygopalatine fossa. Given that Gray's description was very complete, while either term seems usable, one could argue historical precedence for SPG. The outflow pathway for the cranial autonomic pathway begins in the superior salivatory nucleus in the pons, which can be excited by trigeminal afferents (21) and is certainly connected to a trigeminal input (22). The outflow proceeds through the seventh cranial (facial) nerve without synapsing in the geniculate ganglion. The important synapses are in the SPG, and to a lesser extent in the otic and carotid miniganglia (23–25). The SPG synapse is a hexamethonium-sensitive classic nicotinic ganglion, and there is nitric oxide synthase located within the SPG (26). When activated SPG stimulation increases cerebral blood flow (27,28) in the absence of a change in brain glucose utilization (29): neurogenic cerebral vasodilation. SPG activation plays a pivotal role in brainstem-induced changes in cerebral blood flow, such as those seen from locus coeruleus (25), and when activated releases vasoactive intestinal polypeptide (VIP) at the cortex (30) and can have its effects reversed if VIP is blocked (31). The SPG also possesses immunoreactivity (32) for pituitary adenylate cyclase-activating peptide (PACAP) (33,34), so that each of the PAC_1 and $VPAC_1$ and $VPAC_2$ receptors (35) could be involved in its activation (36).

On this basis the SPG has been proposed as a target for the treatment of cluster headache. Schoenen and

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colleagues (11) here present a fascinating sham-controlled randomized study of SPG stimulation to treat cluster headache. Certainly targeting the SPG is not new (37), and blockade with local anesthetic (38) or radiofrequency (39) approaches are well reported. The authors here have used a novel, miniaturized stimulator with an external control device targeted directly to the SPG by implantation. They report on 28 patients with chronic cluster headache who had a 67% pain relief outcome at 15 minutes. Perhaps more remarkable, 10 patients had a reduced frequency of attack during the treatment period, suggesting it may be better thought of as a cluster headache preventive device. The device seems well tolerated and safe, with some apparent learning curve to successful implantation. The most interesting side effect is what is described as localized loss of sensation in distribution of the maxillary nerve; this is predictable from the anatomical arrangement wherein the SPG drapes over and near the maxillary nerve in the pterygopalatine ganglion.

What I find exciting about this approach is the rational development of a new therapy based solidly on knowledge of the anatomy and physiology of the condition—translational medicine at work in a way the headache community can be proud of. With every new development in cluster headache my practice day brightens; even if it is not usable immediately, since it offers hope for tomorrow. Patients are looking to us—the headache community—for new understanding and new treatments of their problems. It is our collective role, nay responsibility, to see that patients with chronic cluster headache do not have to . . . abandon all hope . . ..

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Conflict of interest

I have consulted for the sponsor Autonomic Technology Industries, a fact declared to the *Journal* before accepting the commission for this editorial.

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