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Autonomic Cross-Innervation in Patients With Neurofibromatosis Type 2: Frey Syndrome and Unilateral Epiphora With Rhinorrhea

Erica Evans, MD[1], David Nascene, MD[2], Katherine Sommer, MS, RN[3], and Christopher Moertel, MD[3]

Abstract

The authors present 2 cases of cross-innervation in patients with neurofibromatosis type 2. In the first case, an iodine test was performed to demonstrate Frey syndrome in a 28-year-old female with neurofibromatosis type 2 who developed symptoms at age 10 years. The second patient is an 18-year-old female with neurofibromatosis type 2, 2 years status post left vestibular schwannoma subtotal resection who presented with paradoxical unilateral lacrimation and rhinorrhea triggered by heat stress and exercise. The pathophysiology of these cases is discussed.

Keywords

neurofibromatosis type 2, paradoxical lacrimation and rhinorrhea, vestibular schwannoma, nervus intermedius, auriculotemporal nerve syndrome

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Neurofibromatosis type 2 is a rare autosomal dominant syndrome classically characterized by bilateral vestibular schwannomas that can cause hearing loss, tinnitus, and balance problems. Other tumors are also seen in this syndrome, including meningioma, nonvestibular schwannoma, and ependymoma.[1] Hearing loss is a common result of vestibular schwannoma and is one focus of treatment in this disorder. However, other overlooked syndromes, such as "crocodile tears," Frey syndrome, and other forms of nervus intermedius dysfunction have also been documented following vestibular schwannoma resection.[2-4] Crocodile tears is a lacrimation hypersecretion disorder in which tearing is induced by oral or olfactory stimuli.[2] Frey syndrome is a related, but distinct, condition in which facial flushing or sweating is triggered by eating or smelling food. Although these syndromes have both been described after vestibular schwannoma surgery, patients with neurofibromatosis type 2 are often not included in these studies. Furthermore, nervus intermedius dysfunction syndromes are rarely discussed as presenting symptoms of neurofibromatosis type 2, occurring prior to corrective surgery. We report 2 unusual clinical scenarios in patients with neurofibromatosis type 2, one with the onset of Frey syndrome occurring 11 years prior to the diagnosis of neurofibromatosis type 2 and another with heat-induced unilateral lacrimation and rhinorrhea following vestibular schwannoma resection.

Case Report 1

A 28-year-old female presented with neurofibromatosis type 2 at age 21 years following computerized axial tomography (CT) of the head ordered for evaluation of head trauma. Her head CT

[1] University of Minnesota Medical School, Minneapolis, MN, USA
[2] Department of Radiology, University of Minnesota Medical School, Minneapolis, MN, USA
[3] Pediatric Hematology-Oncology, Department of Pediatrics, University of Minnesota Masonic Children's Hospital, Minneapolis, MN, USA

Corresponding Author:
Christopher Moertel, MD, Pediatric Hematology-Oncology, Department of Pediatrics, University of Minnesota Masonic Children's Hospital, 2450 Riverside Ave, Minneapolis, MN 55455, USA.
Email: moert001@umn.edu

revealed calcified extra-axial lesions in the left posterior fossa, left frontal region, and right parietal region thought to probably represent small meningiomas. She was subsequently assigned the clinical diagnosis of neurofibromatosis type 2 when magnetic resonance imaging revealed bilateral vestibular schwannomas and underwent γ knife radiosurgery for one of the lesions, a posterior clinoid (cranial nerve III) schwannoma, in close proximity to the ipsilateral optic nerve and optic chiasm. Genetic testing for the neurofibromatosis type 2 mutation was refused following radiosurgery; she had ongoing issues with headache, tinnitus, and strabismus. Her tinnitus was controlled with bevacizumab therapy that was prescribed for hearing preservation. She subsequently completed strabismus surgery for right cranial nerve III palsy secondary to her right third nerve schwannoma therapy.

This patient reported that she had been experiencing profuse left-sided neck perspiration since the age of 10 years. She described focal diaphoresis in the distribution of her left trigeminal nerve (V_3), triggered by seeing or tasting cheese or potatoes. The diaphoresis had been so profuse that she occasionally had to rewash her hair after eating. In September 2013, the patient agreed to participate in a starch iodine test[5] to document her atypical case of Frey syndrome. We applied betadine solution to the left lateral aspect of the patient's neck, just below the ear, and then dusted the area with cornstarch. The patient was then given cheese sticks and potato chips to eat. Over a period of 5 to 10 minutes, perspiration was visible along and below the hairline in the left postauricular area as well as along the hairline above and anterior to the left ear. This region, previously painted with betadine and dusted with cornstarch, developed a confluent purple black color. A scopolamine patch was somewhat effective in ameliorating her aberrant cranial nerve function.

Case Report 2

An 18-year-old female with neurofibromatosis type 2, genetic severity score 3[6] (truncating mutation in exon 13), underwent subtotal resection of a left vestibular schwannoma at age 16 years via a left middle fossa approach with image guidance. At the time of surgery, she was found to have tumor filling the lateral portion of the internal auditory canal with the facial nerve along the anterior surface of the tumor. Cranial nerve VII was intact and stimulatable at the end of the case at 0.05 mA. She returned to clinic 8 days postoperatively with rhinorrhea secondary to a CSF leak, which resolved completely with lumbar drain placement. She had moderately severe left-sided facial weakness following the surgery (House-Brackmann IV), which resolved by 4 months postoperatively (House-Brackmann I). However, left dry eye persisted. One year after the schwannoma resection, the patient underwent left retrosigmoid craniectomy for resection of a left-sided posterior fossa (petrous ridge) meningioma. The patient now reports that over the past year, when her body temperature increases or when she is exercising heavily, she develops left-sided lacrimation and rhinorrhea. The rhinorrhea is so intense that she had to use gauze plugs in her left nostril while exercising. We exercised the patient in clinic and documented that the rhinorrhea was not due to CSF leak by absence of β-2 transferrin in the collected fluid.

Discussion

In both of these cases patients with neurofibromatosis type 2 exhibit clinical phenomena caused by interruption of one neural pathway followed by cross-innervation via an alternate pathway. Frey syndrome, also known as auriculotemporal nerve syndrome, is characterized by facial flushing, sweating, and warmth in the preauricular and temporal areas that is triggered by the normal stimuli for salivation (eating or smelling food). Frey syndrome is most commonly caused by parotid gland surgery but can arise from any surgery, trauma, infection, or inflammation involving the auriculotemporal nerve that is a branch of the mandibular division of the trigeminal nerve (V3).[7] Frey syndrome is rare in children but has been described following obstetric forceps trauma and herpes zoster infection.[7,8] There are also 3 case reports of Frey syndrome in children with neurofibromatosis type 1 and facial plexiform neurofibromas involving the parotid gland.[9] Our first case describes Frey syndrome beginning in childhood, likely attributed to a schwannoma or meningioma associated with neurofibromatosis type 2 (Figure 1). To our knowledge, this is the first case report of a patient with neurofibromatosis type 2 presenting with Frey syndrome.

The parasympathetic nervous system induces salivation by releasing acetylcholine on muscarinic receptors of salivary acinar cells.[10] There are 2 primary pathways, beginning in the inferior and superior salivatory nuclei, located in the dorsal pons.[11] Preganglionic fibers originating in the inferior salivatory nucleus travel on the glossopharyngeal nerve to the otic ganglion. Postganglionic fibers then travel from the otic

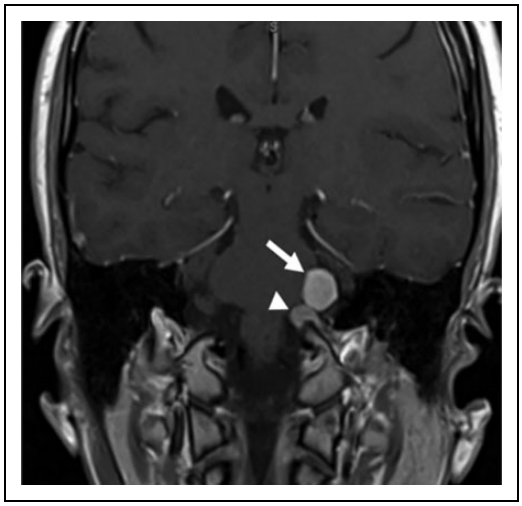

Figure 1. Arrow denotes a vestibular schwannoma in the left cerebellopontine angle cistern. Arrowhead denotes a meningioma inferior to the schwannoma that extends slightly into the pars nervosa region of the jugular foramen.

ganglion on the auriculotemporal and buccal nerves (branches of the mandibular nerve) to trigger salivation in the parotid gland. Preganglionic fibers from the superior salivatory nucleus travel on the chorda tympani and lingual nerves to synapse in the submandibular ganglion. Postganglionic fibers from the submandibular ganglion trigger salivation in the submandibular and sublingual salivary glands. There are also sympathetic nerve fibers nearby that supply the sweat glands and blood vessels in the temporal region.[11] Frey syndrome is likely caused by abnormal regeneration of parasympathetic nerves after surgery or other damage to sympathetic nerves. Parasympathetic nerve fibers grow into the damaged sympathetic pathways, leading to inappropriate connections between salivatory nuclei and distal sweat glands and blood vessels.[11] Thus, stimuli for salivation ultimately trigger sweating and flushing.

The mechanism of paradoxical lacrimation and rhinorrhea in patients who have undergone vestibular schwannoma surgery is remarkably similar. Paradoxical gustatory lacrimation (crocodile tears) is characterized by tearing in response to oral or olfactory stimuli. This is caused by rerouting of salivary parasympathetic fibers to the lacrimal gland, which can occur during development or following injury to the facial nerve.[12-14] The incidence of crocodile tears following vestibular schwannoma resection ranges from 10.9% to 44%, likely varying widely based on the surgical technique and extent of resection.[2,15] Our patient experienced lacrimation and rhinorrhea in response to exercise and heat, suggesting a sympathetic rather than gustatory stimulus. This is less well-documented in the literature, but one study of 10 patients with facial nerve palsy following acoustic neuroma surgery showed a significant increase in lacrimation before and after heating.[16]

Lacrimation is typically controlled by parasympathetic innervation. Parasympathetic neurons in the nervus intermedius (part of the facial nerve) exit the pons between the motor root of the facial nerve and the vestibulocochlear nerve. These parasympathetic fibers pass through the geniculate ganglion without synapsing, form the greater petrosal nerve, and eventually join with the deep petrosal nerve (sympathetic fibers) to form the vidian nerve. The vidian nerve thus contains parasympathetic and sympathetic fibers. Parasympathetic fibers from the vidian nerve synapse on lacrimal secretomotor nerves in the sphenopalatine ganglion to induce lacrimation.[17] The nervus intermedius parasympathetic fibers can be stretched, displaced anteriorly, or disrupted by a vestibular schwannoma, tumor compression, or surgery. Somewhat analogous to the mechanism described previously for Frey syndrome and gustatory lacrimation, the intact sympathetic nerves of the more distal vidian nerve could then ultimately resupply the deafferented lacrimal neurons in the sphenopalatine ganglion, leading to lacrimation following sympathetic stimulation.[16] However, unlike the "misrouting" of parasympathetic synapses as seen in crocodile tears, the sympathetic neurons do not typically synapse in the sphenopalatine ganglion, but could develop cross-innervation through neural plasticity.

Paradoxical rhinorrhea likely occurs in a similar fashion and has been briefly described in the literature. Huy and Sauvaget[18] described 3 cases of unilateral rhinorrhea triggered by exercise and stress after translabyrinthine surgery. Another study of 6 cases of schwannoma resection demonstrated dryness of the ipsilateral eye and nasal cavity after surgery of vestibular or facial schwannoma[19] but did not report on cross-innervation. In our patient, eye dryness developed immediately after the surgery, but the heat- and exercised-induced lacrimation and rhinorrhea developed a year later, suggesting that it takes some time following the injury to establish cross-innervation in concert with a presumed Meckel cave meningioma (Figure 2).

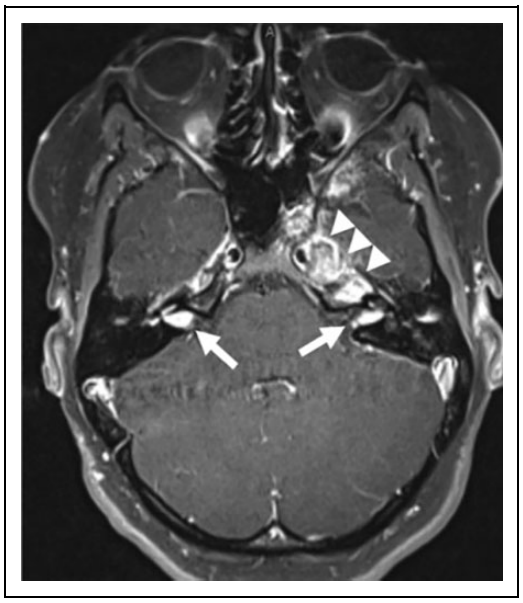

Figure 2. Magnetic resonance imaging (MRI) after left vestibular schwannoma resection. Arrows denote bilateral internal auditory canal schwannomas. The 3 arrowheads denote a presumed meningioma in the left Meckel cave.

Neurofibromatosis type 2 is characterized by bilateral vestibular schwannomas which can compromise parasympathetic function and place these patients at greater risk for Frey syndrome, paradoxical lacrimation, and rhinorrhea. One study found that 18% of vestibular schwannoma patients had nervus intermedius dysfunctions of lacrimation, salivation, nasal secretion, or taste prior to radiosurgery, increasing to 18 (36%) of 50 after radiosurgery.[4] This suggests that both the primary tumor itself and the treatment of the tumor can lead to disruption of nervus intermedius pathways. Once the normal neurologic pathways have been damaged, cross-innervation can occur, even before surgery, as evidenced by our first patient. Mature autonomic nerves do have the ability to reinnervate following denervation. In one key study, removal of parasympathetic innervation in a rat iris induced collateral sprouting of both sympathetic and sensory fibers. The authors proposed this occurs due to competition between presynaptic nerves for nerve growth factor released from target tissues.[20] Another animal study demonstrated that infusion of nerve growth factor induced sprouting of sympathetic neurons, suggesting that mature, uninjured sympathetic neurons remain responsive to nerve growth factor.[21]

Conclusions

We report 2 cases of cross-innervation of autonomic fibers due to different causes associated with neurofibromatosis type 2. The first is a case of Frey syndrome that developed spontaneously in childhood. This suggests that Frey syndrome can be an unusual presentation of neurofibromatosis type 2 and that the tumor burden alone is enough to disrupt parasympathetic pathways, allowing for cross-innervation. The second case demonstrates exercise- and heat-induced unilateral lacrimation and rhinorrhea in a neurofibromatosis type 2 patient following vestibular schwannoma resection. This supports the concept of cross-innervation resulting in inappropriate sympathetic nervous system control of the parasympathetic neurons controlling secretion in the nose and lacrimal gland after surgery for vestibular schwannoma.

Authors' Note

This study has been approved by the institutional review board of University of Minnesota.

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Author Contributions

CM and EME collaborated on the project concept and case report design. EME performed detailed retrospective chart review and drafted the manuscript. CM provided critical review of the manuscript. DN provided neuroradiological images and associated figure legends, in addition to critical review of the manuscript. KS conducted the cornstarch and betadine test, assisted with chart review, and reviewed the manuscript. All authors gave final approval.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Moertel is a consultant for Recombinetics, Inc.

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ORCID iD

Christopher Moertel, MD https://orcid.org/0000-0002-5474-588X

Ethical Approval

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