Clinical Reasoning:

A 51-year-old woman with syncopal episodes and multiple cranial neuropathies

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SECTION 1

Case presentation. A 51-year-old right-handed woman was admitted to the hospital because of two syncopal episodes. Both events had similar features with sudden onset of loss of consciousness. There were no preceding symptoms. They lasted only few seconds and were not accompanied by any abnormal movements, incontinence, or tongue biting. There was no confusion following the events. A feeling of vertigo, which gradually

dissipated over the following 2 days, was the only residual symptom following both episodes.

The patient also had a history of hypertension. She was on no medications. She consumed alcohol occasionally but denied tobacco or drug abuse. Her family history was positive only for heart disease in her mother.

Question for consideration:

1. What is the differential diagnosis of syncope in this case?

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SECTION 2

Syncopal is a sudden and brief loss of consciousness, associated with a loss of postural tone, with spontaneous recovery. It results from transiently decreased or interrupted cerebral blood flow. Frequently, the etiology remains unknown. Among diagnosed cases, neurocardiogenic syncope (including vasovagal attack, situational syncope, and carotid sinus syncope) is the most frequent cause. It stems from reflex-mediated changes in the vascular tone or heart rate. Other causes include cardiac (organic heart disease or arrhythmia) or neurologic diseases (concussion or seizure), orthostatic hypotension, medications, or psychiatric disorders.^{1,2} In this patient, based on the history, both reflex-mediated and primary cardiac causes were contemplated.

On admission, the patient reported 3 years of right hearing defect without tinnitus or ear pain. She denied dysphagia or hoarseness of her voice. She was otherwise asymptomatic.

On neurologic examination, cranial nerves I–VII were intact. There were multiple lower cranial neuropathies (VIII–XII) on the right side. There was significant right ear hearing loss. The tuning fork tests

were equivocal: the Weber test lateralized to the affected ear (suggesting a conductive hearing loss in the right ear) and the Rinne test indicated air greater than bone conduction on the right side (suggesting a sensorineural hearing loss in the right ear). Her gag reflex was weaker on the right side. The right sternocleidomastoid was atrophic and there was winging of her right scapula. The right side of her tongue was mildly atrophic and exhibited prominent fasciculations (video 1). The remainder of the neurologic examination was unremarkable.

The otorhinolaryngologic examination was remarkable for a reddish hue behind the right tympanic membrane and mildly sluggish abduction of her right true vocal cord (video 2). The vocal cords had good approximation on phonation and swallowing suggesting compensation from the left true vocal cord. A formal audiogram was obtained to elucidate the discrepancy of the tuning fork test and identified profound sensorineural hearing loss in the right ear.

Question for consideration:

1. What is the differential diagnosis of multiple cranial neuropathies?

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SECTION 3

In a large series of multiple cranial nerve palsies, tumors comprised 30% of the cases, followed by vascular disease (12%), trauma (12%), infection (10%) and Guillain-Barré syndrome (6%). Most commonly, a schwannoma (17%) was the culprit, followed by metastases (16%), meningioma (13%), lymphoma (10%), and pontine glioma (9%). The cranial nerve damage was usually at the cavernous sinus (25%), and less frequently at the brainstem (21%), the nerve itself (18%), the skull base (13%), and the subarachnoid space (10%). The affected cranial nerves varied depending on the etiology and the location of the damage, but the cranial nerves VI, VII, V, and III were most commonly involved in descending order of frequency.³

In this patient, the history of a hearing defect 3 years ago and the presence of atrophy and fasciculations in her tongue pointed more to a chronic condition than a vascular event. There was no clinical suspicion of trauma or infection. Thus a slow growing neoplasm appeared the most plausible explanation of her multiple cranial neuropathies. The involvement of the cranial nerves VIII–XII only on the right, without long tract signs, pointed toward skull base localization.

The patient had a negative cardiac evaluation (telemetry and echocardiogram) for her syncope. She had an unremarkable EEG. CT of the head showed a hyper-

Figure 1 CT head without contrast showing hyperattenuating mass at the right jugular foramen with associated destruction of the temporal bone

dense mass at the right jugular foramen with associated destruction of the temporal bone (figure 1).

Question for consideration:

1. How can you differentiate jugular foramen tumors based on neuroimaging?

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SECTION 4

Jugular foramen tumors are classified as primary (i.e., located in the jugular foramen and extending into the adjacent structures) and as secondary (i.e., extending from the adjacent structures into the jugular foramen). In descending order of frequency, glomus jugulare tumors, schwannomas, and meningiomas are the most common primary tumors. The secondary tumors comprise chordomas, chondrosarcomas, chondroblastomas, giant cell tumors, cholesterol granulomas, giant cholesterol cyst, endolymphatic sac tumors, reactive myofibroblastic tumors, temporal bone carcinomas, and metastases. In the group of primary tumors, glomus jugulare tumors can cause destruction of the jugular foramen margins, may have “salt-and-pepper” appearance in the T1 and flow voids on T2-weighted images, exhibit drop out effect with contrast administration, and are hypervascular lesions with large feeding vessels and early draining veins seen on angiography. Schwannomas can cause foramen enlargement without invasion, are hypointense in the T1-weighted and hyperintense in the T2-weighted images, enhance strongly with contrast administration, and are mildly to moderately vascular. Some cases may give cystic degeneration. Finally, meningiomas preserve the architecture of the foramen, present with a “dural tail,” are hypo/isointense on the T1-weighted and hyperintense in the T2-weighted images, enhance uniformly with contrast administration, and exhibit mild to moderate vascularity.⁴

Our patient underwent further evaluation. MRI of the brain revealed extension of the tumor, measuring $3.4 \times 2.4 \times 2.4$ cm, to the petrous apex, mastoid air cells, and superior cerebellopontine angle. The tumor surrounded the right internal carotid artery. There was also extension of the mass through the skull base within the right internal jugular vein and the hypoglossal canal (figure 2). CT angiography of the brain demonstrated right glomus tumor (jugulotympanicum) with involvement of the middle ear, otic capsule, hypoglossal canal, jugular foramen, encasement of right ICA, and invasion of right sigmoid sinus and upper jugular vein (figure 3). Biochemical screening for catecholamines was within normal limits.

Question for consideration:

1. What was the cause of the patient's syncopal episodes and of her subsequent vertigo?

Figure 2 MRI head with contrast showing a $3.4 \times 2.4 \times 2.4$ cm tumor extending through the skull base

Figure 3 CT angiogram of the head and neck showing right glomus tumor (jugulotympanicum) with involvement of the middle ear, otic capsule, hypoglossal canal, jugular foramen, encasement of right ICA, and invasion of right sigmoid sinus and upper jugular vein

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SECTION 5

Syncope is not commonly reported as a manifestation of glomus tumor. Its etiology should be sought in the baroreflex failure. Baroreflexes originate in the great vessels of the neck and thorax and prevent arterial pressure from fluctuating excessively. Information about distention of the vessel wall is transmitted from baroreceptors in each carotid sinus via the glossopharyngeal nerves and in the aortic arch via the vagus nerves. The brainstem structures receiving the information are the commissural, dorsolateral, and medial portions of the nucleus tractus solitarii. The vagus nerves are the efferent pathway of the reflex. Abnormalities in the baroreceptors, the IX or X nerves, or the brainstem could lead to baroreflex failure.⁵ A few cases

of paragangliomas leading to blood pressure dysregulation⁶ and to syncope⁷ have been reported in the literature. The postsyncopal vertigo was likely peripheral, possibly due to impairment in the microcirculation of the labyrinth. A plausible explanation is that the patient had compensated vestibulopathy (i.e., the affected side had no vestibular responses) and the syncope reduced the microcirculation to the contralateral functional vestibular system, resulting in imbalance and vertigo.

Question for consideration:

1. What is the natural history of the disease and what are the management options for this patient?

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SECTION 6

Paragangliomas are slow-growing, mostly benign tumors. Radiation and observation are palliative and surgery is curative. A treatment plan should be individualized based on the diagnostic tests, the tumor type, and the patient age and health.⁸

This patient had an MRI and CT scan that showed encasement of the right internal carotid artery. There was extensive discussion with the patient regarding the best course of action. Curative treatment with surgery would entail a combined otologic-neurosurgical approach with sacrifice of the internal carotid artery and the cranial nerves VII, VIII, IX, X, XI, and XII. The resection of the internal carotid would have to be done at the level of the circle of Willis with preoperative test occlusion. This surgical approach could put the patient at high risk for postoperative stroke. It was felt that radiation therapy, alternatively, might result in poor wound healing and risk of persistent CSF leak and meningitis. Given her high functional level, the patient elected not to pursue any treatment.

DISCUSSION Paragangliomas are slowly growing hypervascular tumors arising from a neural crest progenitor cell. Paragangliomas can be divided into the adrenal and the extra-adrenal system. The latter can be further subdivided into the branchiomeric (carotid, jugulotympanic, subclavian, laryngeal, coronary, aorticopulmonary, and orbital paraganglia), the intravagal, and the aortic sympathetic paraganglia. The last are often chromaffin positive and secrete catecholamines.⁹

The most frequent paragangliomas above the neck are carotid body tumors followed by glomus jugulare tumors. Although mostly benign, their critical location next to important neurovascular structures renders these tumors clinically aggressive. Most of these tumors will manifest with a palpable neck mass, tinnitus, pulsatile mass in the ear, and various lower cranial nerve palsies.¹⁰

Only a small proportion (<10%) of head and neck paragangliomas is hyperfunctional. The combined sensitivity for all three catecholamines in identifying hypersecreting extra-adrenal paragangliomas has been reported close to 90%.¹¹ However, it is important to recognize these cases preoperatively to allow adequate pharmacologic preparation before anesthesia and surgery.

Extra-adrenal paragangliomas can be solitary or multicentric and can arise sporadically or in familial patterns. Only 6% of jugulotympanic paragangliomas metastasize. Previous studies have emphasized the significance of identifying immunohistologically two distinct cell populations, the

chief cells (type I) and the sustentacular cells (type II). The latter are typically absent in aggressively metastasizing paragangliomas.⁹

Most head and neck paragangliomas exhibit a slowly progressive course. Surgery is the definitive therapeutic modality. Radiotherapy is indicated for older patients, those at risk for surgery, and extensive tumors in order to stabilize the tumor, improve the symptoms, and decrease morbidity.¹² Embolotherapy must be basically preoperative and is not curative.¹³ Approximately one third of patients have persistent or recurrent disease and long-term follow-up is necessary.¹¹

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