Clinical Problem-Solving

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A Nerve-Racking Syncope

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A 70 year old woman was admitted to hospital because of recurrent syncope. Her history was notable for hypertension, heavy smoking and ischemic heart disease, which had been asymptomatic since a coronary bypass graft surgery performed 5 years before admission. Three years prior to admission, the appearance of squamous cell carcinoma necessitated a right subtotal maxillectomy and orbital enucleation followed by radiotherapy. Right subtotal parotidectomy with radical neck dissection was subsequently performed due to tumor recurrence 18 months before admission. Two lung metastases were noted at that time, which showed little enlargement during 18 months of computed tomographic follow-up. During the 3 weeks prior to admission the patient experienced five syncopal episodes with loss of consciousness lasting up to 5 minutes. The syncopal episodes, occurring in both the upright and recumbent positions, were sudden, without palpitations or dizziness, and in some instances accompanied by urinary incontinence. Medication on admission included low dose aspirin and captopril.

Syncope has a wide differential diagnosis, recently reviewed elsewhere [1]. Although vasovagal syncope and orthostatic hypotension are among the leading causes of syncope, they are unlikely to be the underlying mechanism for recurrent true syncopes in the supine position and to occur without preceding dizziness. Syncopes at recumbency, along with a history of coronary heart disease mandate a thorough evaluation for cardiogenic and arrhythmogenic etiologies. Given our patient's history of malignant disease in which brain metastasis may be manifested by seizures, epileptiform disturbance should also be considered. More information is needed about the nature of the syncopes and the accompanying symptoms, if any.

Further questioning revealed that following a return to consciousness, the patient remained weak and confused for up to 30 minutes. No convulsions were witnessed. Prior to some episodes, but not all, the patient felt a sharp pain "inside her right jaw" that continued after she regained consciousness. Some episodes were triggered by turning her head to the left (for instance, to hold a phone set); she denied wearing tight collars. Other sensory complaints, motor deficiencies, chest pain or palpitations were all denied.

This additional information is valuable in narrowing the differential diagnosis. Seizures are often accompanied by urinary incontinence, and the post-syncope weakness and confusion in this patient could reflect a post-ictal state. However, no convulsions were reported, the post-ictal state was relatively short, and urinary incontinence could also have resulted from global cerebral ischemia. Syncopes at recumbency, sometimes occurring after turning the head, are highly suggestive of carotid sinus syndrome, which could explain most of her symptoms. The pain accompanying some episodes may suggest glossopharyngeal neuralgia, or perhaps trigeminal neuralgia. However, patients with glossopharyngeal neuralgia usually have dysphagia and attacks precipitated by swallowing [2], which were not reported in this case. Finally, despite clues to other etiologies, significant brady-tachyarrhythmias should still be considered in this patient who had recurrent syncope and organic heart disease. We would proceed to meticulous physical examination, including monitored carotid massage.

Upon examination the patient appeared robust, with a post-surgery deformity and scars in her right maxillary zone and a patched right eye. Pulse was regular at 70 beats per minute, and blood pressure was 153/70 mmHg, which fell to 124/78 after 3 minutes of standing. The carotid pulse was palpable bilaterally. A 2/6 mid-systolic murmur was heard at the base of the heart, radiating to the neck. A midsternotomy scar was present. Touching the tonsils and palate with an applicator tip did not elicit any pain. The rest of the physical examination was

> unremarkable. Bilateral carotid massage did not produce bradycardia or blood pressure drop.

Orthostatic hypotension is a common cause of syncope. It can be caused by decreased intravascular volume, autonomic insufficiency, and drugs such as angiotensin-converting enzyme inhibitor, which this patient was taking. However, orthostatism was unlikely to cause fainting in this patient while lying supine. The systolic murmur could reflect aortic stenosis, of which syncope is a classic manifestation. However, syncope of aortic stenosis is usually effort-induced and due to the inability to appropriately increase cardiac output to meet metabolic demand. The pain of glossopharyngeal and trigeminal neuralgia can typically be elicited by touching certain trigger points – in the tonsils or palatine arch, and on the cheek, respectively. This was not the case in our patient. The negative carotid massage argues against carotid hypersensitivity, but it can sometimes be falsely negative when not properly performed. We would proceed to routine blood tests and electrocardiogram, although their yield in identifying causes of syncope is low [1]. In addition, in this patient with organic heart disease, we would order echocardiogram and 24 hour continuous electrocardiogram (Holter). Because of the non-conclusive symptoms, epileptic disturbance would be hard to exclude without electroencephalogram.

> Complete blood count and chemistry results were normal except for normocytic anemia with hemoglobin level of 11.1 g/dl. The ECG demonstrated normal sinus rhythm with no signs of ischemia or conduction disturbance. Holter recording showed normal sinus rhythm with occasional ventricular premature beats. Echocardiogram showed good left ventricular function, with non-stenotic calcific aortic valve. A mobile calcified plaque was suspected at the aortic arch, adjacent to the outlet of the brachiocephalic and common carotid arteries. CT of the brain showed an old lacunar infarct of the left thalamus. Non-invasive carotid evaluation showed 25% stenosis at the left internal carotid artery. Electroencephalogram was normal.

Anemia is a possible cause for syncope, but was unlikely to be the culprit responsible for recurrent syncope, without accompanying weakness and orthostatism between the episodes. A comparison with a previous blood count is imperative. Brain imaging and Doppler of the carotid arteries are rarely indicated in patients with syncope, as their yield in identifying a responsible lesion is very low [1]. The echocardiogram was helpful in ruling out aortic stenosis. The plaque at the aorta is a disturbing finding for its embolic potential but was unlikely to be the cause for recurrent syncope, especially when other neurologic deficits were absent. Trans-esophageal echocardiogram could be performed to accurately evaluate this plaque, but

ECG = electrocardiogram

will probably not contribute to clarifying the cause of this patient's symptoms. The rest of the tests proved unhelpful. Tilt-testing is probably not warranted in this case, as vasovagal syncope is unlikely with episodes in a supine position and in the absence of provocative triggers such as venopuncture [3]. Since the patient reported frequent syncopes, we would observe her for several days in the hope of documenting a syncopal episode. If syncopes were further apart, a continuous loop monitoring by an external or implantable recorder could be considered. A patient-operated cardiac rhythm recorder, initiated by the patient upon sensation of an imminent syncope, is another alternative but is inappropriate in a patient with abrupt fainting.

> Blood count done 7 months earlier showed a hemoglobin level of 11.4 g/dl. The possibility of trans-esophageal echocardiogram was declined by the patient. Atenolol was substituted for captopril. Two days after admission, the patient fainted while lying in bed and turning her head to the left for right carotid artery auscultation. Loss of consciousness lasted for 5 minutes and was accompanied by urinary incontinence. The monitor strip documented extreme sinus bradycardia with a rate of 30 beats per minute. Blood pressure was 60/30 mmHg. The patient remained weak and somewhat confused for 15 minutes after regaining consciousness. A 12 lead ECG revealed no signs of ischemia. Two hours later, another episode occurred while she was sitting in a chair but without prior turning of the head. The episode was terminated by atropine administration. After becoming conscious, the patient reported a sharp pain in her right pharynx and jaw that preceded the syncope.

Documentation of the syncope enables classifying it as most probably due to a neurally mediated mechanism, for instance, secondary to carotid hypersensitivity. Carotid massage done previously was negative. However, this test is not always consistently reproducible in patients with carotid sinus syndrome, possibly due to fluctuations of carotid sensitivity [4]. We would therefore repeat the carotid massage. Inferior myocardial ischemia producing sinus bradycardia and low blood pressure is unlikely in the absence of chest pain, electrocardiographic changes or regional hypokinesia on echocardiogram. The symptomatic extreme bradycardia is an indication for an urgent pacemaker implantation.

> A bilateral carotid massage was performed again in the cardiology unit, and was negative for symptoms, bradycardia or blood pressure drop. A dual-chamber permanent pacemaker was implanted. The next day, while in bed, the patient suffered another syncopal episode, despite adequate pacemaker operation, with a weak palpable carotid pulse at a rate of 70 beats per minute, and a measured blood pressure of 65/35 mmHg. Right pharyngeal pain was again

reported to precede the syncope, and lasted a few minutes after she regained consciousness. Fludocortisone at a dose of 0.1 mg a day was started. Atenolol was discontinued, and clonidine was started due to increased basal blood pressure to levels of up to 210/100 mmHg. A 24 hour blood pressure monitoring under this regimen showed values ranging between 100/60 and 170/90 mmHg.

Clearly, in this patient the vasodepressor component was the dominating cause of syncope, as abrogating the bradycardia component by a pacemaker did not abolish the symptoms. Predominantly vasodepressor-mediated syncope can occur with carotid sinus hypersensitivity as well as in glossopharyngeal syncope [5,6]. Carotid sinus denervation and intracranial sectioning of the glossopharyngeal nerve are the most consistently efficient therapies, respectively [7,8]. Differentiation between the two syndromes in this case is not easy. However, the twice negative carotid massage and the increasing number of episodes associated with pharyngeal pain, which is not a feature of carotid sinus hypersensitivity, support glossopharyngeal neuralgia-associated syncope as the probable cause. Glossopharyngeal neuralgia with syncope is usually idiopathic, but some cases have been attributed to multiple sclerosis, space-occupying lesions, compression by arterial loop, calcified stylohyoid ligament, and Paget's disease.

Suspecting a glossopharyngeal neuralgia-associated syncope, a neck CT scan was performed without contrast, due to iodine sensitivity and the patient's refusal to pretreatment with corticosteroids. This revealed a mass extending from the right hypopharynx down to the larynx, which was not present in a previous CT scan of the neck, suggesting local recurrence of her neoplastic disease.

Local recurrence of neoplastic parapharyngeal disease, precipitating episodes of glossopharyngeal neuralgia by nerve compression, was probably the cause of recurrent syncope in this patient. Despite this probable mechanism, local control of the tumor has not been reported to successfully abolish syncope. Further follow-up will be needed to ascertain whether the mineralocorticoid treatment will suffice to abate syncopal episodes. We suspect that neurosurgical glossopharyngeal denervation will ultimately be required.

Oncologic consultation advised against systemic chemotherapy, which would not alter the course of her metastatic disease. Radiotherapy and local resection were also withheld since they were not expected to affect her symptoms. The patient was well for 4 days, and 24 hour continuous blood pressure recording revealed no pressure drops. She was discharged to a rehabilitation center. One day after discharge the patient was readmitted with syncope followed by pharyngeal pain. Carbamezapine was started at a dose of 100 mg three times daily, with instructions for gradual increase of dose. At 4 months follow-up the patient had no further episodes of syncope or pain. However, she complained of shortness of breath and lost 8 kg of weight. A CT scan then showed progression of the tumor in the neck. Lung metastases also enlarged, and compression of intermedius bronchus by the right hilar mass was seen. A short radiotherapy course was administered to the right hilar metastasis, with some relief of dyspnea. The patient died 7 months after admission due to the progression of her disease. No further syncopes or pharyngeal pain attacks occurred prior to her death.

Commentary

The etiologies of syncope are numerous, yet in up to 47% of cases the underlying etiology remains unknown despite medical assessment [9]. In evaluating syncope, a detailed history and careful physical examination are especially rewarding, as they alone can provide the correct etiology in the majority of diagnosed patients. Indeed, the characteristics of this patient's syncopes, which occurred in bed and were preceded by pain or turning of the head, pointed strongly to a neurocardiogenic mechanism, most likely carotid sinus syndrome or glossopharyngeal neuralgia. The negative carotid massage and the recurrent episodes of pain eventually suggested the correct diagnosis. Pitfalls, stemming from incidental findings on physical examination and laboratory or imaging studies, may complicate the diagnostic effort. Thus, orthostatic hypotension was found in 55% of elderly patients with other causes of syncope [9] and was probably a non-relevant finding in our patient as well. Similarly, the mild anemia and the aortic plaque were probably unassociated, albeit confusing findings arising from routine diagnostic tests. Documentation of syncope is invaluably helpful but is not always feasible, particularly when syncope is single or not frequent. In this patient it had paramount importance in focusing the diagnostic attention to the pertinent clues. Once the possibility of glossopharyngeal neuralgia-associated syncope was placed on the top of the list, the patient's history of neck and cranial neoplastic disease could direct the appropriate study – in this case imaging of the neck region. This, in turn, resulted in additional support of the diagnosis, by demonstrating local recurrence of the malignant disease.

Glossopharyngeal neuralgia is an uncommon craniofacial pain syndrome, usually localized to the tonsils, ear, pharynx and larynx, and is evoked by swallowing, talking or sneezing, as well as by touching trigger points in the above mentioned zones [2]. Syncope associated with glossopharyngeal neuralgia is a rare phenomenon. In a study of 217 patients examined for glossopharyngeal neuralgia at the Mayo Clinic, only one patient was reported to suffer from recurrent associated syncope [2]. The mechanism is believed to be related to the neuro-anatomy of the carotid reflex. Afferent impulses from baroreceptors in the carotid sinus are conveyed by the Hering nerve, which runs in

the glossopharyngeal trunk, until they reach the nucleus of tractus solitarius in the midbrain [6]. Secondary neurons then relay these impulses to the dorsal nucleus of the vagus nerve in the medulla oblongata and to the venteromedial medulla, exciting parasympathetic efferent impulses and inhibiting sympathetic outflow respectively. Thus, pain stimuli cross-activating or 'spilling over' to the autonomic fibers of the glossopharyngeal nerve are interpreted by the vasocardiocenters of the brain stem as evidence of increased pressure in the carotid sinus. This in turn leads to activation of the efferent loop, with ensuing cardio-inhibition due to vagally mediated parasympathetic impulses, and peripheral vasodilatation due to sympathetic outflow reduction [6,8].

Most cases of glossopharyngeal neuralgia-associated syncope are idiopathic, but there are several reports of cases associated with parapharyngeal tumor [10–15]. Intriguingly in these cases, as well as in the patient under discussion, dysphagia and triggering points and actions (such as swallowing) were mostly absent, in contrast with their presence in cases of idiopathic glossopharyngeal neuralgia and syncope. This is perhaps due to nerve ending receptor pathology in the oropharynx in idiopathic glossopharyngeal neuralgia-associated syncope, as opposed to nerve compression along its course in tumor-related cases. In a few cases, as in the present patient, some episodes were evoked by turning of the head. The reason for this is unclear, but the two patients reported to be treated by carotid sinus denervation did not benefit from the procedure [15]. Local control of the tumor has mostly failed in preventing symptoms. Pacemaker implantation has not abolished syncopes, but some patients, as in this case, benefited from treatment by carbamezapine with or without a permanent pacemaker [11,15,16]. Patients who fail to respond to this medical therapy should be considered for the neurosurgical option of the Adson procedure. Consisting of intracranial section of the glossopharyngeal and upper two rootlets of the vagus nerve, it is uniformly successful in termination of syncope and pain [15]. Microvascular decompression of the glossopharyngeal nerve in the posterior fossa has also been successful in cases where a compressing lesion was found at craniotomy [8].

Despite being a rare cause of syncope, glossopharyngeal neuralgia vividly demonstrates the value of history-taking and physical examination in patients with syncope, and no other tests are required to identify this etiology. This may help to avoid excessive workup and to confront confusing pathologic findings that often coexist in the elderly patient with syncope. Once the diagnosis of glossopharyngeal associated syncope is established, imaging or other tests may be warranted to exclude secondary causes of this syndrome, which in turn may help in selecting the appropriate management.

References

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I was proud of the youths who opposed the war in Vietnam because they were my babies

Benjamin Spock (1903–98), American pediatrician and author