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Case Report

Pheochromocytoma: An Often-Overlooked Differential in Patients with Syncope and Hypertension

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Abstract

Diagnosis of pheochromocytoma is often overlooked in elderly presenting with uncontrolled hypertension, palpitations, syncope or other cardiovascular emergencies. The first patient presented with recurrent syncope, which is a rare presentation of pheochromocytoma, and the second patient was misdiagnosed as generalized anxiety disorder (GAD) and uncontrolled hypertension. Timely recognition of atypical presentations can have a profound impact on patient outcomes, such as preventing stroke and other life-threatening complications. Through the presentation of these cases, we hope to emphasize the importance of considering uncommon etiologies in cardiovascular complaints among the elderly population.

Keywords: syncope; palpitations; pheochromocytoma; hypertension; catecholamines

Introduction

Pheochromocytoma, a rare neuroendocrine tumor, originates from chromaffin cells of the adrenal medulla or extra-adrenal paraganglion chromaffin tissue and secretes catecholamines [12, 16]. The clinical manifestations of patients with pheochromocytoma are diverse, ranging from asymptomatic to cardiac arrest [12]. The typical triad of clinical presentations of pheochromocytoma, including episodic headache, palpitations and sweating, only occurs in 24% of patients [16]. Hypertension is one of the most common manifestations of pheochromocytoma and can be persistent or paroxysmal [16].

The diagnosis of pheochromocytoma is often overlooked in seniors presenting with uncontrolled hypertension, palpitations or other cardiovascular emergencies, leading to delay in diagnosis and treatment [1]. However, recent advances in understanding the molecular biology of pheochromocytomas offer potential to improve therapeutic interventions for these tumors [12].

Case Presentation, Management, and Outcomes

Case 1:

An 82-year-old female presented to the emergency room with three episodes of syncope, each preceded by prodromal tinnitus, over the span of a year. The patient had reported feelings of light-headedness prior to the syncopal episodes. The patient denied any headaches, flushing, or palpitations. Despite multiple hospitalizations and extensive workup of possible cardiovascular causes, her etiology remained undiagnosed.

Her past medical history included lung nodules, hyperthyroidism, and hypertension. Medications included amlodipine, hydrochlorothiazide, methimazole, and aspirin. Her blood pressure, heart rate, and thyroid function were well controlled on this regimen. Upon referral to a cardiologist, a CardioNet study was done, showing no significant arrhythmia and a carotid ultrasound revealed no significant stenosis. An incidental finding of a 3-centimeter heterogeneous left adrenal mass was found on a computerized tomography (CT) scan of the chest, which was ordered due to her shortness of breath and history of lung disease. This prompted a referral to endocrinology and biochemical testing revealed plasma metanephrines test and 24-hour urine metanephrines were 2.3 times the ULN (upper limit of normal).

Her plasma metanephrines were elevated at 244 pg/mL (normal 0-62 pg/mL), and her 24-hour urine normetanephrines and metanephrines were 673 mcg hours (normal 75 to 375 mcg/24 hours) and 324 mcg (normal 140-785 mcg/24 hours), respectively. These values were confirmed on repeat testing, which confirmed the diagnosis of pheochromocytoma. To treat her pheochromocytoma, she was managed preoperatively, according to protocol, with α and β blockade in order to prevent an intraoperative hypertensive crisis as a result of a catecholamine storm [9]. The patient underwent laparoscopic retroperitoneal adrenalectomy. She did well postoperatively,

with resolution of syncope. Her blood pressure optimized and repeat catecholamine levels were within the normal limits.

Case 2:

A 72-year-old white female presented with tachycardic episodes which began 2 years prior and were associated with severe headaches. After a year, she also developed chest pain and palpitations and uncontrolled hypertension, on one instance 194/120. Her blood pressure was uncontrolled on 25 mg metoprolol (2 times daily) and hydrochlorothiazide (25 mg daily). Over the course of the 2 years of spells, her metoprolol was titrated up from 50 mg b.i.d. to 100 mg b.i.d. She was referred to cardiology and underwent a stress test which was unremarkable.

Eventually, she was referred to a psychiatrist. She was diagnosed with Generalized Anxiety Disorder and prescribed escitalopram. Because her symptoms remained unresolved, she saw an endocrinologist where a full workup was done. Urinary normetanephrines were 5 times the ULN (2096 μg, normal is 75-375 μg/24 hrs) and urinary norepinephrine was 7 times the ULN (622 μg, normal is 15-80 μg/24 hrs). Her norepinephrine level in the blood was 4141 pg/mL, 2.4 times the ULN (normal is <1700 pg/mL). A CT scan of the abdomen revealed a 3.2-centimeter tumor in the right adrenal gland, which was followed by biochemical testing. The patient was subsequently started on a regimen of phenoxybenzamine, which was effective in lowering blood pressure as well as β blockade prior to surgery. The patient underwent a successful laparoscopic right adrenalectomy, which resolved the catecholamine elevation.

Discussion

The classic triad of symptoms of pheochromocytoma consists of episodic headache, sweating, and tachycardia [19, 4]. Headaches occur in 90 percent of symptomatic patients [15]. In contrast, a much rarer presentation of pheochromocytoma is that of episodic hypotension as seen in our first case. Additionally, there can also be rapid fluctuations of hypertension and hypotension in some patients [23]. This sometimes happens in tumors that secrete only epinephrine and no other metanephrines [8].

Pheochromocytoma can often be difficult to diagnose due to the rarity of the disease and the nonspecific clinical manifestations. As in our first case, syncope may be the first symptom, making the diagnosis of pheochromocytoma challenging yet important. If pheochromocytoma is suspected, biochemical testing should be initiated, including measurement of fractionated metanephrines and catecholamines in a 24-hr urine or plasma specimen. Measurement of plasma fractionated metanephrines is often advised as a first diagnostic test for pheochromocytoma [6]. This has a sensitivity of 96 to 100 percent [18].

It's also crucial to recognize the episodic nature of pheochromocytoma spells, which can introduce complexities in diagnostic accuracy. False negatives and false positives may arise due to various factors, including dietary influences, medications, and concomitant medical conditions [6]. To mitigate these diagnostic challenges, repeated biochemical testing should be considered, especially when clinical suspicion remains high.

Pheochromocytoma rarely presents as syncope or hypotension. Although syncope is relatively common in the older population, most incidences of syncope stem from neurocardiogenic etiology. Many people suffer from recurrent syncope without being diagnosed. It is estimated that the annual incidence of syncope in older patients is 7% [19, 22]. Although orthostatic hypotension has been reported in pheochromocytoma [21], that of the first case was extremely severe and not related to posture. Aronoff et al. reported a patient who suffered from recurrent cardiopulmonary arrests and the patient's hypotension was spontaneous [3].

A literature review finds that there are few similar cases of pheochromocytoma induced syncope, and these cases are often misdiagnosed due to the highly improbable nature of pheochromocytoma as an etiology of syncope. Thus, it is our recommendation that practitioners consider uncommon causes of syncope should they not find evidence of the more common causes.

In the first case, since the patient's hypotension disappeared after the excision of tumor, her hypotension was deduced to be likely from excess catecholamine secretion. Several reasons for this phenomenon could be considered: e.g., hypovolemia, intermittent secretion of catecholamines, ratio of epinephrine to norepinephrine in the secretions, impairment of peripheral responses to catecholamine elevation, adrenocortical insufficiency, or baroreflex failure [14].

Importantly, pheochromocytomas can be misdiagnosed in women as anxiety disorders, as it was in case 2. The patient was misdiagnosed with Generalized Anxiety Disorder (GAD) and remained untreated for a further 2 years. In this case, institutional expectations and gender-related biases prevented the patient from seeking treatment. Given these concerning findings, we would like to highlight the need for comprehensive and unbiased diagnostic approaches.

Previous studies have shown that up to 40% of patients who develop pheochromocytoma carry germline mutations [11, 13]. Ideally, all patients with pheochromocytoma should undergo genetic testing because the results of genetic testing can better guide the clinical treatment and prognosis [5].

The average age at diagnosis of pheochromocytoma is 47.1 years of age, making all of our cases remarkable outliers [10]. This underscores the importance of recognizing the potential for atypical presentations across a wide age spectrum, especially in elderly patients.

Conclusion and Clinical Implications

In conclusion, the cases presented in this series illuminate the remarkable diversity of presentations that pheochromocytoma can manifest. These cases underscore the critical importance of considering uncommon presentations, especially in elderly patients, and the need for a comprehensive and unbiased diagnostic evaluation.

The infrequent occurrence of pheochromocytoma should not dissuade its consideration as a diagnosis when encountering symptoms that deviate from the classic triad. Swiftly identifying these unusual presentations can significantly influence patient outcomes.

Future Directions and Research Opportunities

Further research is warranted to delve deeper into the mechanisms behind these atypical presentations of pheochromocytoma. Avenues for exploration include the identification of novel genetic markers, the elucidation of pathophysiological pathways contributing to unusual clinical manifestations, and the development of advanced diagnostic tools that account for the episodic nature of this condition.

A comprehensive understanding of the diverse presentations and diagnostic challenges associated with pheochromocytoma is paramount for improving

patient care and outcomes. By continuing to explore these atypical cases and refining diagnostic approaches, we can advance our ability to identify and manage this rare but potentially life-threatening condition effectively.

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