Catecholamine Excess: Pseudopheochromocytoma and Beyond

Amarinder S. Garcha and Debbie L. Cohen

Symptoms of catecholamine excess or pseudopheochromocytoma can be clinically indistinguishable from pheochromocytoma. Patients usually present with paroxysmal or episodic hypertension and have a negative evaluation for pheochromocytoma. It is important to exclude other causes of catecholamine excess that can be induced by stress, autonomic dysfunction due to baroreflex failure, medications, and drugs. Patients with pseudopheochromocytoma appear to have an amplified cardiovascular responsiveness to catecholamines with enhanced sympathetic nervous stimulation. The exact mechanism is not well understood and increased secretion of dopamine, epinephrine, and norepinephrine, and their metabolites have been identified as potentiating this clinical scenario leading to differing hemodynamic presentations depending on which catecholamine is elevated. Management of this condition is often difficult and frustrating for both the physician and the patient. Most patients respond reasonably well to medications that reduce sympathetic nervous system activity. Anxiolytics, antidepressants, and psychotherapy also play an important role in managing these patients' symptoms.

Key Words: Pseudopheochromocytoma, Catecholamine excess, Renalase, Pheochromocytoma, Labile hypertension

INTRODUCTION

Causes of catecholamine excess are numerous and include pheochromocytoma, stress, medications, and ingestion of exogenous substances, such as cocaine or amphetamines. Clinical features of pheochromocytoma that are directly related to catecholamine excess typically include labile or paroxysmal hypertension, headaches, palpitations, and sweating. Interestingly many patients with a confirmed histologic diagnosis of pheochromocytoma can often be relatively asymptomatic despite high catecholamine secretion.[1] The presence of paroxysmal hypertension almost always raises the possibility of a pheochromocytoma, yet a vast majority of patients with paroxysmal hypertension have a negative evaluation for pheochromocytoma. These patients often get labeled with a diagnosis of pseudopheochromocytoma or catecholamine excess, for which there is very little guidance in the literature as to the optimal management for this condition.[2] Patients with pseudopheochromocytoma often exhibit the same symptoms as a pheochromocytoma, and the clinical presentation can be very similar. This review will focus on the patients in whom the diagnosis of pheochromocytoma has been excluded and present with symptoms attributable to catecholamine excess with increased sympathetic nervous stimulation.

PATHOGENESIS

Pseudopheochromocytoma or catecholamine excess is poorly understood but is thought to be a result of hyperactivation of the sympathetic nervous system. Patients with pseudopheochromocytoma appear to have an amplified cardiovascular responsiveness to catecholamines and enhanced adrenal release of epinephrine in response to sympathetic nervous stimulation. Some investigators have identified dopamine as the catecholamine responsible for the clinical manifestations, whereas others have identified either increased secretion of epinephrine and its metabolite metanephrine or norepinephrine and its metabolite normetanephrine as being the catecholamine responsible for inducing symptoms. Kuchel[3] identified elevated dopamine levels as a marker of sympathetic nervous system activation in pseudopheochromocytoma in the 1980s. In his observation, plasma epinephrine and norepinephrine levels were usually normal. He acknowledged the difficulty in identifying elevated levels of dopamine because of rapid metabolism of dopamine compared with epinephrine and norepinephrine. The same author subsequently described a series of patients with pseudopheochromocytoma who had elevated plasma dopamine concentrations but epinephrine and norepinephrine levels within normal range.[4] Head and neck paragangliomas, however, are often purely dopamine secreting, but these patients are frequently asymptomatic.[5] In a study of 11 patients with pseudopheochromocytoma by Sharabi and coworkers,[6] patients with pseudopheochromocytoma had normal baseline plasma concentrations of norepinephrine but higher baseline plasma concentrations of epinephrine and metanephrines. Additionally, these patients had a 6-fold larger increase in plasma epinephrine after stimulation of the sympathetic nervous system with glucagon. Compared with controls, these patients demonstrated a greater decrease in blood pressure after trimethaphan, a nicotinic ganglion blocker that inhibits the sympathoneural release of norepinephrine, and a greater increase in blood pressure relative to the changes in plasma norepinephrine after yohimbine, an alpha-adrenergic agonist that stimulates the sympathoneural release of norepinephrine.[6] Hamada and colleagues[7] demonstrated increased blood pressure reactivity in patients with pseudopheochromocytoma compared with pheochromocytoma. This

From Renal, Electrolyte and Hypertension Division, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

Financial Disclosure: The authors declare that they have no relevant financial interests.

Address correspondence to Debbie L. Cohen, MD, Renal, Electrolyte and Hypertension Division, Perelman School of Medicine at the University of Pennsylvania, 1 Founders Building, 3400 Spruce Street, Philadelphia, PA 19104. E-mail: debbie.cohen@uphs.upenn.edu

1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2014.11.002

phenomenon is believed to be a result of hyperactivity of adrenergic receptor function in patients with pseudopheochromocytoma and desensitization of these receptors in pheochromocytoma in response to chronic catecholamine excess.

CLINICAL PRESENTATION

Pseudopheochromocytoma typically presents as paroxysmal hypertension.[8,9] Hypertensive episodes are usually sudden in onset and are often accompanied by physical symptoms, such as headaches, dizziness, nausea, diaphoresis, chest pain, and palpitations.[8] The frequency of these episodes ranges from daily to less than once per month, and the duration of each episode may range from minutes to days.[2,8] These symptoms may be clinically indistinguishable from the symptoms observed in a patient with pheochromocytoma. The blood pressure tends to be lower in the interparoxysmal period in pseudopheochromocytoma. This disorder is more common among women.[8] A potential explanation for this could be increased cardiac-specific sympathetic nervous system activation in women compared with men.[10] Patients are usually not able to identify a trigger for these paroxysms, such as emotional disturbances, but a thorough psychosocial analysis often reveals a history of severe abuse or trauma in the past.[8] Interestingly, in a series of 21 such patients, 14 of 21 patients eventually acknowledged a history of severe emotional trauma or physical or emotional abuse.[8] These patients insisted that these events had no emotional impact on their lives and had repressed these emotions from their conscious awareness. Although the remaining 7 individuals did not report a history of overt emotional trauma or abuse, these patients, on psychosocial interviewing, demonstrated a pattern of minimizing awareness of emotional distress and not confiding in anyone.[8]

CLINICAL SUMMARY

- Patients with pseudopheochromocytoma usually present with paroxysmal or episodic hypertension and have a negative evaluation for pheochromocytoma.
- It is important to exclude other causes of catecholamine excess that can be induced by stress, autonomic dysfunction due to baroreflex failure, medications, and drugs.
- Patients have an amplified cardiovascular responsiveness to catecholamines with enhanced sympathetic nervous stimulation however the exact mechanism is poorly understood.
- Management of this condition is often difficult and frustrating for both the physician and the patient.
- Pharmacologic treatment options include antihypertensive agents, antidepressants, and anxiolytic agents. Psychotherapeutic interventions may also be helpful.

In the series of patients of mentioned earlier, antihypertensive medications were not very successful in treating these patients, and most of them, in fact, had at least 1 hospitalization attributable to this disorder.[8] Additionally, the physical and emotional impact of this disorder can potentially adversely affect the quality of life of the patients.[2]

Although pseudopheochromocytoma is often considered once a pheochromocytoma has been excluded as a cause of paroxysmal hypertension, Mann[2] attempted to define the disorder with the following characteristic features as listed in Table 1:

1. Sudden onset of hypertensive paroxysms without any identifiable trigger.
2. Blood pressure elevation is associated with physical symptoms, such as headache, lightheadedness, flushing, diaphoresis, nausea, chest pain, palpitations, shortness of breath, and sense of impending doom.
3. Episodes are not triggered by emotional distress or panic. However, the episodes themselves can evoke an emotional response and typically provoke a fear of dying.
4. Absence of biochemical evidence of a pheochromocytoma.
5. In-depth psychosocial analysis invariably reveals a history of abuse, trauma, or a defensive personality.

In his contribution, Mann described 2 patterns of paroxysms based on different patterns of sympathetic nervous system stimulation. In 1 scenario, the hypertensive paroxysms were accompanied by increased heart rate and palpitations in the setting of a manifold increase in epinephrine level without any change in norepinephrine level. In the second scenario, hypertensive paroxysms were accompanied by cold extremities, reflex bradycardia, and an increase in plasma norepinephrine without an increase in epinephrine level.[2]

The first situation was postulated to arise from stimulation of the adrenal limb of the sympathetic nervous system resulting in increased secretion of epinephrine from the adrenal glands, whereas the second scenario is believed to arise when stimulation of the neural limb of the sympathetic nervous system results in increased release of norepinephrine from sympathetic nerve endings in vascular smooth muscle.[2] Furthermore, different stressors can potentially stimulate 1 limb of the sympathetic nervous system preferentially, thus leading to the observation of different hemodynamic patterns.

DIFFERENTIAL DIAGNOSIS OF CATECHOLAMINE EXCESS

1. Pheochromocytoma: Pheochromocytoma needs to be ruled out before considering a diagnosis of pseudopheochromocytoma. Therefore, catecholamine levels have to be measured before making this diagnosis. Normal