NEW RESEARCH

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Obstructive Sleep Apnea Presenting as Pseudopheochromocytoma

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CASE REPORTS

A 39-year-old man with a history of poorly controlled hypertension presented with a 2-year history of fatigue, daytime somnolence, and intermittent episodes of diaphoresis and palpitations. Episodes were self-limiting, lasting approximately 5-10 minutes and occurred several times per month, most notably at night. Laboratory evaluation was significant for elevated 24-h urinary catecholamine levels, suggestive of pheochromocytoma. However, thorough imaging failed to identify a catecholamine-secreting tumor. Subsequent polysomnography revealed severe obstructive sleep apnea, with an apnea-hypopnea index of 112 events/h. After one month of continuous positive airway pressure therapy, the patient experienced resolution of his presenting symptoms, improved blood pressure control and normalization of his urinary catecholamine levels. This case highlights sleep disordered breathing as a potentially reversible cause of pseudopheochromocytoma.

Keywords: Obstructive sleep apnea, pheochromocytoma, pseudopheochromocytoma, endocrinopathy

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Obstructive sleep apnea (OSA) can result in elevated catecholamine secretion and increased sympathetic activity which may mimic the biochemical profile of pheochromocytoma.[1] Likewise, sleep disruptions, diaphoresis, fatigue, and hypertension are common clinical presentations for both conditions. As such, OSA may present similar to a pseudopheochromocytoma. Treatment of OSA may normalize the effects of this sympathetic overdrive and resolve excessive catecholamine secretion.

REPORT OF CASE

A 39-year-old man, non-smoker, with a history of uncontrolled hypertension presented with a 2-year history of fatigue, daytime somnolence, and paroxysmal nocturnal dyspnea. He reported intermittent episodes of diaphoresis, flushing, and palpitations. These episodes occurred several times per month, particularly at night, and were self-limiting, lasting approximately 5-10 minutes. He denied a history of anxiety, depression, or posttraumatic stress disorder. He also denied the use of stimulants, tobacco or illicit drugs. No other potential precipitating factors were identified. His past medical history was significant only for poorly controlled hypertension despite adherence with atenolol, hydrochlorothiazide, and lisinopril. Review of symptoms was notable for sleep fragmentation, hypersomnolence, and habitual snoring. Family history was notable only for hypertension.

On exam he was an obese, well appearing man in no apparent distress. Blood pressure was 156/89 mm Hg and his heart rate was 90 beats/ minute. Pertinent findings included a slight buffalo hump, abdominal striae and 1-2+ pitting edema in both lower extremities. No cardiac murmurs were appreciated, and the remainder of his physical exam was otherwise normal.

Electrocardiogram and lower extremity Doppler ultrasound were unremarkable. Laboratory testing was significant for elevated levels of 24-h urinary catecholamines (**Figure 1**). Epinephrine levels were normal. A 24-h urinary free cortisol was slightly elevated (61 mcg/24h, normal 4-50). However, low dose dexamethasone suppression testing, midnight salivary cortisol, and morning serum cortisol levels were all normal.

His presenting symptoms, refractory hypertension, and elevated urine metanephrines strongly suggested the presence of a pheochromocytoma. Thorough imaging with both computed tomography (CT) and magnetic resonance imaging of his chest, abdomen and pelvis were normal. An octreotide scan did not identify a catecholamine secreting tumor, and the patient was diagnosed with a pseudopheochromocytoma.

Given his fatigue, daytime somnolence, and sleep fragmentation, he underwent polysomnography, which was significant for severe OSA with an apnea-hypopnea index (AHI) of 112 events/hour. Considerable nocturnal hypoxia was noted, with an oxygen desaturation index of 60 events/h and an oxygen saturation (SpO_2) nadir of 75%. SpO_2 was below 90% for 28% of the total sleep time. Treatment with continuous positive airway pressure (CPAP) was initiated. Within one month of initiating therapy, the patient experienced resolution of his presenting symptoms, improved blood pressure control, and normalization of his urinary catecholamine levels (**Figure 1**). His blood pressure was normal (116/76 mm Hg) during a follow-up evaluation 2 months later.

DISCUSSION

OSA is associated with repetitive arousals from sleep caused by upper airway collapse. These events are associated with

excessive catecholamine secretion and can result in increased sympathetic activity and tone.[2] This, in part, contributes to the endothelial dysfunction and development of hypertension commonly seen in patients with sleep disordered breathing. As such, both symptoms and the biochemical profile can mimic those seen in patients with a pheochromocytoma.

When clinical and/or biochemical findings suggest the presence of pheochromocytoma but extensive imaging fails to identify a catecholamine secreting tumor, a diagnosis of *pseudopheochromocytoma* should be considered. Originally used to describe patients with the mistaken diagnosis of pheochromocytoma, the term pseudopheochromocytoma is now defined as the presence of symptoms suggestive of catecholamine excess with: (1) normal catecholamines; (2) elevated catecholamines not due to pheochromocytoma; or (3) adrenal tumors that mimic pheochromocytoma on imaging.[1,3,4]

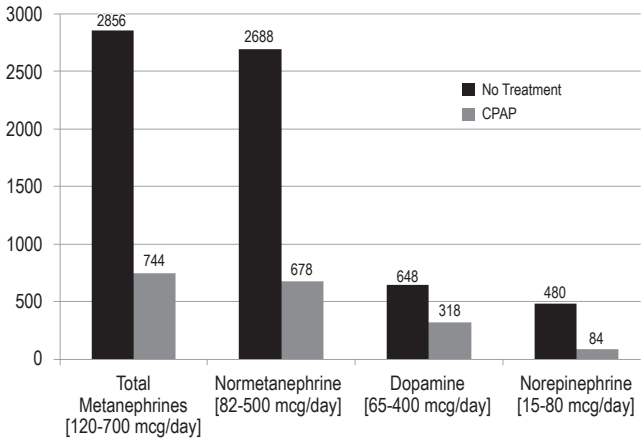
Previous cases of OSA-induced pseudopheochromocytoma have been described.[1,5] In one series, Hoy et al described 5 patients in whom no tumors were identified, and primary treatment for OSA normalized both clinical features and catecholamine excess.[1] These and similar reports strengthen the link between OSA and elevated sympathetic activity. While the exact mechanism of this association is unknown, hypoxia-induced endothelial dysfunction and oxidative stresses are thought to contribute. Further, repetitive arousals in response to anoxic/hypoxic episodes can lead to increased urinary catecholamine and metanephrine levels.[6]

CPAP therapy can reduce this increased sympathetic tone by preventing upper airway closure and mitigating repetitive arousals, as evidenced by normalization of sympathetic markers following treatment. In a study by Minemura et al, the initiation of CPAP was shown to significantly decrease urinary norepinephrine levels.[6] Further, CPAP has been shown to decrease parameters of sympathetic tone[2] and decrease day and nighttime blood pressure recordings.[6]

As in our patient with normal epinephrine levels, previous reports of OSA-induced pseudopheochromocytoma observed that elevations in norepinephrine and metanephrines were more common than elevations in epinephrine.[1,5] This discrepancy, and a response to the initiation of CPAP, may help to distinguish OSA-mediated effects from true pheochromocytoma and obviate the need for extensive testing to exclude the presence of a tumor. Future studies investigating the mechanisms and true prevalence of OSA-induced pseudopheochromocytoma are warranted to guide the need for such testing and define their effects on resource utilization.

This case represents a patient with untreated OSA and difficult to control hypertension, with clinical and biochemical evidence of increased sympathetic activity mimicking a pheochromocytoma. When imaging fails to reveal the presence of a catecholamine secreting tumor, a diagnosis of OSA-induced pseudopheochromocytoma should be considered. Recognizing this association is important, as primary treatment for OSA may lead to a resolution of symptoms and normalization of urinary catecholamine and metanephrine levels.

Figure 1—24-hour urinary metanephrine and catecholamine levels.



Note increased metanephrine and catecholamine levels prior to treatment (No treatment) and improvement in all measures one month following the initiation of continuous positive airway pressure (CPAP) therapy.

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