Case report

Obstructive sleep apnoea; a rare cause of pseudophaeochromocytoma

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Introduction

Phaeochromocytomas are catecholamine-producing neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal para-ganglia.1 These tumours characteristically present with episodes of headaches, sweating, palpitations and hypertension.1 Although rare, phaeochromocytomas are a potentially correctable cause of hypertension and delay in diagnosis can lead to increased neurological and cardiovascular morbidity and mortality.2 Surgical removal of the catecholamine-secreting tumour is the definitive therapy, and the cornerstone of pre-operative medical management is sympathetic blockade.3 Phaeochromocytomas, however, are not the only cause of elevated catecholamine levels as they could be elevated in other causes, notably physiological stress,4 antipsychotic drugs,5 anti-parkinson drugs,6 tricyclic antidepressants and cocaine use.7 The term ‘Pseudophaeochromocytoma’ is used to describe these cases where a surgically amenable chromaffin tumours are not identified as the source for elevated catecholamine levels.8

In this article, we report a series of three cases with elevated catecholamines levels caused by obstructive sleep apnoea (OSA); a common medical condition which is less recognized as a cause of raised catecholamines.8

Case 1

A 39-year-old man was referred to the endocrine clinic with a 2-year history of hypertension and episodic flushing. At the time of consultation, he was taking ramipril 5 mg once daily (od), atenolol 50 mg od and intra-muscular testosterone 250 mg (Sustanon 250; Organon, Cambridge, UK) every 4 weeks. He denied using any recreational drugs, anabolic steroids or antipsychotics, and had no known family history of endocrine disorders.

On examination, he was uniformly obese with body mass index (BMI) of 35 kg/m². He had generalized plethoric facies and raised blood pressure (BP) of 168/105 mmHg, but no other abnormal clinical findings.

Investigations revealed elevated 24-h urinary nor-adrenaline levels on four occasions (Table 1). His thyroid function tests, urinary 5HIAA, dexamethasone suppression test (9 am cortisol 18 nmol/l) (normal <50), renin 0.8 pmol/ml/h (1.1-2.7), aldosterone 175 pmol/l (100–450) and chromogranin-A 9 U/l (0–20) were all within reference ranges. CT and MRI imaging were negative and iodine-123 metaiodobenzylguanidine (123I MIBG) nuclear imaging showed no evidence of abnormal tracer uptake.

On further questioning, he admitted to a long history of loud snoring and day time somnolence. His Epworth sleepiness score (ESS) was 14,
suggesting excessive daytime sleepiness (normal <10). Subsequently, a home-based overnight polysomnography showed evidence of severe OSA with an apnoea hypopnoea index (AHI) of 52 events/hour (normal <5).

Following 6 months of overnight continuous positive airway pressure (CPAP) therapy, his urinary noradrenaline levels normalized and remained normal for 2 years of follow up (Table 1). His BP is better controlled and the episodic flushing is no longer a symptom.

Case 2
A 51-year-old man was referred with a 4-year history of uncontrolled hypertension despite being on four antihypertensive agents (quinapril 40 mg od, bendrofluazide 2.5 mg od, lercanidipine 20 mg od and hydralazine 50 mg bd). He also described a history of regular snoring, erectile dysfunction and daytime somnolence. His ESS was 15 indicating excessive daytime sleepiness.

Clinical examination revealed raised BP (174/133 mmHg) and obesity (BMI 42 kg/m²). Twenty-four hours urine collections on three occasions showed elevated noradrenaline levels at 556, 708 and 804 nmol/d, respectively (normal range 0–530), but 24-h urine adrenaline levels were within the reference range. Overnight home-based polysomnography showed evidence of severe OSA with an AHI of 40 events/hour for which CPAP was commenced. Two years after starting on CPAP therapy, his urinary catecholamines were within the reference ranges with normetanephrine/creatinine ratio of 0.21 μmol/mmol cr (0—0.35), and metanephrine/creatinine ratio 0.06 μmol/mmol cr (0—0.30).

Case 3
A 68-year-old man was referred with recurrent attacks of excessive sweating and raised 24-h urinary noradrenaline on three separate occasions (536, 567 and 738 nmol/d, normal range 0–530). His average daytime BP was 134/77 and clinical examination was unremarkable apart from obesity (BMI 36 kg/m²). Routine biochemical investigations were within the reference ranges including chromogranin A at 1.5 μl (0–20). Abdominal CT scan and MIBG scan were normal.

On further questioning, he described symptoms of snoring and excessive daytime sleepiness. While awaiting formal polysomnography, he managed to lose 15 kg in weight (12% of his initial body weight) through diet, exercise and orlistat treatment. Subsequently, his symptoms improved and home-based polysomnography showed only mild OSA (AHI = 10.4 events/hour). He did not require CPAP therapy. Repeat 24-h urinary catecholamine levels after weight loss were within the reference range and remained stable after 2 years of follow up (Table 2). It is worth noting that he subsequently gained 8.2 kg in weight during follow up with no recurrence of OSA symptoms or change in urinary noradrenaline excretion.

Discussion
OSA is a common medical disorder that affects at least 4% of men and 2% of women. OSA is strongly associated with obesity, and OSA prevalence could be as high as 77% in subjects with BMI ≥40 kg/m². OSA is characterized by instability of the upper airway during sleep, which results in markedly reduced (hypopnoea) or absent (apnoea) airflow at the nose or mouth. These apnoea/hypopnoea episodes are usually accompanied by intermittent hypoxia, microarousals and sympathetic overactivation.

The association between OSA, increased sympathetic activity and elevated urinary and/or plasma levels of noradrenaline and/or adrenaline has been described in previous studies. More recently,
McArdle and colleagues performed a matched case–control study in 42 men with moderate–severe OSA (AHI >15/h) compared with no OSA (AHI < 5/h).12 Patients with OSA had higher 24 h and nocturnal (12-h) urinary noradrenaline excretion (348 nmol/24 h, 140 nmol/12 h) compared with those without OSA (224 nmol/24 h, 88 nmol/12 h); P < 0.02. The relation between OSA and nocturnal and daytime urinary noradrenaline levels remained significant after adjusting for central obesity, age and alcohol consumption.12

It is likely that both the recurrent hypoxia13 and recurrent arousals are contributing to the activation of the sympathetic system in OSA patients. In contrast to most reported studies, Elmasry et al.14 reported a significant relationship between elevated urinary metanephrine levels and hypertensive patients with OSA, suggesting increased sympathoadrenal activity. However, the elevated plasma or urinary noradrenaline and to a less degree adrenaline levels which have been reported in OSA patients are likely to reflect neuronal, rather than adrenal release.14

Several studies reported an inverse relationship between pre-treatment oxygen saturation and urinary noradrenaline levels in OSA.15,16 Bratel et al. measured nocturnal oximetry, and plasma and urinary catecholamine levels in 16 male patients with OSA immediately before and 7 months after treatment with nasal CPAP.15 There was a significant correlation between low pre-treatment nocturnal arterial oxygen saturation and high plasma and urinary noradrenaline levels. The reduction in urinary noradrenaline, after CPAP treatment, was most pronounced in the subjects with the worst pre-treatment nocturnal hypoxaemia.15

Although weight reduction is recommended, it is not known how much weight loss is required to eliminate OSA.17 In our series, Case 3 lost 12% of initial body weight with normalization in urinary noradrenaline excretion and improved OSA symptoms. The urinary noradrenaline levels remained normal despite weight regain back to its baseline at 6 months of follow up. Further follow up was not possible as the patient moved outside our area. The poor correlation between further weight gain, after the initial reduction, and recurrence of OSA symptoms has been suggested by Pillar et al.18 who followed 14 obese patient with OSA for an average of 7.5 years after bariatric surgery and did not establish clear correlation between follow up BMI and either AHI score or the amount of initial weight loss following the obesity surgery.18

Patients with OSA could present in a similar picture to phaeochromocytoma. However, OSA is not a widely recognized cause of raised catecholamine levels, as it has only been reported a few times in the literature.8,19,20 It is worth noting that pheochromocytomas with low expression of phenylethanolamine N-methyltransferase (PNMT), the enzyme that converts noradrenaline to adrenaline, as in Von Hippel Lindau syndrome produce almost exclusively noradrenaline in amount proportional to the adrenal tumour size.21 This make these type of hereditary pheochromocytomas an important differential to be considered for cases presenting with isolated mild elevation of noradrenaline levels such as pseudopheochromocytoma secondary to OSA.

As the prevalence of obesity and OSA is increasing,11 recognition of the association with elevated catecholamine levels becomes important.

**Table 2** 24 hour urine catecholamine values for Case 3 before and after weight loss

<table>
<thead>
<tr>
<th>Date (month/year)</th>
<th>Normal range</th>
<th>October/04</th>
<th>November/04</th>
<th>April/05</th>
<th>June/06</th>
<th>December/06</th>
<th>June/07</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>115–117</td>
<td>117</td>
<td>122</td>
<td>107</td>
<td>115.2</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Noradrenaline (nmol/24 h)</td>
<td>0–530</td>
<td>536</td>
<td>567</td>
<td>738</td>
<td>300</td>
<td>331</td>
<td>366</td>
</tr>
<tr>
<td>Adrenaline (nmol/24 h)</td>
<td>0–200</td>
<td>31</td>
<td>117</td>
<td>99</td>
<td>43</td>
<td>76</td>
<td>50</td>
</tr>
<tr>
<td>Urine volume (ml)</td>
<td>2225</td>
<td>2342</td>
<td>2998</td>
<td>3065</td>
<td>2053</td>
<td>2257</td>
<td></td>
</tr>
</tbody>
</table>

NA: not available.

**Conclusions**

It is important to consider obstructive sleep apnoea in the differential diagnosis of phaeochromocytomas. This is particularly important in patients with raised catecholamine levels and unidentifiable catecholamine-secreting tumour. Treatment for OSA results in normalization of the raised catecholamines and improvement in patients’ symptoms and BP.
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References