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Case report

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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 paraganglia.[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 'Pesudophaechromocytoma' 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/m^2. 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 noradrenaline 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 (^{123}I 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,

Table 1 24 hour urinary catecholamine and BP measurements for Case 1 before and after CPAP therapy

Date	Normal range	Before CPAP (month/year)				After CPAP (month/year)			
		November/02	October/03	November/03	December/05	November/06	February/07	April/08	October/08
Noradrenaline (nmol/24 h)	0–530	574	821	1036	734	316	306	296	296
Systolic BP (mmHg)	<130	180	168	160	161	149	169	157	146
Diastolic BP (mmHg)	<85	120	105	100	94	99	90	109	94

suggesting excessive daytime sleepiness (normal <10).[9] 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/m^2). 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/m^2). Routine biochemical investigations were within the reference ranges including chromogranin A at 1.5 µ/l (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.[10] OSA is strongly associated with obesity, and OSA prevalence could be as high as 77% in subjects with BMI $\geqslant$40 kg/m^2.[11] 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.[10] These aponea/hypopnoea episodes are usually accompanied by intermittent hypoxia, microarousals and sympathetic overactivation.[10]

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.[12,13] More recently,

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

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

NA: not available.

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 hypoxia[13] 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 pseudophaechromocytoma secondary to OSA.

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

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

1. Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. *Endocr Rev* 2003; **24**:539–53.
2. Kizer JR, Koniaris LS, Edelman JD, St John Sutton MG. Pheochromocytoma crisis, cardiomyopathy, and hemodynamic collapse. *Chest* 2000; **118**:1221–3.
3. Duh QY. Evolving surgical management for patients with pheochromocytoma. *J Clin Endocrinol Metab* 2001; **86**:1477–9.
4. Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, *et al. Harrison's Principles of Internal Medicine*. 17th edn. Europe, McGraw-Hill Education, 2008.
5. Krentz AJ, Mikhail S, Cantrell P, Hill GM. Drug Points: Pseudophaeochromocytoma syndrome associated with clozapine. *BMJ* 2001; **322**:1213.
6. Montastruc JL, Chamontin B, Senard JM, Tran MA, Rascol O, Llau ME, *et al.* Pseudophaeochromocytoma in parkinsonian patient treated with fluoxetine plus selegiline. *Lancet* 1993; **341**:555.
7. Kuchel O. Increased plasma dopamine in patients presenting with the pseudopheochromocytoma quandary: retrospective analysis of 10 years' experience. *J Hypertens* 1998; **16**:1531–7.
8. Hoy LJ, Emery M, Wedzicha JA, Davison AG, Chew SL, Monson JP, *et al.* Obstructive sleep apnea presenting as pseudopheochromocytoma: a case report. *J Clin Endocrinol Metab* 2004; **89**:2033–8.
9. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; **14**:540–5.
10. McNicholas WT. Diagnosis of obstructive sleep apnea in adults. *Proc Am Thorac Soc* 2008; **5**:154–60.
11. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *J Appl Physiol* 2005; **99**:1592–9.
12. McArdle N, Hillman D, Beilin L, Watts G. Metabolic risk factors for vascular disease in obstructive sleep apnea: a matched controlled study. *Am J Respir Crit Care Med* 2007; **175**:190–5.
13. Smith ML, Niedermaier ON, Hardy SM, Decker MJ, Strohl KP. Role of hypoxemia in sleep apnea-induced sympathoexcitation. *J Auton Nerv Syst* 1996; **56**:184–90.
14. Elmasry A, Lindberg E, Hedner J, Janson C, Boman G. Obstructive sleep apnoea and urine catecholamines in hypertensive males: a population-based study. *Eur Respir J* 2002; **19**:511–7.
15. Bratel T, Wennlund A, Carlstrom K. Pituitary reactivity, androgens and catecholamines in obstructive sleep apnoea. Effects of continuous positive airway pressure treatment (CPAP). *Respir Med* 1999; **93**:1–7.
16. Sukegawa M, Noda A, Sugiura T, Nakata S, Yoshizaki S, Soga T, *et al.* Assessment of continuous positive airway pressure treatment in obstructive sleep apnea syndrome using 24-hour urinary catecholamines. *Clin Cardiol* 2005; **28**:519–22.
17. Gami AS, Caples SM, Somers VK. Obesity and obstructive sleep apnea. *Endocrinol Metab Clin North Am* 2003; **32**:869–94.
18. Pillar G, Peled R, Lavie P. Recurrence of sleep apnea without concomitant weight increase 7.5 years after weight reduction surgery. *Chest* 1994; **106**:1702–4.
19. Makino S, Iwata M, Fujiwara M, Ike S, Tateyama H. A case of sleep apnea syndrome manifesting severe hypertension with high plasma norepinephrine levels. *Endocr J* 2006; **53**:363–9.
20. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. *J Clin Endocrinol Metab* 2003; **88**:553–8.
21. Eisenhofer G, Walther MM, Huynh TT, Li ST, Bornstein SR, Vortmeyer A, *et al.* Pheochromocytomas in von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2 display distinct biochemical and clinical phenotypes. *J Clin Endocrinol Metab* 2001; **86**:1999–2008.