CASE REPORT

Hypertensive emergency masquerading as phaeochromocytoma: a report of two cases

Raphael Hulkower, Sriram Gubbi, Mimoza Meholfi, Ulrich Schubart

Jacobi Medical Center, Albert Einstein College of Medicine, Yeshiva University, Bronx, New York, USA

Correspondence to
Dr Raphael Hulkower,
RHulkower@gmail.com

Accepted 23 July 2017

SUMMARY

We report two cases of patients who were hospitalised for hypertensive emergency. In both cases, laboratory testing during admission revealed elevated normetanephrines in the range of 4–5 times the upper limit of normal using liquid chromatography with mass spectrometry. Imaging studies did not localise any phaeochromocytoma or paraganglioma (PPGL). Repeat biochemical testing after discharge was within normal limits in both cases. These observations suggest that hypertensive emergency should be recognised as a potential cause of 'false-positive' laboratory findings in the diagnostic assessment for PPGL.

BACKGROUND

Making the diagnosis of phaeochromocytoma or paraganglioma (PPGL) requires a high level of suspicion, as illustrated by autopsy findings showing that a significant number remain undiagnosed during the lifetime of the carrier.¹ Another challenge relates to the diagnostic tests for PPGL which rely on measuring plasma and/or urine metanephrines, which include normetanephrine (NMN) and metanephrine (MN). Although the currently employed methods are highly sensitive and specific, false-positive results remain a concern. While mild to moderate elevations in MNs can be caused by medications, illness or stress, values in the range of 3–4 times the upper limit of normal (ULN) are usually indicative of a true PPGL and warrant further imaging workup to localise a lesion.^{2,3} Although certain medical conditions have been reported to cause severely elevated MNs, to our knowledge such markedly elevated values have not been described in patients presenting with hypertensive emergency. Here we report two such cases.

CASE PRESENTATION**Case 1**

A 75-year-old man with a history of hypertension, chronic kidney disease and heart failure with preserved ejection fraction was hospitalised for a 1 week history of worsening dyspnoea and reduced exercise tolerance. He denied chest pain. At home, his blood pressure (BP) was poorly controlled, taking five antihypertensive medications including clonidine. On presentation, his examination was notable for BP 230/83 mm Hg, oxygen saturation of 88% (on 3 L of nasal oxygen), bilateral inspiratory crackles and pitting oedema up to the mid-shin.

There were no abnormal skin or mucous membrane findings on examination and no family history of PPGL. Laboratory studies showed raised serum creatinine (256 $\mu\text{mol/L}$, previously 141), B-type natriuretic peptide (236 ng/L, ULN <99) and troponin-I (TnI 0.228 $\mu\text{g/L}$, ULN <0.09) without significant electrocardiographic changes. A chest radiograph showed vascular congestion and bilateral pleural effusions. The patient was treated with intravenous furosemide, nitroglycerin and BiPAP, in addition to four antihypertensive agents including clonidine. A transthoracic echocardiogram showed an ejection fraction of 70%. Further testing on hospital day 2 revealed elevated levels of plasma-free NMN (2719 pmol/L, ULN <808), 24 hours urinary NMN (15 337 mmol/day, ULN <3058) and MN (2113 mmol/day, ULN <1425). CT and MRI were not obtained because of the patient's reduced renal function and the presence of a penile implant, respectively. A metaiodobenzylguanidine scan showed no evidence of PPGL. At an outpatient follow-up 2 weeks after the initial testing, repeat levels of plasma-free NMN and MN were within normal limits. The fractionated urine NMN remained only minimally elevated (see table 1).

Case 2

A 56-year-old man with a history of untreated hypertension and cluster headaches presented with a 1 week history of altered mental status, hallucinations and shortness of breath. The patient had not been taking blood pressure medications for the past 6 months due to insurance problems. He denied chest pain or fever, but reported decreased exercise tolerance. On arrival, his examination was notable for BP 254/176 mm Hg, heart rate of 116/min, a fourth heart sound, jugular venous distension >10 cm and reduced breath sounds at the lung bases, without lower extremity oedema. There were no abnormal skin or mucous membrane findings on examination and no family history of PPGL. Laboratory studies showed elevated levels of serum creatinine (239 $\mu\text{mol/L}$, previously 88) and TnI (0.54 $\mu\text{g/L}$). ECG showed voltage changes consistent with left ventricular hypertrophy but no Q waves or ST changes. A transthoracic echocardiogram showed a left ventricular ejection fraction of 15% with diffuse hypokinesis. Treatment was initiated with intravenous nitroglycerin and labetalol. As the patient displayed labile BP in response to his initial antihypertensive therapy, with periodic decreases of up to 50 mm Hg systolic BP, additional workup was pursued on hospital day 3. Results

CrossMark

To cite: Hulkower R, Gubbi S, Meholfi M, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-217628

Table 1 Plasma and urine MN values during hypertensive emergency and at follow-up (in comparison with ULNs)

	Case 1		Units (ULN)	Case 2		Units (ULN)
	Initial	F/U		Initial	F/U	
Plasma-free NMN	2719	541	pmol/L* (<808)	3975	819	pmol/L* (<808)
Plasma-free MN	284	127	pmol/L* (<289)	385	<127	pmol/L* (<289)
Urinary NMN	15337	3991	mmol/day† (<3058)	946	NA	nmol/mmol creat‡ (<174)
Urinary MN	2113	639	mmol/day† (<1425)	126	NA	nmol/mmol creat‡ (<86)

*Quest Diagnostics Nichols Institute, Chantilly, Virginia, USA.

†Mayo Clinic Labs, Rochester, Minnesota, USA.

‡Mayo Clinic Laboratories, Rochester Main Campus, Rochester, Minnesota, USA.

F/U, follow-up test; NMN, normetanephrine; MN, metanephrine; NA, not assessed; ULN, upper limit of the normal range.

showed elevated levels of plasma-free NMN (3975 pmol/L, ULN <808), MN (385 pmol/L, ULN <289), urinary NMN (946 nmol/mmol creat, ULN <174) and MN (126 nmol/mmol creat, ULN <86). An abdominal CT scan did not identify any adrenal lesions. An octreotide scan that was obtained to assess for the possibility of an extra-adrenal PPGL was also negative. At outpatient follow-up 1 month later the patient's BP was well controlled and a repeat plasma-free NMN level was at the upper limit of the normal range and the plasma-free MN level was undetectable.

OUTCOME AND FOLLOW-UP

In both cases described, the marked elevations in NMNs seen during admission for hypertensive emergency resolved within 2–4 weeks after hospital discharge. Both patients' final diagnosis was hypertensive emergency without any endocrine abnormalities. In case 1, this episode may have occurred due to dietary indiscretions leading to volume overload. In case 2, hypertensive emergency occurred in the setting of medication non-adherence.

DISCUSSION

Metanephrines (which include NMN and MN) are key metabolites of catecholamines. They are formed by *o*-methylation of norepinephrine and epinephrine, forming NMN and MN, respectively, by the action of the enzyme catechol-*o*-methyl transferase, which is present in its most active membrane-bound form within chromaffin cells and chromaffin cell-derived tumours (PPGL).⁴ Plasma and urine 24 hours fractionated MNs are the currently recommended initial tests for the work-up of a suspected PPGL.³ Marked elevations (>3 – 4 times the ULN) in plasma and urine MNs are highly suggestive of the presence of PPGL.^{2,5}

Certain drugs and medical conditions other than PPGL may cause elevations in plasma and urine MN and NMN levels (see table 2).

Marked elevations caused by drugs could be a result of sympathomimetic action (eg, nicotine and caffeine), reduced norepinephrine uptake into cells caused by drugs like selective serotonin reuptake inhibitors, as well as due to analytical interference from agents, such as paracetamol (acetaminophen) or labetalol.^{5–7} However, most of the literature on medication-associated false positives includes studies using high-performance liquid chromatography, whereas liquid chromatography with tandem mass spectrometry methods, which were employed in our two cases, are considered less susceptible to interference.⁵

This is highlighted by the fact that in our second case, the patient had normalisation of his NMN levels, despite remaining on labetalol therapy.

Marked elevations of MN and NMN levels have also been reported in patients presenting with myocardial infarction.^{8,9} Although cardiac enzymes were transiently elevated in both of our patients, they were considered to represent demand ischaemia. Obstructive sleep apnoea, another potential cause of elevated MN levels, was not assessed in our patients.^{10,11} However, the presence of this condition was unlikely, considering that normalisation of the elevated levels occurred without treatment for this condition. Renal failure is also a known cause of elevated MNs. However, studies using current assays have only reported values considerably less than three times the ULN in cases of renal failure.¹² Furthermore, as our patients had only mild to moderate renal insufficiency and not end-stage renal disease, renal failure is unlikely to have been the primary cause of their markedly elevated MN levels. Other potential causes of marked elevations of plasma and/or urine MNs, which primarily include medical conditions associated with severe stress, such as surgery, stroke, diabetic ketoacidosis or takotsubo cardiomyopathy, were not present in our cases.^{9,13} A recent report discussing the difficulties in diagnosing PPGL in critically ill patients presented markedly elevated MN levels in six patients with not otherwise specified acute severe illness who did not have a PPGL.¹⁴ However, it

Table 2 Major causes of markedly elevated plasma or urinary MNs (aside from PPGL)

Drugs	Medical conditions
Paracetamol (acetaminophen)*	Myocardial infarction
Labetalol*	Obstructive sleep apnoea
Sympathomimetics†	Chronic kidney disease
Tricyclic antidepressants†	Takotsubo cardiomyopathy‡
Selective serotonin reuptake inhibitors†	Acute severe illness§

*Analytical Interference mostly using liquid chromatography with electrochemical detection assays.

†Pharmacodynamic interference with all assays.

‡Although takotsubo cardiomyopathy may be seen in patient harbouring a PPGL, when seen in other clinical settings, it may be associated with marked elevations of MNs in the absence of a PPGL.

§Report of six patients with not otherwise specified acute severe illness¹⁴ (chart partially adapted from Lenders *et al*).¹⁴

MN, metanephrine; PPGL, pheochromocytoma or paraganglioma.

was not stated whether any of these patients presented with hypertensive emergency.

It should also be noted that even relatively minor physiologic stresses, such as sitting upright or exercise, can lead to 30% higher values of MN or NMN and become a significant source for false positives in biochemical testing.¹⁵ For this reason, ideally biochemical testing for PPGL should be performed in complete rest rather than during an acute illness.³ This is especially true since acutely ill patients may have a combination of factors or comorbidities leading to elevated MN/NMN values, including medications, hypoxia and renal failure, as described above.

However, in clinical practice, waiting for these ideal testing conditions is not always feasible, and up to 20% of true cases of PPGL are diagnosed during episodes of acute cardiovascular complications.¹⁴ Furthermore, while any acute episode of medical illness expectantly leads to an increase in physiologic stress and sympathetic activation, less than 10% of critically ill patients have plasma or urine MN levels greater than two times the ULN. By comparison, median values for patients with true PPGL are four times the ULN.¹⁶ Thus, although the normative references ranges for MN and NMN are *not reliable* in acutely ill patients, we believe careful attention to the *extent* of the elevation beyond the normal range may still be informative, as values greater than 3–4 times the ULN are more likely to represent a true PPGL rather than simply the result of the stress of critical illness alone, and such patients might warrant further evaluation for PPGL through imaging studies. Indeed, some authors have suggested that repeat testing under ideal conditions may only be necessary when the extent of elevation is less than 3–4 times the ULN.⁵

The two cases described presented with hypertensive emergency and were found to have plasma and urine NMN levels that would generally be considered consistent with the diagnosis of PPGL. However, imaging studies failed to reveal evidence of PPGL and follow-up testing, after the hypertensive crisis had resolved, showed normalisation of the levels. No other cause for markedly elevated MN or NMN levels was identified in our patients and we feel that PPGL was conclusively ruled out in both cases. Interestingly, in case 1 the patient was receiving

clonidine, an agent that is known to inhibit sympathetic outflow, making the marked elevation of NMN even more remarkable. Therefore, hypertensive emergency should be recognised as a potential cause of false-positive test results in the diagnostic work-up of PPGL.

Raising awareness of this phenomenon is important since it is not uncommon for physicians to suspect a diagnosis of PPGL in patients presenting with hypertensive emergency, who often have a history of resistant hypertension or are taking more than three antihypertensive agents. Nevertheless, the cases reported here imply that biochemical testing shortly after or during the acute hypertensive event may not be ideal. If clinical suspicion for PPGL is low, it may be more prudent to defer testing until after discharge. If clinical suspicion is high or urgent diagnosis is necessary, one might even consider proceeding directly to imaging tests, since these patients are likely to have at least moderately elevated MNs from physiologic stress (and waiting for biochemical testing may delay intervention), as was suggested previously.¹⁴ Thus, using pretest probabilities will prevent many patients from receiving unnecessary testing while prioritising others who may genuinely have a life-threatening PPGL.

Contributors All authors made significant contributions to the management of the original case and to the composition of the manuscript and revision. RH is the primary and corresponding author. SG and MM made significant contributions to the management and the manuscript and its revision. US supervised and contributed to both the care of the patient and the composition of the manuscript and revision.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Sutton MG, Sheps SG, Lie JT. Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series. *Mayo Clin Proc* 1981;56:354–60.
- Eisenhofer G, Goldstein DS, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. *J Clin Endocrinol Metab* 2003;88:2656–66.
- Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2014;99:1915–42.
- Eisenhofer G, Kopin IJ, Goldstein DS. Catecholamine metabolism: a contemporary view with implications for physiology and medicine. *Pharmacol Rev* 2004;56:331–49.
- van Berkel A, Lenders JW, Timmers HJ. Diagnosis of endocrine disease: biochemical diagnosis of pheochromocytoma and paraganglioma. *Eur J Endocrinol* 2014;170:R109–R119.
- Feldman JM. Falsely elevated urinary excretion of catecholamines and metanephrines in patients receiving labetalol therapy. *J Clin Pharmacol* 1987;27:288–92.
- Lenders JW, Eisenhofer G, Armando I, et al. Determination of metanephrines in plasma by liquid chromatography with electrochemical detection. *Clin Chem* 1993;39:97–103.
- Jéquier E, Perret C. Urinary excretion of catecholamines and their main metabolites after myocardial infarction; relationship to the clinical syndrome. *Eur J Clin Invest* 1970;1:77–83.
- Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;352:539–48.
- Hoy LJ, Emery M, Wedzicha JA, et al. Obstructive sleep apnea presenting as pseudopheochromocytoma: a case report. *J Clin Endocrinol Metab* 2004;89:2033–8.
- Cheezum MK, Lettieri CJ. Obstructive sleep apnea presenting as pseudopheochromocytoma. *J Clin Sleep Med* 2010;6:190–1.
- Eisenhofer G, Huysmans F, Pacak K, et al. Plasma metanephrines in renal failure. *Kidney Int* 2005;67:668–77.
- Kudva YC, Sawka AM, Young WF. Clinical review 164: the laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. *J Clin Endocrinol Metab* 2003;88:4533–9.
- Amar L, Eisenhofer G. Diagnosing pheochromocytoma/paraganglioma in a patient presenting with critical illness: biochemistry versus imaging. *Clin Endocrinol* 2015;83:298–302.

Learning points

- Patients suspected of having a pheochromocytoma or paraganglioma (PPGL) who have markedly elevated metanephrines (MNs) in the range of 3–4 times the upper limit of normal are considered highly suspicious of having a true PPGL.
- To our knowledge, hypertensive emergency has not been reported as a cause of such markedly elevated plasma or urine MNs.
- Identifying hypertensive emergency as a possible cause of falsely elevated MNs—to levels often seen in true PPGL—is important because patients presenting with severe uncontrolled hypertension may raise clinical suspicion for PPGL.
- Our cases suggest that biochemical testing for PPGL in patients with hypertensive emergency (as with most cases of acute illness) should either be delayed or repeated after resolution of the condition.
- In very select *emergent* cases where clinical suspicion for PPGL is high, one may consider proceeding with imaging studies prior to biochemical studies.

- 15 Lenders JW, Willemsen JJ, Eisenhofer G, *et al.* Is supine rest necessary before blood sampling for plasma metanephrines? *Clin Chem* 2007;53:352–4.
- 16 Hickman PE, Leong M, Chang J, *et al.* Plasma free metanephrines are superior to urine and plasma catecholamines and urine catecholamine metabolites for the investigation of pheochromocytoma. *Pathology* 2009;41:173–7.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow