Endocrine (2011) 40:75–79
DOI 10.1007/s12020-011-9471-4

ORIGINAL ARTICLE

Is there still a place for adrenal venous sampling in the diagnostic localization of pheochromocytoma?

Roland Därr · Graeme Eisenhofer · Jörg Kotzerke · Klaus Zöphel · Christian Stroszczynski · Jaap Deinum · Leo J. Schultze Kool · Steffen Pistorius · Hartmut Neumann · Stefan R. Bornstein · Lorenz C. Hofbauer

Received: 8 March 2011 / Accepted: 29 March 2011 / Published online: 21 April 2011

Abstract Our objective is to outline the utility of adrenal venous sampling (AVS) with measurements of metanephrine to normetanephrine ratios for diagnostic localization of phaeochromocytoma in a patient with normal plasma levels of catecholamines. A 53-year-old-woman was referred for evaluation of recurrent pheochromocytoma following a right adrenalectomy 14 years earlier. Diagnosis of recurrent disease was established from elevations in plasma metanephrines with normal levels of catecholamines. Magnetic resonance imaging indicated two 1–2 cm masses in the right surgical bed and another 1-1.5 cm mass in the left adrenal. These masses were negative on ^{123}I-metaiodobenzylguanidine scintigraphy. There was no evidence of a hereditary syndrome. We, therefore, carried out two investigational approaches to identify the tumor masses. Hybrid positron emission tomography/computed tomography with ^{68}Ga-DOTATOC (^{68}Ga-DOTATOC-PET/CT) confirmed the presence of recurrent disease in the right surgical bed and also suggested additional left adrenal involvement. Normal plasma catecholamines precluded the use of adrenal venous sampling (AVS) with catecholamine measurements. Hence, we performed AVS with measurements of plasma metanephrines, which were 4- to 7-fold higher in the left adrenal vein than in central venous plasma. We observed a reversal of the normally high metanephrine to normetanephrine ratio (mean value ± SD 5.28 ± 1.86; range 3.36–8.84, $n = 13$) to 0.73, establishing the presence of a left adrenal pheochromocytoma. Surgical pathology confirmed bilateral disease. This case highlights a scenario where a combination of ^{68}Ga-DOTATOC-PET/CT and AVS with measurement of the metanephrine to normetanephrine ratio was crucial for the preoperative assessment of a patient with bilateral pheochromocytoma.

R. Därr · G. Eisenhofer · S. R. Bornstein · L. C. Hofbauer (✉)
Division of Endocrinology, Diabetes, and Bone Diseases, Department of Medicine III, Dresden Technical University Medical Center, Fetscherstr. 74, 01307 Dresden, Germany
e-mail: lorenz.hofbauer@uniklinikum-dresden.de

G. Eisenhofer
Institute of Clinical Chemistry and Laboratory Medicine, Dresden Technical University Medical Center, Fetscherstr. 74, 01307 Dresden, Germany

J. Kotzerke · K. Zöphel
Department of Nuclear Medicine, Dresden Technical University Medical Center, Fetscherstr. 74, 01307 Dresden, Germany

S. Pistorius
Department of Visceral, Thoracic and Vascular Surgery, Dresden Technical University Medical Center, Fetscherstr. 74, 01307 Dresden, Germany

C. Stroszczynski
Institute for Radiodiagnostics, University Hospital Regensburg, Franz-Joseph-Strauss-Allee 11, 93042 Regensburg, Germany

J. Deinum
Department of Internal Medicine, Radboud University Nijmegen Medical Center, Geert Grooteplein Zuid 8, 6525 GA Nijmegen, The Netherlands

L. J. Schultze Kool
Department of Radiology, Radboud University Nijmegen Medical Center, Geert Grooteplein Zuid 10, 6525 GA Nijmegen, The Netherlands

H. Neumann
Department of Internal Medicine IV, University Hospital Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany

Keywords Adrenal venous sampling · Pheochromocytoma · Plasma free metanephrines · ^{68}Ga-DOTATOC-PET/CT

Introduction

Adrenal venous sampling (AVS) with measurements of catecholamines has previously proven useful for diagnostic localization of pheochromocytoma [1, 2], but has largely been phased out by advances in non-invasive radiological techniques, including computerized tomography (CT) and magnetic resonance imaging (MRI), that now make tumor localization relatively straightforward. Introduction of functional imaging techniques, such as ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy, has further relegated AVS to vestigial status for tumor localization. In practical terms, AVS is also a labor- and cost-intensive diagnostic tool requiring the expertise of an experienced radiologist.

There are, nevertheless, isolated situations in which conventional imaging procedures provide equivocal results about the location of a suspected pheochromocytoma [3–5]. In such situations, AVS may offer a useful tool to better establish the location of a tumor. This, however, usually requires evidence of elevated plasma concentrations of norepinephrine that may be used to establish a reversed epinephrine to norepinephrine concentration gradient in the venous plasma draining the affected adrenal gland [2, 3].

Here, we present a patient in whom imaging studies yielded ambiguous results about the location of bilateral pheochromocytomas and in whom findings of normal plasma concentrations of catecholamines precluded reliance on these analytes for diagnostic localization by AVS. This diagnostic dilemma was resolved by two novel approaches for diagnostic localization, including AVS with measurements that focussed on the plasma metanephrine to normetanephrine ratio.

Case report

Presentation

A 53-year old woman, who 14 years earlier had undergone right adrenalectomy for pheochromocytoma, was referred to the Dresden University Medical Center for evaluation recurrent disease. Four months earlier, she had presented to a cardiologist for episodic palpitations and was found to have premature atrial and ventricular complexes. Echocardiography revealed hypertrophic cardiomyopathy with a left ventricular ejection fraction of 60% and mild mitral regurgitation.

For the 3 months preceding admission, the patient reported episodes of palpitations, sweating, and flushing lasting several minutes and occurring about twice per week. Her past medical history included arterial hypertension treated with metoprolol (190 mg per day). Blood pressure while on treatment was normal, but an ECG showed sinus bradycardia with 48 beats per minute and mild non-specific intraventricular conduction defects. Physical examination was unremarkable. Family history was negative and there were no clinical stigmata indicating a hereditary condition. The patient provided written informed consent for use of her data in this report.

Biochemical testing

Outside biochemical test results indicated mildly elevated urinary outputs of metanephrine at 384 μg/day (upper limit 236 μg/day) and normetanephrine at 904 μg/day (upper limit 605 μg/day). Biochemical testing on admission further indicated moderately elevated plasma concentrations of metanephrine and normetanephrine, but normal plasma catecholamines (Table 1).

A clonidine-suppression test was performed and showed no decrease in elevated plasma concentrations of normetanephrine (Table 1), which by previously established criteria provided close to 100% probability of a catecholamine-producing tumor [6]. Beta-blocker therapy was discontinued and treatment with phenoxybenzamine initiated.

Initial imaging studies

MRI of the abdomen indicated two abdominal masses of 9 × 16 × 12 mm caudoventrally to the right kidney and of 15 × 18 × 20 mm cranially to the right kidney. Another small mass of 11 × 16 × 13 mm was detected adjacent to the left kidney and related to the medial part of the left

Table 1 Plasma concentrations of catecholamines and metanephrines at presentation and before and after the clonidine-suppression test

	Upper limits of reference intervals	Sampling at presentation	Clonidine-suppression test	
			Baseline	180 min
Norepinephrine (pg/ml)	497	435	396	648
Epinephrine (pg/ml)	82	72	106	95
Normetanephrine (pg/ml)	112	594	605	647
Metanephrine (pg/ml)	61	170	160	152

adrenal gland. On T2 weighted MRI scans, both the right- and the left-sided lesions showed a hyperintensive and homogeneous pattern. However, ^{123}I-MIBG scintigraphy showed no accumulation of radioactivity at any tumor sites. Although the left adrenal mass showed enhancement, this was not considered sufficient evidence to rule out a non-functional adenoma. With these findings and considerations in mind, together with the lack of evidence of a hereditary syndrome that might explain bilateral disease, there remained considerable doubt about the identity of the left adrenal lesion.

The diagnostic impasse justified further investigational procedures to confirm or exclude a left adrenal pheochromocytoma. Two procedures were carried out: (1) hybrid positron emission tomography with computed tomography (PET/CT) utilizing ^{68}Ga-DOTATOC (tetraazacyclododecanetetraacetic-acid-tyr3-octreotide) and (2) AVS aimed at measurements of plasma concentrations of metanephrines rather than catecholamines.

PET/CT with ^{68}Ga-DOTATOC

Using ^{68}Ga-DOTATOC as a PET imaging agent, the right-sided lesions were clearly characterized as recurrent pheochromocytoma (Fig. 1). Imaging of the left-sided lesion indicated a less intense signal on that side, with uptake increased by a factor of 2 compared to our experience with uptake of the agent by the normal adrenal gland [7].

AVS with measurements of plasma metanephrines

AVS established elevated plasma concentrations of free normetanephrine and metanephrine in the left adrenal vein compared to peripheral sampling sites, but most importantly a higher left adrenal venous plasma concentration of normetanephrine than metanephrine (Table 2). Comparison of data for plasma concentrations of free metanephrines from AVS studies in 13 other patients—including some reported previously [4, 8] and others studied at the Radboud University Nijmegen Medical Center indicated that increased plasma concentrations of metanephrine in the venous drainage of pheochromocytoma-free adrenal glands are much higher than for normetanephrine [4, 8]. Our patient, therefore, showed a reversal of the normally high metanephrine to normetanephrine ratio.

Surgery and follow-up

Because of the previous right adrenal surgery and the evident bilateral nature of the disease, the patient underwent an open laparotomy. The two tumors on the right and the single left adrenal tumor were removed and confirmed histopathologically as pheochromocytomas. Postoperatively, the patient continues to require full steroid replacement therapy with hydrocortisone and fludrocortisone.

Although family history and clinical examination revealed no evidence of a hereditary syndrome, the bilateral nature of the disease justified testing of the RET proto-oncogene, the von Hippel-Lindau (VHL) gene, genes for succinate dehydrogenase (SDH) subunits B, C and D, and the recently described transmembrane protein 127 (TMEM127). Multiplex-ligation-dependent probe amplification was carried out to detect large deletions/rearrangements of the VHL gene, whereas quantitative multiplex PCR of short fluorescent fragments was carried out to search for large deletions for SDH and TMEM127 genes. No mutations were detected.

Discussion

This report illustrates the utility of ^{68}Ga-DOTATOC PET/CT and AVS with measurement of plasma free metanephrine to normetanephrine ratios as novel tools for diagnostic localization of pheochromocytoma in isolated situations in which conventional imaging approaches are insufficient for localizing the source of elevated plasma concentrations of metanephrines.

The present case was complicated by radiological findings of recurrent disease in the area of the previous right adrenalectomy and another small mass in the left adrenal

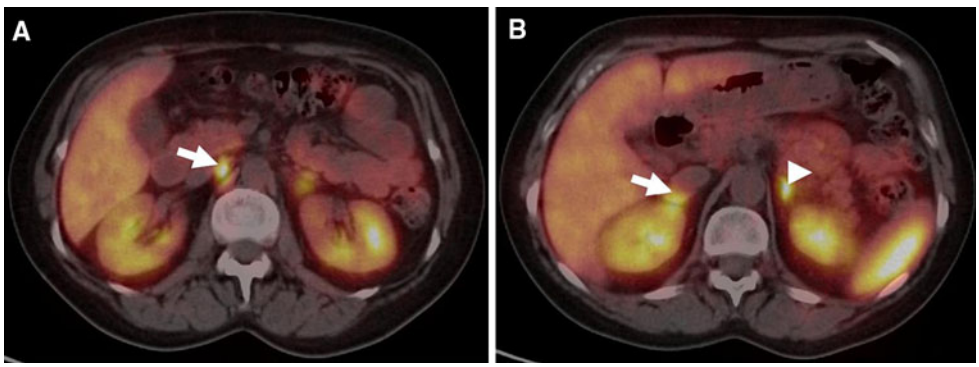

Fig. 1 ^{68}Ga-DOTATOC-PET/CT (GPET). **a** *White arrow* indicating right-sided uptake of locally recurrent pheochromocytoma. **b** *Arrow* indicating right-sided uptake of a pheochromocytoma's recurrence and *white arrow-head* indicating enhanced uptake of the left adrenal gland which is 2-fold higher than physiological

Table 2 Plasma concentrations of normetanephrine and metanephrine during AVS in the case patient and in thirteen reference patients

	Normetanephrine (pg/ml)		Metanephrine (pg/ml)		MN/NMN
	Caval[a]	Adrenal	Caval[a]	Adrenal	Ratio
Case patient	554	2191	219	1607	0.73
Reference patients					
1	59	346	73	1347	3.89
2	79	123	39	483	3.93
3	77	1863	73	14305	7.68
4	64	564	32	2682	4.76
5	225	628	61	3139	5.00
6	115	337	55	2980	8.84
7[b]	167	1235	609	10462	8.47
8	49	586	13	2616	4.46
9	25	239	30	1308	5.47
10	65	799	21	2922	3.66
11	28	2465	18	9926	4.03
12	53	615	58	2067	3.36
13	44	2027	34	10347	5.10

Plasma concentrations of normetanephrine and metanephrine are shown for inferior vena caval or central venous (Caval) and adrenal venous (Adrenal) sampling sites. Metanephrine to normetanephrine (MN/NMN) ratios are for adrenal venous sites. Adrenal venous concentrations for reference patients number were from previous published reports on adrenal venous plasma concentrations of metanephrines [4, 8] and additional patients studied at the Radboud University Nijmegen Medical Center and represent the venous drainage of pheochromocytoma-free adrenal glands

[a] Vena caval catheter-derived samples for reference patients number 8–13 were drawn from the inferior vena cava, whereas those from all other patients were central venous sites

[b] As previously reported elsewhere [4], reference patient 7 also had multiple recurrent epinephrine-producing pheochromocytomas in the right surgical bed, but the left adrenal gland from which adrenal venous samples were taken was disease free

suggesting bilateral pheochromocytomas in a patient without evidence of a hereditary syndrome. While bilateral adrenal pheochromocytomas are common in patients with hereditary syndromes, such as in MEN 2 and VHL disease, bilateral tumors are rarely encountered in patients with sporadic disease [9]. Thus, the diagnosis of a left adrenal pheochromocytoma in our patient was highly questionable.

Functional imaging with MIBG scintigraphy is recommended for distinguishing pheochromocytomas from other lesions [10], and was, therefore, particularly warranted in our patient. Presumably, however, small size of the tumors contributed to the negative findings of MIBG scintigraphy, which thus failed to assist in elucidating the nature of the small left adrenal mass.

At this stage, the patient presented a diagnostic dilemma with three options on how to proceed: (1) resect the right-sided masses leaving the left adrenal intact, but with potential need for further surgical intervention; (2) resect all masses with potential risk of unnecessary life-long steroid replacement; and (3) undertake further studies to better characterize the nature of the left adrenal mass. We decided to avoid the risk of multiple surgeries associated with the first option. Partial adrenalectomy can provide a solution that avoids or minimizes morbidity associated with adrenal insufficiency, but as illustrated in our patient this is not always easily or successfully carried out. We, therefore, avoided the second "if in doubt, cut it out" option and proceeded with further studies to characterize the left adrenal mass.

Use of PET/CT with ^{68}Ga-DOTATOC as a functional imaging agent in these additional studies was based on previous experience with this agent, including our previously published data showing some uptake by the normal adrenal glands [7]. On the other hand, ^{68}Ga-DOTATOC PET/CT has been suggested to be useful in the diagnosis of malignant pheochromocytoma and might offer superior sensitivity (92 vs. 63%) for detecting lesions in malignant disease compared to ^{123}I-MIBG scintigraphy [11]. Therefore, the issue of the general application of ^{68}Ga-DOTATOC PET/CT in the diagnosis of pheochromocytoma remains unsettled. Using this agent in our case, recurrent disease in the right surgical bed was indeed revealed where MIBG scintigraphy failed to indicate the two masses. Uptake of the ligand in the left adrenal gland was also increased relative to the normal adrenal, providing suggestive evidence for disease in that gland. Nevertheless,

due to considerations that the latter uptake could also reflect compensatory hypertrophy of the left adrenal as a consequence of the previous right-sided adrenalectomy, and because of limited documented utility for pheochromocytomas, we proceeded to AVS for further characterization of the mass.

As outlined previously [2], AVS should ideally take advantage of the usual situation in pheochromocytomas of a more prominent secretion of norepinephrine than epinephrine, enabling diagnosis based on reversal of the normally high epinephrine to norepinephrine ratio in adrenal venous plasma. Our patient, however, had normal plasma concentrations of catecholamines. The elevated plasma concentrations of metanephrines led us to instead focus on novel use of the normetanephrine to metanephrine ratio for diagnosis.

As published elsewhere [8], plasma concentrations of metanephrines show minimal differences at most venous sampling sites throughout the body with the exception of the adrenal veins, where plasma concentrations are much higher than at other sites. Similar findings in our patient confirmed that the catheter tip was correctly positioned. In the 13 reference patients, plasma concentrations of metanephrine were consistently and substantially higher than normetanephrine concentrations in adrenal venous plasma reflecting the more predominant production of epinephrine than of norepinephrine by the adrenal glands (Table 2). The metanephrine to normetanephrine ratios ranged from 3.36 to 8.84 (mean ± SD 5.28 ± 1.86; 95% CI 4.16–6.40). In contrast, in the patient with suspected bilateral pheochromocytoma there was a reversal of this normally high metanephrine to normetanephrine ratio to a value of 0.73. This reversal indicated that the left adrenal gland was contributing to the elevated plasma concentrations of normetanephrine at other sampling sites and, therefore, likely harbored a norepinephrine-producing pheochromocytoma. Although the use of ^{68}Ga-DOTATOC PET/CT helped in the diagnosis in our case, currently available data suggest that it is mainly useful for the detection of lesions in malignant pheochromocytoma.

In summary, this case highlights that by measurements of metanephrines, AVS can be used to localize pheochromocytoma in ambiguous cases even when plasma catecholamines are normal. Since release of metanephrines by chromaffin cells is continuous and not prone to the same fluctuations as release of catecholamines, it is possible that measurements of the metabolites might offer other advantages for localization of pheochromocytoma by AVS. This, however, requires further study.

Acknowledgments Roland Därr was supported by a clinical investigator fellowship and training award from the Dresden University Cancer Center.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. T.S. Harrison, J.F. Seaton, J.C. Cerny, J.J. Bookstein, J.D. Bartlett Jr., Arch. Surg. **95**, 339–343 (1967)
2. R.C. Causon, M.J. Brown, Ann. Clin. Biochem. **19**, 396–404 (1982)
3. E.C. Newbould, G.A. Ross, J.E. Dacie, P.M. Bouloux, G.M. Besser, A. Grossman, Clin. Endocrinol. (Oxf) **35**, 55–59 (1991)
4. K. Pacak, D.S. Goldstein, J.L. Doppman, B.L. Shulkin, R. Udelsman, G. Eisenhofer, J. Clin. Endocrinol. Metab. **86**, 3641–3646 (2001)
5. U. Srirangalingam, B. Khoo, M. Matson, R. Carpenter, R. Reznek, E.R. Maher, S.L. Chew, W.M. Drake, Horm. Res. Paediatr. **73**, 135–139 (2010)
6. G. Eisenhofer, D.S. Goldstein, M.M. Walther, P. Friberg, J.W. Lenders, H.R. Keiser, K. Pacak, J. Clin. Endocrinol. Metab. **88**, 2656–2666 (2003)
7. H. Hartmann, K. Zöphel, R. Freudenberg, L. Oehme, M. Andreeff, G. Wunderlich, G. Eisenhofer, J. Kotzerke, Nuklearmedizin **48**, 201–207 (2009)
8. G. Eisenhofer, B. Rundquist, A. Aneman, P. Friberg, N. Dakak, I.J. Kopin, M.C. Jacobs, J.W. Lenders, J. Clin. Endocrinol. Metab. **80**, 3009–3017 (1995)
9. E. Korpershoek, B.J. Petri, F.H. van Nederveen, W.N. Dinjens, A.A. Verhofstad, W.W. de Herder, S. Schmid, A. Perren, P. Komminoth, R.R. de Krijger, Endocr. Rel. Cancer **14**, 453–462 (2007)
10. K. Pacak, G. Eisenhofer, H. Ahlman, S.R. Bornstein, A.P. Gimenez-Roqueplo, A.B. Grossman, N. Kimura, M. Mannelli, A.M. McNicol, A.S. Tischler, Nat. Clin. Pract. Endocrinol. Metab. **3**, 92–102 (2007)
11. A. Kroiss, D. Putzer, C. Uprimny, C. Decristoforo, M. Gabriel, W. Santner, C. Kranewitter, B. Warwitz, D. Waitz, D., Kendler, I.J. Virgolini, Eur. J. Nucl. Med. Mol. Imaging (2011) (in press)