

Dopamine Excess in Patients with Head and Neck Paragangliomas

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Abstract. *Aim: This study aimed to determine the prevalence of excess dopamine in relation to clinical symptoms and nuclear imaging in head and neck paraganglioma (PGL) patients. Patients and Methods: Thirty-six consecutive patients with head and neck PGLs, evaluated between 1993 and 2009, were included. Clinical symptoms, dopamine excess (urinary 3-methoxytyramine (3-MT) or dopamine and/or plasma dopamine or 3-MT) and (nor)epinephrine excess (urinary (nor)metanephrine) as well as ¹¹¹In-octreotide and ¹²³I-metaiodobenzylguanide (MIBG) scintigraphy were documented. Results: Dopamine excess was found in seven patients (19.4%), but was unrelated to clinical signs and symptoms. Excretion of other catecholamines was unremarkable, except in one patient with adrenal pheochromocytoma. ¹²³I-MIBG uptake (present in 36.1% of patients) was associated with dopamine excess ($p=0.03$). Conclusion: Dopamine excess is present in a considerable percentage of patients with head and neck PGL, and its measurement may be useful in follow-up. Measurement of other catecholamines is necessary to rule out co-existent pheochromocytoma.*

Head and neck paragangliomas (PGL) are neuroendocrine tumors which originate from the paraganglia of the autonomic nervous system (1). Head and neck PGLs represent 0.6% of all tumors in the head and neck region (2), and these PGLs are classified according to their site of development as carotid body PGLs arising at the bifurcation of the carotid arteries, vagal PGLs arising at the vagal nerve, tympanic PGLs arising

at the tympanic plexus, jugular PGLs arising at the wall of the jugular bulb and PGLs of the temporal bone associated with the facial nerve (temporal PGLs). Measurement of epinephrine and norepinephrine metabolites in urine and plasma remains the cornerstone of the biochemical evaluation of intra-adrenal PGL (pheo- chromocytomas) and functional PGL (3, 4). In contrast to pheochromocytomas, catecholamine excess is considered to be infrequent in head and neck PGL (5). In a recent National Institute of Health series predominant dopamine secretion was found in only 9 of 120 PGL patients and pheo- chromocytoma patients with catecholamine excess (6). Dopamine excess is not routinely measured in patients with head and neck PGLs and has been only documented in a limited number of patient series (7-11). Dopamine excess in patients with pheochromocytomas and PGLs has been linked to atypical symptoms such as nausea and weight loss (6, 11-13). Moreover, catecholamine excess can lead to hemodynamic instability, particularly during diagnostic and surgical interventions of these tumors (14).

The present prospective cohort study was initiated to document the prevalence of catecholamine excess, with an emphasis on elevated dopamine secretion in relation to clinical signs and symptoms, in consecutive patients with head and neck PGLs. Since PGLs are considered to express cell membrane-bound norepinephrine transporters (15), this study also assessed the association of elevated dopamine secretion with nuclear imaging.

Patients and Methods

Patients. Consecutive patients, who were referred to the Outpatient Clinic of the Department of Endocrinology of the University Medical Centre of Groningen between January 1993 and January 2009 and who were found to have a head and neck PGL were included in the present cohort. The diagnosis of head and neck PGL was based on clinical symptoms, morphological imaging (computed tomography (CT) or magnetic resonance imaging (MRI)), and nuclear imaging, including ¹¹¹In-octreotide and ¹²³I-MIBG scintigraphy (16). In 6 patients [¹⁸F]-dihydroxyphenylalanine (¹⁸F-

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Table I. Clinical characteristics, tumor localization, clinical signs and symptoms of patients with head and neck paragangliomas.

	All	DA excess	No DA excess	p-Value
Number of patients	36	7	29	
Male	14 (38.9)	3 (38.9)	11 (37.9)	1.0
Age, years, median (range)	53 (25-85)	62 (38-65)	50 (25-82)	0.13
Tumor localization				
Carotid body tumor PGL	13 (36.1)	4 (57.1)	9 (31.0)	0.225
Vagal PGL	4 (11.1)	1 (14.3)	3 (10.3)	1.00
Tympanic PGL	8 (19.4)	0 (0)	8 (27.6)	0.31
Jugular PGL	10 (27.8)	2 (28.6)	8 (27.6)	1.00
Temporal PGL	7 (16.7)	2 (28.6)	5 (17.2)	0.60
Clinical symptoms and signs				
Tinnitus	19 (52.8)	2 (28.6)	17 (58.6)	0.22
Hearing loss	17 (47.2)	3 (42.9)	14 (48.3)	1.00
Dizziness	10 (27.8)	3 (42.9)	7 (24.1)	0.37
Cranial nerve palsies	10 (27.8)	3 (42.9)	7 (24.1)	0.37
Diaphoresis	8 (22.2)	3 (42.9)	5 (17.2)	0.17
Weight loss	7 (19.4)	2 (28.6)	5 (17.2)	0.62
Palpitations	5 (13.9)	1 (14.3)	4 (13.8)	1.00
Headache	4 (11.1)	0 (0.0)	4 (13.8)	0.57
Nausea	1 (2.8)	0 (0.0)	1 (3.4)	1.00
Systolic BP, mean \pm SD (mmHg)	148 (\pm 20)	145 (\pm 17)	148 (\pm 21)	0.73
Diastolic BP, mean \pm SD (mmHg)	80 (\pm 13)	78 (\pm 11)	83 (\pm 13)	0.33
Hypertension	26 (72.2)	5 (71.4)	21 (72.4)	1.00
¹²³ I-MIBG-positive	13 (36.1)	5 (71.4)	8 (27.6)	0.03
¹¹¹ In-octreotide-positive	33 (94.3)	7 (100)	26 (92.9)	0.67

Data in numbers (%) unless stated otherwise. DA: Dopamine, PGL: paraganglioma, BP: blood pressure, ¹²³I-MIBG: ¹²³I-metaiodobenzylguanidine, ¹⁸F-DOPA-PET: [¹⁸F]-dihydroxyphenylalanine positron-emission tomography.

DOPA) positron emission tomography (PET) was also performed. Since cytological nor histological verification of PGL is not feasible or justifiable in many patients, clinical presentation combined with morphological and nuclear imaging was used to establish the diagnosis. To this end, all individual cases were discussed in a multidisciplinary team. Head and neck PGLs were categorized as carotid body PGLs, jugular PGLs, vagal PGLs, tympanic PGLs and temporal PGLs. Data on clinical symptoms of patients were obtained from their medical charts. Patients complaints, possibly related to tumor localization, catecholamine excess (with the emphasis on dopamine), nausea, weight loss, blood pressure and the use of antihypertensive drugs were also documented. Blood pressure was measured after ten minutes of supine rest using a sphygmomanometer. Hypertension was defined as a blood pressure above 140 mmHg systolic and/or 90 mmHg diastolic, and/or the use of antihypertensive medication.

Laboratory analysis. Twenty-four hour urine collections were obtained for measurement of total fractionated metanephrines (normetanephrines: upper reference limit 260 μ mol/mol of creatinine; metanephrine: upper reference limit 99 μ mol/mol of creatinine) and 3 methoxytyramine (3-MT): upper reference limit 197 μ mol/mol of creatinine) and dopamine (upper reference limit 300 μ mol/mol of creatinine) (17, 18). These reference ranges were documented as the mean \pm 2 standard deviation in a healthy population that consisted of 30 men and 30 women in which 24 hour urine collections were obtained while the patients consumed their habitual diet (17). All urine measurements were expressed per

mol of creatinine, in order to correct for sampling errors (17). In addition to urine collection, blood samples were obtained from an indwelling intravenous catheter with the patient being in the supine position for at least ten minutes. Plasma was analyzed for dopamine (upper reference limit 0.05 nM) (18). Dopamine excess was defined as plasma dopamine, plasma 3-MT, urinary dopamine, or urinary 3-MT above the upper reference limit.

Imaging. CT and MRI were carried out at the Department of Radiology as described (16). ¹¹¹In-octreotide and ¹²³I-MIBG scintigraphy were performed 24 hours after administration of 200 MBq of the respective isotope (16). ¹⁸F-DOPA-PET images were obtained 60 min after intravenous use of the tracer (180 \pm 50 MBq) as described in detail elsewhere (19).

Statistical analyses. Statistical analyses were performed using SPSS version 16.0. Data are given as the median (range), mean \pm standard deviation and percentages. Inter-group differences in continuous variables were determined with Mann-Whitney *U*-tests or Student's *t*-tests where appropriate. Differences in proportions of categorical variables were determined by Chi-square analysis. A two-sided *p*-value <0.05 was considered statistically significant.

Results

Patient characteristics, clinical symptoms and nuclear imaging. A total of 21 women and 14 men were included in the study. Their clinical characteristics, tumor localization

Table II. Plasma dopamine, urinary 3-methoxytyramine values and MIBG scintigraphy in seven patients with dopamine excess.

	Plasma dopamine nM	Urinary 3-MT μmol/mol creatinine	¹²³ I-MIBG scintigraphy
Patient 1	0.06	136	Positive
Patient 2	0.38	444	Positive
Patient 3	0.00	234	Negative
Patient 4	0.00	581	Positive
Patient 5	6.05	679	Negative
Patient 6	missing	280	Positive
Patient 7	1.71	1688	Positive

3-MT: 3-Methoxytyramine, ¹²³I-MIBG: ¹²³I-metaiodobenzylguanidine.

and disease signs and symptoms are presented in Table I. Six patients (16.7%) presented with two or more head and neck PGLs. A unilateral pheochromocytoma was present in one patient, who was found to have a succinate dehydrogenase type D (SDHD) mutation. Genetic test results were available for eight additional patients. Two of these patients also had an SDHD mutation and one patient was found to have an SDHB mutation.

Hypertension was present in 26 patients (72.2%). Sixteen of them (44.4%) were using antihypertensive medication. Six patients were using a β-blocker, eight were using an angiotensin converting enzyme (ACE) inhibitors or angiotensin (AT) receptor blocking agent, nine were using diuretics and three patients were using a calcium antagonist. ¹¹¹In-octreotide scintigraphy was positive in 33 out of 35 patients (94.3%), whereas ¹²³I-MIBG scintigraphy was positive in 13 out of 36 patients (36.1%). ¹⁸F-DOPA-PET detected a single head and neck lesion in five evaluated patients and multiple lesions in one patient; in five of these patients ¹¹¹In-octreotide scintigraphy was performed and detected the same lesions, whereas in five out of these six patients the ¹²³I-MIBG scintigraphy was negative.

Dopamine excess. Urinary 3-MT was measured in all patients; median excretion: 120 (range 48-1688) μmol/mol creatinine. Urinary 3-MT was elevated in 6 out of 36 patients (16.7%). Plasma dopamine was determined in 31 patients. Plasma dopamine was elevated (range 0.06-6.05 nM) in four patients. Urinary 3-MT was within the reference range (136 μmol/mol creatinine) in one patient with a plasma dopamine of 0.06 nM. Urinary dopamine was within the reference range in all 29 tested patients. Dopamine excess was considered to be present in seven patients (19.4%). Plasma dopamine and urinary 3-MT levels of these seven patients are provided in Table II. Four out of these seven patients were on an antihypertensive regime, including an ACE inhibitor (n=2), a β-blocker (n=2) and a diuretic (n=2). Plasma dopamine or urinary 3-MT was not elevated in the patient with the pheochromocytoma.

Epinephrine and norepinephrine excess. Urinary metanephrine and normetanephrine excretion was measured in all patients; median excretion: normetanephrine: 140 (range 61-373) μmol/mol; median metanephrine: 66 (range 30-118) μmol/mol creatinine. Urinary metanephrine was elevated in four patients (11.1%); range 101-118 μmol/mol creatinine. Urinary normetanephrine was elevated in three patients (8.3%), range 291-373 μmol/mol creatinine, including the patient with pheochromocytoma (normetanephrine excretion 373 μmol/mol creatinine). In this patient, urinary normetanephrine normalised after removal of the pheochromocytoma. Altogether, excess epinephrine or norepinephrine was found in six patients (16.7%). Three out of these six patients were using antihypertensive medication, of whom two were using a β-blocker.

A combination of elevated urinary (nor)metanephrine and dopamine excess was present in two patients. A total of 12 out of 36 patients (33.3%) had either elevated urinary metanephrine, normetanephrine, 3-MT or plasma dopamine levels.

Comparison between patients with and without dopamine excess. The comparison of patients with and without dopamine excess regarding tumor localization, clinical symptoms, blood pressure and nuclear imaging is presented in Table I. A carotid body PGL tended to be more frequent in patients with dopamine excess, although this did not reach significance. Clinical symptoms, blood pressure and prevalence of hypertension were unrelated to dopamine excess. The sensitivity of a ¹²³I-MIBG scintigraphy in patients with dopamine excess was 71.4% compared to the sensitivity of 27.6% in patients without dopamine excess ($p=0.030$).

The urinary 3-MT and plasma dopamine in the two patients with dopamine excess and a negative ¹²³I-MIBG scintigraphy was 234 and 678 μmol/mol creatinine and <0.0 and 6.05 nM, respectively (Table II)

Discussion

This consecutive series of patients presenting with head and neck PGLs demonstrates that dopamine excess is present in approximately 20% of cases. Dopamine excess was associated with abnormal ¹²³I-MIBG uptake in the head and neck region, which supports the possibility that these PGLs are able to synthesize catecholamines and hence should be considered to be functional. One of the two patients with dopamine excess, who did not have ¹²³I-MIBG uptake, showed only marginally elevated urinary 3-MT. Thus, the possibility of false-positive classification of dopamine excess exist for only one patient of this series. Furthermore, no relation between dopamine excess and clinical signs or symptoms was found. Therefore, it is unlikely that dopamine excess has direct clinical consequences, at least in the majority of head and neck PGL patients.

Table III. Case reports and series demonstrating dopamine excess in patients with head and neck paragangliomas.

	N	Tumor	Catecholamine excess
Hirano <i>et al.</i> (24)	1	Carotic body PGL	Elevated plasma and urinary DA
Koch <i>et al.</i> (25)	1	Carotic body PGL	Elevated plasma DA
Kouzaki <i>et al.</i> (26)	1	Tympanic PGL	Elevated plasma NE, DA and urinary VMA
Levin <i>et al.</i> (27)	1	Vagal PGL	Elevated plasma DA
Reuland <i>et al.</i> (28)	1	PGL	Elevated urinary NE and DA
Rhigini <i>et al.</i> (29)	1	Carotic body PGL	DA excess
Throughton <i>et al.</i> (30)	1	Jugular PGL	Elevated urinary catecholamines/metabolites, elevated plasma DA
Goutcher <i>et al.</i> (14)	2	Jugular PGL	In 1 patient elevated urinary NM, in 1 patient elevated urinary DA
Azzarelli <i>et al.</i> (22)	2	Jugular PGL	DA in tissue, in 1 patient elevated urinary VMA
Crowell <i>et al.</i> (23)	2	Carotic body PGL	Both patients tissue catecholamines and DA
Anand <i>et al.</i> (8)	20	PGL	In 2 patients elevated plasma DA, NE and E, in 1 patient elevated plasma NE
Erickson <i>et al.</i> (7)	204	PGL	In 103 patients urinary DA available, elevated catecholamine in 40
Van Gils <i>et al.</i> (9)	14	PGL	7 With elevated catecholamines, 1 with elevated DA in urine
Houten van <i>et al.</i> (10)	40	PGL	17 Patients elevated urinary E, NE, DA or VMA (7 with an additional phoe, 1 with an additional extra adrenal PGL), 1 patient with elevated urinary DA
Van Duinen <i>et al.</i> (11)	136	PGL	31 With elevated urinary 3-MT

VMA: Vanillylmandelic acid, HVA: homovanillic acid, NE: norepinephrine, E: epinephrine, DA: dopamine, M: metanephrine, NM: normetanephrine, 3-MT: 3-methoxytyramine, phoe: pheochromocytoma.

In addition, epinephrine or norepinephrine excess was found in 16.7% of patients. However, elevations of urinary metanephrine and normetanephrine were marginal (<1.2 times above the upper reference limit), except in one patient with a concomitant pheochromocytoma. Of note, two of these patients were using β -blocking agents that can elevate urinary (nor)metanephrine excretion (20, 21). Thus, in patients with isolated head and neck PGL, relevant epinephrine or norepinephrine excess seems to be infrequent.

For comparison, case reports and patient series obtained from English, German and French literature between 1965 and 2009 were reviewed. As shown in Table III, ten case reports were retrieved in which dopamine secretion, either demonstrated by dopamine in tissue or elevated dopamine concentration in plasma or urine was reported (14, 22-30). Table III also shows the prevalence of dopamine excess in five series (7-11). Anand *et al.* found dopamine excess combined with abnormal norepinephrine or norepinephrine secretion in 2 out of 20 patients (10.0%) and isolated catecholamine excess in another patient (8). In a series of 14 patients, elevated urinary dopamine excretion was reported in one patient (7.1%) with a vagal PGL (9). In a selected series of head and neck PGL patients referred for either a positive family history or a mutation in the *SDHD* gene, elevated urinary catecholamines were observed in 17 out of 40 patients (10). In nine of these patients, catecholamine excess was attributable to head and neck PGLs; urinary dopamine was elevated in one patient (2.5%) (10). Erickson *et al.* reported on 204 PGL in 236 patients (7). Catecholamine excess was present in nine out of 103 patients with a head and neck PGL, but the prevalence of dopamine

excess attributable to PGLs of the head and neck was not specified (7). Finally a recent study by van Duinen *et al.*, which was published while the present manuscript was in preparation, showed an increased urinary 3-MT in 23% (31 out of 136) patients with a head and neck PGL, consistent with the current findings (11). These differences in the reported prevalence of dopamine excess, ranging from 2.5% to 23%, are likely to be due, at least in part, by referral-based selection of patients and the selected laboratory work-up. In this respect, it is important to note that the presently evaluated cases were referred for endocrine work-up by the Department of Otorhinolaryngology from the University Medical Centre, although there was no selection regarding the co-occurrence of other PGL or pheochromocytoma localizations, nor with respect to genetic PGL predisposition. Of the selected work-up in previous reports and the current series, urinary 3-MT seems to be the most sensitive (11). The inferiority of urinary dopamine measurement as a diagnostic test (6), as confirmed in the current study, has been attributed to the fact that dopamine presence in urine originates from renal extraction and decarboxylation of circulating of 3,4-dihydroxyphenylalanine.

In support of the contention that there is no well-defined clinical correlation of dopamine excess, clinical characteristics and symptoms were not significantly different between patients with and without dopamine excess, and the presence of hypertension appeared to be unrelated to abnormal dopamine secretion (6, 12, 13). Nevertheless, in clinical practice there are several arguments that underscore the necessity for routine assessment of catecholamine excess in the work-up of patients with head and neck PGL. Firstly,

catecholamine excess may result in hemodynamic instability during surgery (8, 14, 24). However, dopamine excess in these tumors is probably not of major relevance regarding hemodynamic instability during surgery, since the amount of dopamine produced is unlikely to affect the cardiovascular system. Secondly, it is important to rule out additional pheochromocytomas, especially in patients with an SDHD or SDHB mutation (10). This is illustrated by the case of SDHD-associated pheochromocytoma in the current study. Thirdly, the present findings would suggest that measurement of plasma dopamine or 3-MT could be useful in the follow-up of head and neck PGLs as a tumor marker.

A limitation of the current study is that results from genetic testing were available in only 9 out of 36 patients, because they were not routinely followed at our Department. Therefore, it is not possible to correlate dopamine secretion to a specific mutation.

Finally, the preliminary findings regarding positive ^{18}F -DOPA-PET imaging in all six tested patients raises the possibility that this imaging modality may be sensitive for the detection of head and neck PGLs (31). Nonetheless, a literature survey has demonstrated that the sensitivity of ^{111}In -octreotide scintigraphy for head and neck PGL detection amounts to 96%, whereas the sensitivity of ^{18}F -DOPA-PET has not yet been established in large series (32).

In conclusion, dopamine excess is present in a relevant percentage of patients with head and neck PGLs. Routine assessment of abnormal secretion of dopamine and other catecholamines in PGL management is proposed, and it is suggested that serial measurement of urinary/plasma 3-MT and plasma dopamine may be useful in the follow-up of PGL patients. Furthermore, measurement of epinephrine and norepinephrine metabolites is required to rule out catecholamine excess resulting from a co-existing (adrenal) pheochromocytoma.

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