CASE REPORT

Paraganglioma in a young patient with asymptomatic severe hypertension: a case report and review of the literature

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Abstract

We present a case of a 19-year old woman who was admitted to our department with a recently, and incidentally, diagnosed severe hypertension [220/140 mmHg systolic/diastolic blood pressure (BP)]. The patient was asymptomatic. The laboratory investigation demonstrated both elevated plasma norepinephrine (1807 pg/ml, normal range 120-350 pg/ml) and 24h urinary free catecholamines (483 μg/24h, normal range <150 μg/24h), making the diagnosis of a catecholamine-producing tumor highly probable. Although magnetic resonance imaging of the abdomen showed normal adrenal glands, it revealed a mass (4x4 cm) anterior to the inferior vena cava. The diagnosis of paraganglioma was confirmed by the ^{131}I-meta-iodobenzylguanidine scintigraphy. Preoperatively, α- and β-adrenergic receptor blockers were administered. After successful resection of the tumor, the patient's BP was restored to normal and remained stable during the 3-month follow up. Plasma and 24h urinary catecholamine levels were also normalized. In conclusion, it is important to consider paragangliomas as a possible cause of secondary hypertension and proceed to diagnosis and treatment as described above, since surgical removal of the tumor, especially in sporadic cases, may cure the patient. Hippokratia 2010; 14 (4): 300-302

Key words: hypertension, catecholamines, paraganglioma

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Paragangliomas (PGLs) are rare neuroendocrine tumors which arise from the extraadrenal chromaffin tissue of the autonomous nervous system[1]. They account for 10-18% of chromaffin cell-derived tumors and their incidence ranges from 2 to 8 cases per million people per year[2]. The importance of proper diagnosis lies in the fact that PGLs constitute one of the few curable causes of hypertension. On the contrary, they may prove to be fatal, when not diagnosed, due to their cardiovascular complications[1,3]. The following case report describes the diagnostic approach and management of a young asymptomatic female patient suffering from PGL-induced severe hypertension.

Case report

A 19-year old female patient was admitted to our department with a recently, and incidentally, diagnosed severe hypertension [220/140 mmHg systolic/diastolic blood pressure (BP)]. The patient reported no relevant symptoms, had never received any medication, her individual history was free and her family medical history was negative for hypertension and early onset of cardiovascular disease.

On physical examination, elevated BP (systolic BP: 170-180 mm Hg and diastolic BP: 110-135 mm Hg) and heart rate (105-120 bpm) were repeatedly observed. Heart examination revealed no vascular murmurs or any pathological signs. No remarkable signs were detected from the other organs. Routine laboratory testing was normal, as well as chest X-ray and electrocardiogram. The transthoracic echocardiogram showed normal size and shape of left cardiac cavities. The captopril renal scintigram and the magnetic resonance angiography of the renal arteries were normal.

A more specific laboratory investigation detected elevated plasma norepinephrine (1807 pg/ml, normal range 120-350 pg/ml) and 24h urinary free catecholamines (483 μg/24h, normal range <150 μg/24h) as well as normal plasma epinephrine, making the diagnosis of a catecholamine-producing tumor highly probable.

Although magnetic resonance imaging of the abdomen showed normal adrenal glands, it revealed a mass (4x4 cm) of lobular margin and uneven enhancement anterior to the inferior vena cava (Figure 1). The diagnosis of PGL was confirmed by ^{131}I-meta-iodobenzylguanidine (MIBG) scintigraphy (Figure 2), eliminating, simultaneously, the possibility of coexistence of other tumors or metastatic lesions.

Syndromes and tumors associated with PGLs were ruled out by: a) biochemical assessment of plasma calcitonin and parathyroid hormone and ultrasound imaging of the thyroid and parathyroid glands, which excluded the presence of any tumor, and b) ophthalmological evaluation,

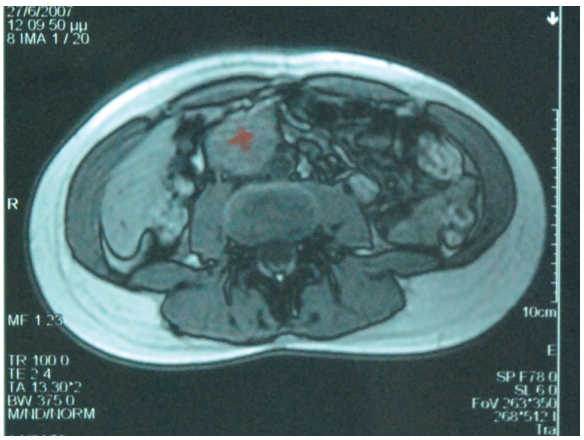

Figure 1: MRI of the abdomen showing a mass (4x4 cm) of lobular margin and uneven enhancement anterior to the inferior vena cava.

which did not reveal hemangioblastoma of the retina.

Preoperatively, the patient was initially treated with an α-adrenergic receptor blocker (terazocin). A β-adrenergic receptor blocker (atenolol) was added five days later, in order to control BP and heart rate. After successful resection of the tumor, the patient's BP was restored to normal and remained stable during the 3-month follow up. The plasma and 24h urinary catecholamine levels were also normalized.

Discussion

Adrenal medulla and ganglia of the sympathetic nervous system (SNS) have common origin from the embryonic neural crest. Pheochromocytomas (PHEOs) are regarded as a form of intraadrenal PGL, most of them are sporadic, but about 9-23% derive from extraadrenal chromaffin tissue and then are referred as PGLs[3,4]. Adrenal and extraadrenal PGLs synthesize and secrete significant amounts of catecholamines, (functioning tumors), while a number of them particularly parasympathetic ones are non-functioning[5]. PHEOs are more common in patients >60 years old, are associated with familial syndromes in about 14% of the cases. Bilateral adrenal tumors are usually found in patients with familial syndromes. It is very important that the malignancy rate of paraganglion tumors varies with the site of origin of the primary tumor. Extraadrenal PGLs have a reported malignancy rate of up to 40%, whereas adrenal PHEOs have a rate of 10%[1,4]. About 10-20% of PHEOs are discovered incidentally, especially in older patients. Conversely, their prevalence in patients with incidentally discovered adrenal tumors ("incidentalomas") is about 1.5-11%[6]. On the other hand, PGLs present multifocally in about 20% of cases, are rarely associated with familial syndromes and are more frequent in younger patients (<20 years old)[4], although some authors have reported conflicting results[7].

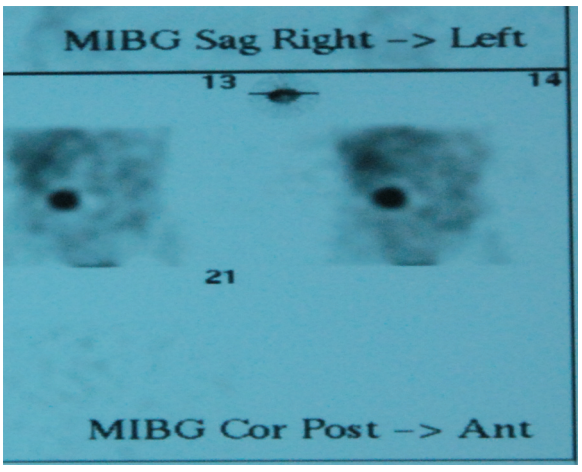

Figure 2: ^{131}I-meta-iodobenzylguanidine (MIBG) scintigraphy confirming the existence of a paraganglioma

Familial syndromes associated with PHEOs are neurofibromatosis 1, von Hippel-Lindau (VHL) disease, multiple endocrine neoplasia type 1 (MEN1) and type 2 (MEN2)[8-10] and the PHEO/PGL syndromes based on mutations of the genes coding for succinate dehydrogenase subunit D (SDHD), B (SDHB) and C (SDHC). It is of outmost importance that about 25% of patients with apparent sporadic PHEOs and without a family history of the disease may be in fact carriers of these germline mutations predisposing to the development of the above familial syndromes[8-10].

Sympathetic PGLs may arise from any ganglia of the SNS chain but are usually localized in the thorax, abdomen and pelvis. They are characterized by uncontrolled and continuous overflow of catecholamines in the circulation and therefore their main manifestation is hypertension[1]. Abdominal PGLs are malignant in about 15-30% of the cases and are more likely to be associated with the SDHB mutation[11,12]. Parasympathetic PGLs are usually localized in the head and neck, are biochemically "silent" and malignant in <10% of the cases[2].

PHEOs manifest with a variety of symptoms and despite the advances in laboratory and imaging techniques they can often be misdiagnosed. Hypertension is the main symptom, which is paroxysmal in 48% and persistent in 29% of the patients, while 13% are normotensive[13]. Sustained hypertension is usually associated with norepinephrine secreting tumors, while paroxysmal hypertension with co-secretion of both catecholamimes. Epinephrine-secreting PHEOs manifest usually with hypotension rather than hypertension. Apart from hypertension, headache (80%), diaphoresis (70%) and palpitations (60%) constitute a common triad of symptoms. Other symptoms include cardiovascular episodes such as shock, myocarditis, dilated cardiomyopathy, cardiac arrhythmias, pulmonary edema and heart failure[14]. Interestingly, 8% of PHEOs are asymptomatic, usually those with familial forms of the disease or the large cystic ones[15]. The risk of recurrence is very high and, thus, careful follow-up is recommended[1].

The diagnosis of a chromaffin-cell derived tumor is based mainly on the measurement of metanephrines, the *O*-methylated metabolites of catecholamines. The advantage of metanephrines is that they are continuously produced and released by the tumor, in contrast to plasma

catecholamines. Plasma and urinary catecholamines as well as urinary vanillyl-mandelic acid (VMA) can also be assessed for the diagnosis of PHEO/PGL[1,4,6,16,17]. The demonstration of urinary norepinephrine >170 μg/24h, urinary epinephrine >35 μg/24h and urinary total metanephrines at least 1.8 mg/24h and VMA at least 11 mg/24h makes the diagnosis of PHEO highly probable. Plasma levels of normetanephrine <112 pg/ml and of metanephrine <61 pg/ml virtually exclude PHEO[1,4,6].

In case of intermediate values of plasma/urinary free metanephrines or catecholamines, pharmacological testing should be performed. This involves provocative test with glucagon and suppressive test with clonidine. The first is rarely used when the clinical findings are highly suggestive of PHEO, but BP is normal or slightly elevated and plasma catecholamines are between 500 and 1000 pg/ml. A positive glucagon test requires at least a 3.0-fold increase and/or more than 2000 pg/ml in total plasma catecholamines. As far as clonidine suppression test is concerned, the normal response is considered as a fall of plasma catecholamines from baseline of at least 50% and below 500 pg/ml[1,4,16,17]. Our patient demonstrated high enough levels of urinary and plasma catecholamines, so the next step was to localize the tumor.

Computerized tomography along with MRI are the first-line imaging techniques to detect PHEOs/PGLs, accompanied by scintigraphy. As far as nuclear imaging is concerned, two methods are widely advocated, ^{123}I-MIBG and ^{131}I-MIBG scintigraphy. MIBG is a noradrenaline analogue that is taken up by PHEO cells. ^{131}I-MIBG was the first tracer adopted, but ^{123}I-MIBG ^{123}I-MIBG uptake is higher in sporadic, benign, intraadrenal and unilateral PHEOs, than in hereditary, malignant, extraadrenal and bilateral ones PGL[18,19]. In our patient, MRI of the abdomen excluded adrenal tumor but revealed a mass anterior to the inferior vena cava which turned to be a PGL on MIBG scintigraphy, excluding any metastatic lesions or other types of chromaffin-cell-derived tumors.

As far as treatment is concerned, preoperative use of the non-selective α-blocker phenoxybenzamine (POB) or selective postsynaptic α_1-receptor antagonists (such as prazocin, terazocin or doxazocin) to avoid the adverse effects of POB is considered valuable to control hypertension. Beta-blockers can be administered if tachycardia and arrhythmias are present, but only after initiation of α-blockers. In order to encounter postoperative hypotension due to catecholamine-induced vasoconstriction, special care should be provided towards the expansion of intravascular volume either with plasma volume expanders or normal saline the evening bofore surgery as well with blood replacement during surgery[20,21]. In conclusion, a rare case of successfully diagnosed and managed cause of secondary hypertension which proved to be a PGL is presented. The potential of these entities should always be excluded during the diagnostic work-up, as their successful surgical management may result in complete cure of the patient's hypertension as well as in early diagnosis of co-morbidities that may exist.

Conflict of interest

The authors have no conflict of interest to disclose.

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