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MANAGEMENT OF PHEOCHROMOCYTOMA–PARAGANGLIOMA

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The term "paraganglioma" identifies a category of tumour arising from neuroendocrine cells that migrate from the neural crest at the time of embryonic development and cluster in the proximity of parasympathetic and sympathetic ganglia, where they form the so-called paraganglia. The term "pheochromocytoma" should be reserved for those paragangliomas originating from catecholamine-producing chromaffin cells located in the adrenal medulla. On the other hand, paragangliomas of parasympathetic origin are usually located in the head and neck region, rarely synthesize catecholamines, and are chromaffin negative — since these non-functioning paragangliomas are not associated with signs of sympathetic overactivity, they are not seen in the context of arterial hypertension and will be excluded from further consideration in this newsletter.

A rare disease?

A reliable estimate of the incidence of pheochromocytoma has been obtained at the Mayo Clinic in the population of Rochester, resulting in approximately one case per 100,000 subject/years [1]. Lower values (approx. 0.2 cases per 100,000 subject/years) have been found in Japan, Sweden, Denmark, and Spain. On the other hand, different groups report the occurrence of pheochromocytoma in 1–5/1000 hypertensive patients. This apparent inconsistency could be explained by a presumable selection bias in hypertensive patients observed at specialized centres. From another perspective, adrenal incidentalomas were found in 0.4% of individuals from a series of more than 60,000 abdominal CT scans, and another report suggests that approximately 4% of adrenal incidentalomas are pheochromocytomas [2].

Presentation of pheochromocytoma

Signs and symptoms of pheochromocytoma and functional paraganglioma are particularly variable [3]. In some instances, the disease is asymptomatic or its manifestations are easily overlooked by the patient; in fact, in a few cases these tumours are detected at autopsy or as incidentalomas. In other cases, the clinical presentation may be dramatic, with major complications such as myocardial infarction, cerebrovascular accident, fatal arrhythmia, or dissecting aortic aneurysm.

However, the most frequent clinical presentation is hyperadrenergic syndrome, with persistent or paroxysmal hypertension as a leading sign and the classic triad of headache, palpitations, and diaphoresis. More than half of pheochromocytoma patients experience paroxysms or crises. Their frequency varies from sporadic to several times a day and usually increases with disease progression. Sometimes precipitating factors can be observed. They may include ingestion of certain foods containing tyramine or synephrine (parmesan cheese, some red wines, orange juice) and some drugs (opiates, histamine, ACTH, glucagon, methyldopa tricyclic antidepressants, etc). In some patients paroxysms may be precipitated by mechanical compression, as is the case during micturition in patients with a urinary bladder tumour. Usually the duration of a paroxysm varies from a few minutes to one hour. Paroxysmal symptoms are variable, but the clinical picture is quite consistent in the same individual. Most often, the crisis is heralded by a sensation of forceful heartbeat, followed by headache, sweating, anxiety, tremor, nausea, vomiting, abdominal or chest pain, paresthesias, fatigue, and dyspnoea, in variable patterns. In addition, the severity of symptoms may increase with disease progression. Hypertension is present as a true paroxysm (~25%) or as a crisis superimposed to sustained hypertension (~25%). Body temperature may rise slightly during a crisis. Arrhythmias and/or electrocardiographic changes may be detected.

Patients without crises, or in the interictal phase, may experience chronic symptoms similar to those listed above. Chronic hypertension is present in more than half of the patients, often accompanied by significant lability and orthostatic hypotension. Symptoms and signs related to increased metabolic rate (heat intolerance, sweating, weight loss) and to increased glycogenolysis (hyperglycaemia, impaired glucose tolerance) are sometimes present.

The concomitant production of one or more different peptides may be responsible for atypical clinical manifestations (hypercalcaemia, Cushing's syndrome, etc).Other atypical symptomatic presentations are orthostatic hypotension, angina pectoris, idiopathic dilated cardiomyopathy, psychiatric disorders, and many others.

The presence of a pheochromocytoma may also be suggested by the presence of peculiar clinical signs of genetic syndromes, such as neurofibromatosis type I (café-au-lait spots, neurofibromas, Lisch nodules, skin freckling of the axilla or groin), von Hippel Lindau disease (retinal angiomas, cerebellar haemangioblastoma, epididymal cystadenoma, renal and pancreatic cysts, pancreatic neuroendocrine tumours, renal cell carcinoma or cysts), multiple endocrine neoplasia, MEN, type 2A (medullary thyroid carcinoma, hyperparathyroidism), MEN, type 2B (medullary thyroid carcinoma, mucosal neuromas, thickened corneal nerves, intestinal ganglioneuromatosis, marfanoid body habitus), or by familial recurrence of pheochromocytomas-paragangliomas without other features.

In addition, as mentioned above, over the last two decades the widespread use of imaging techniques has frequently lead to the incidental discovery of adrenal (or in some cases, extra-adrenal) masses, the so-called incidentalomas, that may represent asymptomatic or paucisymptomatic pheochromocytomas.

From clinical suspicion to diagnosis

The diagnosis of pheochromocytoma is relatively straightforward provided the suspicion is raised. Besides patients with suggestive clinical picture, two conditions call for specific diagnostic investigation: subjects with incidentalomas and relatives of patients with a genetic predisposition to pheochromocytoma (*see below*). International guidelines do not recommend screening for pheochromocytoma in the general hypertensive population unless clinical data suggest the diagnosis [4].

Biochemical tests

The fundamental screening procedure is to obtain biochemical evidence of increased catecholamine production. Test sensitivity is of crucial relevance, since false-positive can be ruled out by further investigation, whereas false--negative may have dramatic clinical consequences. There is now evidence from several independent studies indicating that measurement of plasma levels of free metanephrines (o-methylated metabolites of catecholamines) attains a diagnostic sensitivity of 97–99% [5, 6]. However, measurement of urinary fractionated metanephrines in a twenty-four-hour urine collection is probably equally reliable and has the advantage that it is much more widely available. To improve specificity, it is necessary to withdraw any pharmacological treatment potentially interfering with biochemical assay. In case of intermittent symptoms (and catecholamine secretion) urine sampling during or immediately after a crisis may be of some help.

Provocative tests (e.g. glucagon IV) should be abandoned in clinical practice due to low sensitivity and potentially dangerous blood pressure increase [7]. On the other hand, the clonidine suppression test, aimed at distinguishing between neurogenically mediated catecholamine increase and catecholamine secretion by a pheochromocytoma, has not proven sufficiently reliable in excluding the diagnosis, unless plasma normetanephrine is used instead of plasma noradrenaline [7].

Other tests, such as plasma catecholamines, urinary vanillylmandelic acid, plasma chromogranin A, or neuropeptide Y, have less accuracy than plasma or urinary fractionated metanephrines.

Localization of the tumour(s)

Careful assessment of clinical history and biochemical testing usually provides sufficient information to decide if imaging studies aimed to locate the tumour are justified. Most pheochromocytomas (97–99%) are located in the abdomen, while only 1–3% are found in the thorax (posterior mediastinum) or the neck. Adrenal glands are involved in more than 80% of cases, with both glands involved in 5–25%. Extra-adrenal pheochromocytomas are mainly located near the kidney or in the organ of Zuckerkandl and can be multicentric. Simultaneous adrenal and extra-adrenal involvement can be observed. Of note, multicentric localizations are more frequent in children and in genetically determined syndromes.

First line imaging relies on computed tomography (CT) and magnetic resonance imaging (MRI) of the abdomen and pelvis [8]; these techniques have similar good sensitivity (90–100%) for detecting adrenal pheochromocytomas, whereas MRI is probably better for detecting extra adrenal tumours. The specificity of both CT and MRI is low (50–70%), mainly because of a relatively high frequency of non-catecholamine-producing incidentalomas. CT has the advantage of a slightly better spatial resolution, while MRI may better differentiate pheochromocytomas (appearing hyperintense on T2-weighted images) from other adrenal tumours that are isointense compared with the liver.

If an abdominal mass is detected, ^{123}I-labeled meta-iodo-benzylguanidine (MIBG) scanning is still the method of choice to assess whether the tumour is indeed a pheochromocytoma and whether there are metastases [9]. The reported sensitivity is 80–95% and specificity is 95–100%. In cases of scintigraphic confirmation of the CT/MRI localization, the diagnostic procedure is concluded and therapeutic options must be considered. If ^{123}I-MIBG scintigraphy is negative, a "third-line" diagnostic option should

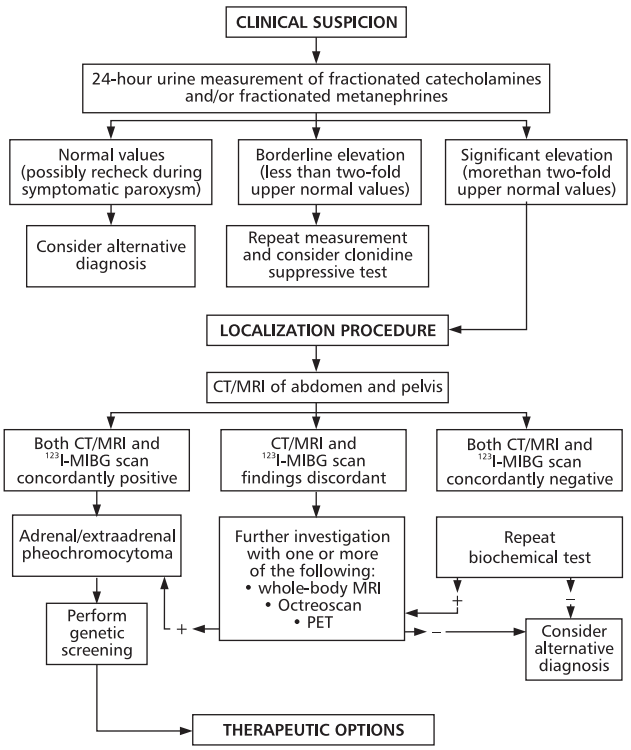

Figure 1. Recommended diagnostic flow-chart

be considered, such as positron emission tomography with different radionuclides (^{18}F-fluorodeoxyglucose, ^{18}F-fluorodopamine, and ^{18}F-fluoroDOPA) [10] and ^{111}-In-pentetreotide scintigraphy (Octreoscan).

If CT/MRI of the abdomen/pelvis is negative, the imaging investigation (preferably MRI) should be extended to the whole body and associated with ^{123}I-MIBG scanning.

When both techniques give positive results, a diagnosis of extra-adrenal pheochromocytoma is made and appropriate therapy can be planned. If only ^{123}I-MIBG scanning is positive, the diagnosis of extra-adrenal pheochromocytoma is strongly suspected, but it needs to be confirmed by one of the above "third-line" procedures. If ^{123}I-MIBG is negative, irrespective of the result of CT/MRI, biochemical tests should be repeated, and if excessive catecholamine secretion is confirmed, "third-line" diagnostic investigation is required.

A simplified diagnostic algorithm is illustrated in Figure 1.

Genetic screening

In our view, a systematic screening for genetic predisposition is mandatory in all patients diagnosed with pheochromocytoma. There are many good reasons for such a recommendation. First, many recent studies have consistently shown that a percentage (approximately 15–30%) of pheochromocytoma patients carry pathogenic mutations [11–12]. In addition to the genes involved in syndromic diseases (NF1, VHL, and RET, respectively, for neurofibromatosis type 1, von Hippel-Lindau disease and MEN 2), three different subunits of the succinate dehydrogenase complex (SDHB, SDHC, and SDHD), a succinate dehydrogenase complex assembly factor 2 (SDHAF2) and, most recently, the transmembrane-encoding gene TMEM127 have shown sequence mutations predisposing to pheochromocytoma-paraganglioma. Second, the detection of mutations in genes responsible of syndromic disease may lead to the diagnosis of otherwise unsuspected concomitant pathologic features.

Third, some forms of genetically determined pheochromocytoma, particularly those associated with SDHB mutations, present a higher risk of malignancy, recurrence, and/or multiplicity, all features that should be carefully sought out at the time of diagnosis or at follow-up. Last but not least, the detection of a pathogenic mutation in apparently sporadic, non-syndromic pheochromocytoma patients may disclose the presence of proband's relatives who also carry the mutation and are affected by subclinical disease. Thanks to validated algorithms aimed at minimizing its cost, a complete screening for the "traditional" genes involved in the disease (RET, VHL, SDHB, SDHC, SDHD) can be performed at less than 500 Euros (and much less in the case of relatives' ascertainment).

Treatment

When the diagnosis of pheochromocytoma is made, surgical removal of the mass(es) should be performed, unless particular circumstances (recent myocardial infarction, third trimester pregnancy, concomitant disease, nonresectable malignant tumour) indicate that the surgical procedure should be postponed or is contraindicated.

In any case, medical treatment with an adrenergic antagonist must be started immediately to block the deleterious effects of increased circulating catecholamines and to restore plasma volume (impaired by chronic vasoconstriction). The α-blocker phenoxybenzamine is still considered the drug of choice by many authors, but it is not available in many countries. Alpha1 selective blockers (prazosin, doxazosin, and similar) are also very effective agents. Beta-blockers (preferably β-1 selective) can be associated with control tachycardia or arrhythmias, when present, but must be started after α-blockers to avoid hypertensive crisis due to loss of β-2-mediated vasodilation. If adrenergic antagonists are insufficient to adequately control blood pressure, other antihypertensive agents (calcium antagonists) can be used. A two-week treatment period is usually sufficient to minimize the risk associated to anaesthesia and surgery, but the treatment can be maintained indefinitely, according to clinical needs.

Surgical treatment has traditionally been performed through laparotomy, but the laparoscopic technique should now be considered the procedure of choice for most patients unless multiple, very large or malignant pheochromocytoma/paraganglioma are present [13]. The laparoscopic approach has been associated with reduced perioperative pain, a shorter period of hospitalisation, and reduced incidence of post-operative complications. Management of intraoperative hypertensive crises, arrhythmias, or sudden hypotension after tumour isolation requires an experienced anaesthesiological team. Symptoms disappear after tumour excision; in particular, blood pressure is normalized in the vast majority of patients, whereas persistence of hypertension after surgery may be an expression of underlying "primary" hypertension or incomplete tumour removal. In any case, postoperative control of urinary or plasma metanephrines must be routinely performed to ensure complete tumour removal; in addition, annual biochemical screening (plasma free metanephrines or urinary fractionated metanephrines) is recommended, given the relatively high percentage of recurrence (about 15%) even several years after first presentation. Perioperative mortality should be less than 2–3% (data mostly collected in laparotomic series), and the expected 5-year survival rate is over 95%.

Malignant pheochromocytoma

The incidence of malignant pheochromocytoma ranges between 5 and 10% and in this case the 5-year survival is less than 50%. Malignancy is about four times more frequent in extra-adrenal forms. A malignant pheochromocytoma is characterized by the presence of local invasion of the surrounding tissues or metastases (mostly in bone, liver, lymph nodes, and lung); invasion of tumour capsule and aberrant chromatin can also be observed in benign forms. Debulking surgery is recommended by many experts although data documenting its effect to improve survival and/or reduce symptoms are lacking [14]. Medical treatment of malignant pheochromocytomas includes, besides antiadrenergic agents, the administration of chemotherapeutic agents (a cyclophosphamide-vincristine-dacarbazine scheme) and the use of therapeutic doses of ^{131}I-MIBG (up to 800 mCi and above) when tumour uptake of the radioligand is maintained. It should be noted, however, that the combination of these two approaches has no advantages in view of increased toxicity [14]. The administration of somatostatin analogues may show some benefit in malignant pheochromocytomas expressing somatostatin receptors (positive ^{111}Indium-octreotide scanning) as well as a related radiotherapeutic approach with the radiolabelled somatostatin analogue [DOTA-Tyr(3)]-octreotide (DOTATOC). Targeted therapy with tyrosine kinase inhibitors (sunitinib, sorafenib, imatinib), VEGF inhibitors (thalidomide), mTOR inhibitors (everolimus), and others are under investigation in controlled trials [14]. In any case, the clinician must be aware that all these treatments are palliative at most and their use should be considered whilst bearing in mind the quality of life of such patients.

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