Review papers

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Phaeochromocytoma : State-of-the-art

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Abstract. Phaeochromocytomas are catecholamine-secreting tumours that arise from chromaffin cells of the adrenal medulla and extra-adrenal sites. Extra-adrenal phaeochromocytomas are called paragangliomas. A diagnosis of phaeochromocytoma is suspected by typical paroxysmal symptoms, unusual or refractory hypertension, discovery of an adrenal incidentaloma or a family history of phaeochromocytoma or paraganglioma, possibly associated with other genetic syndromes (multiple endocrine neoplasia type 2 A or B, neurofibromatosis type 1 and von Hippel-Lindau disease). It can be confirmed by measurements of urinary or plasma fractionated catecholamines and metanephrines. The best diagnostic performances are achieved by metanephrines. Twenty-four hour urine fractionated metanephrines are still recommended as a screening test but some experts prefer plasma measurements in high-risk patients. Increased serum chromogranin-A levels, combined with high catecholamine or metanephrine in a patient with normal renal function is also a tool, virtually diagnostic of phaeochromocytoma. Recent studies have suggested that 25% of patients with phaeochromocytoma have germline mutations of several genes (NF1, VHL, SDHD, SDHB and RET). Thus, genetic testing should be carried out according to an algorithm of risk factors and specific characteristics. Once a biochemical diagnosis of phaeochromocytoma is made, a CT scan or MRI of the abdomen and pelvis should be performed first. If these investigations remain negative, the chest and neck should be explored. After anatomical imaging, functional imaging by ^{123}I-MIBG should be considered. If the MIBG scan is negative, other imaging modalities have recently proven to be useful (PET, Octreoscan). After localization, the treatment of phaeochromocytoma is a surgical resection, which may be laparoscopic. Preoperative preparation with α- and β-adrenergic blockade and/or calcium channel blockers associated with volume expansion is essential. Malignant phaeochromocytoma is rare and its treatment still unsatisfying. Phaeochromocytoma during pregnancy is also rare and its diagnosis easily missed because of its clinical resemblance to pre-eclampsia.

Historic background

The first case of phaeochromocytoma was reported by Felix Fränkel in 1886 (1-2). The patient was an 18-year-old woman presenting with attacks of sudden-onset palpitations, anxiety, dizziness, headache, vomiting, constipation and increasing weakness. She was admitted to the hospital of Freiburg. Clinical examination revealed an "agitated heart action and a strong pulse" whereas fundoscopy showed signs of malignant hypertension. Ten days after admission, she died, probably from the consequences of a phaeochromocytoma. On autopsy, bilateral adrenal tumours were found as well as a thyroid goitre. Pathological examination concluded to bilateral adrenal sarcoma and angiosarcoma. Recently, a German team reanalysed the case, addressing the hypothesis that the patient had an inherited disorder. A family-lineage tracing and a pedigree construction revealed that six descendants had evidence of the development of phaeochromocytoma between the ages of 36 and 44 years and four had medullary thyroid carcinoma. Four descendants accepted to provide DNA, which allowed the identification of the germ-line RET mutation typical of multiple endocrine syndrome type 2 (MEN2). On this basis, it is likely that the original patient suffered from MEN2, a diagnosis unknown at the time but that would have been easy to make nowadays thanks to the new techniques of genetic analysis.

Definition and epidemiology

Phaeochromocytomas are catecholamine-secreting tumours that arise from chromaffin cells of the adrenal medulla or extra-adrenal sites, both derived from the embryonic neural crest (3-7). The term 'phaeochromocytoma' is reserved to intra-adrenal tumours whereas paragangliomas are extra-adrenal. The latter represent 10-18% of all chromaffin tissue-related tumours and are classified as sympathetic or parasympathetic according to their origin (4). Sympathetic paragangliomas are usually located in the chest, abdomen or pelvis (e.g. heart, organ of Zuckerkandl, urinary bladder) whereas

parasympathetic tumours are found in head and neck region (glomus caroticum, glomus jugulare and glomus tympanicum). Contrary to abdominal paragangliomas, the latter are usually biochemically silent. They will be suspected because of a cervical mass, cranial nerve palsy, tinnitus or hypoacousia.

Epidemiological studies have shown that phaeochromocytomas occur in 0.1 to 0.6% of patients with hypertension and in 4% of those with an adrenal incidentaloma (4, 8). In autopsy series, a phaeochromocytoma is discovered in 0.05% of autopsies (9). Phaeochromocytoma is commonly qualified as the «tumour of tens» : 10% are bilateral, 10% are extra-adrenal, 10% are malignant, 10% are asymptomatic and 10% are hereditary (10). However, this rule is currently no longer tenable because the discovery of new mutations has shown a genetic predisposition in 25 to 30% of cases (11-15) even if the case is considered as sporadic.

Clinical presentation

The clinical presentation of phaeochromocytoma is characterized by a triad of symptoms comprising episodic headache, sweating and tachycardia. Sensitivity and specificity of this triad are 90.9 and 93.8% respectively. However, these symptoms are not always present and many others, less typical may occur, such as anxiety, psychiatric disorders, chest and abdominal pain. Sustained (in half of cases) or paroxysmal (in one third of cases) hypertension is usually considered as the most common sign of phaeochromocytoma but in 21% of cases, the patient is asymptomatic and even present with a normal blood pressure (6). Symptoms of hyperglycaemia, due to a 'de novo' diabetes mellitus may sometimes be the primary manifestation (16, 17). This diabetes most often occurs in young subjects with a normal body mass index. Another clinical picture may also be dominated by cardiovascular symptoms, a dilated or hypertrophic cardiomyopathy, heart failure or a myocardial infarction (18). Independently of these conditions, the electrocardiogram may show transitory changes like an elevation or depression of ST segment, T wave inversion, arrhythmias (19). A diverse set of other symptoms may be due to the secretion of other peptides, such as diarrhoea caused by vasoactive intestinal peptide or hypercalcaemia provoked by parathormone-related peptide overproduction (20, 21). A distinctive syndrome characterized by severe paroxysms occurring during or after micturition may be produced by a paraganglioma of the urinary bladder. Finally, a phaeochromocytoma may be suspected because of a family history or other clinical signs typical of a familial syndrome. Those include the multiple endocrine neoplasia type 2A and B (MEN2A and MEN2B), the von Hippel-Lindau syndrome, the neurofibromatosis type 1 and hereditary syndromes, such as glomus tumours. The clinical features of MEN2A consist of medullary thyroid carcinoma, unilateral or bilateral phaeochromocytoma and less commonly hyperparathyroidism. Hyperparathyroidism lacks in MEN2B. In MEN2B, medullary thyroid carcinoma and phaeochromocytoma are associated with a marphanoid habitus and multiple mucosa neuromas on the distal portion of the tongue, lips, and subconjonctival areas and throughout the gastrointestinal tract (17). von Hippel-Lindau syndrome is suspected in the presence of retinal angiomas, haemangioblastoma in the cerebellum and spine, cysts and carcinoma in the kidney as well as cysts and endocrine tumours in the pancreas (2). A diagnosis of neurofibromatosis is usually made on the following clinical criteria : six or more café-au-lait spots, two or more cutaneous neurofibromas, inguinal or axillary freckles, iris hamartomas (Lish nodules) and typical bone lesions (such as dysplasia of sphenoid bone or pseudarthrosis).

Biochemical evaluation

Catecholamines and metabolites

The diagnosis of phaeochromocytoma requires measurements of catecholamines and their metabolites (Fig. 1). Three principal catecholamines are found in the body : adrenaline (or epinephrine), noradrenaline (or norepinephrine) and dopamine. Adrenaline is specifically synthesized and secreted by the adrenal medulla. Dopamine and noradrenaline can be found in the adrenal medulla where they are used for adrenaline synthesis. However, they are also neurotransmitters of the central and sympathetic nervous systems. Metabolism of catecholamines occurs through two enzymatic pathways. The first one involves the catechol-O-methyltransferase (COMT), which is found in non-neuronal (kidney and liver) tissues and in the adrenal medulla. This enzyme allows the conversion of adrenaline to metanephrine (or metadrenaline) and of noradrenaline to normetanephrine (or normetadrenaline). Metanephrine and normetanephrine are oxidized by monoamine oxidase (MAO) to vanillylmandelic acid (VMA). In the second enzymatic pathway, which is neuronal, MAO allows the oxidation of noradrenaline to dihydroxymandelic acid (DHMA) and to dihydroxyphenylglycol (DHPG). Under the effect of COMT, DHMA is converted to VMA, which is itself excreted. Dopamine is also metabolized by MAO and COMT to form its final metabolite, homovanillic acid (HVA).

The type of catecholamine secretion by a phaeochromocytoma varies according to its size or its location (adrenal or extra-adrenal). Indeed, it is worth remembering that adrenaline synthesis occurs thanks to phenylethanolamine-N-methyltransferase (PNMT), an enzyme which is induced by high concentrations of

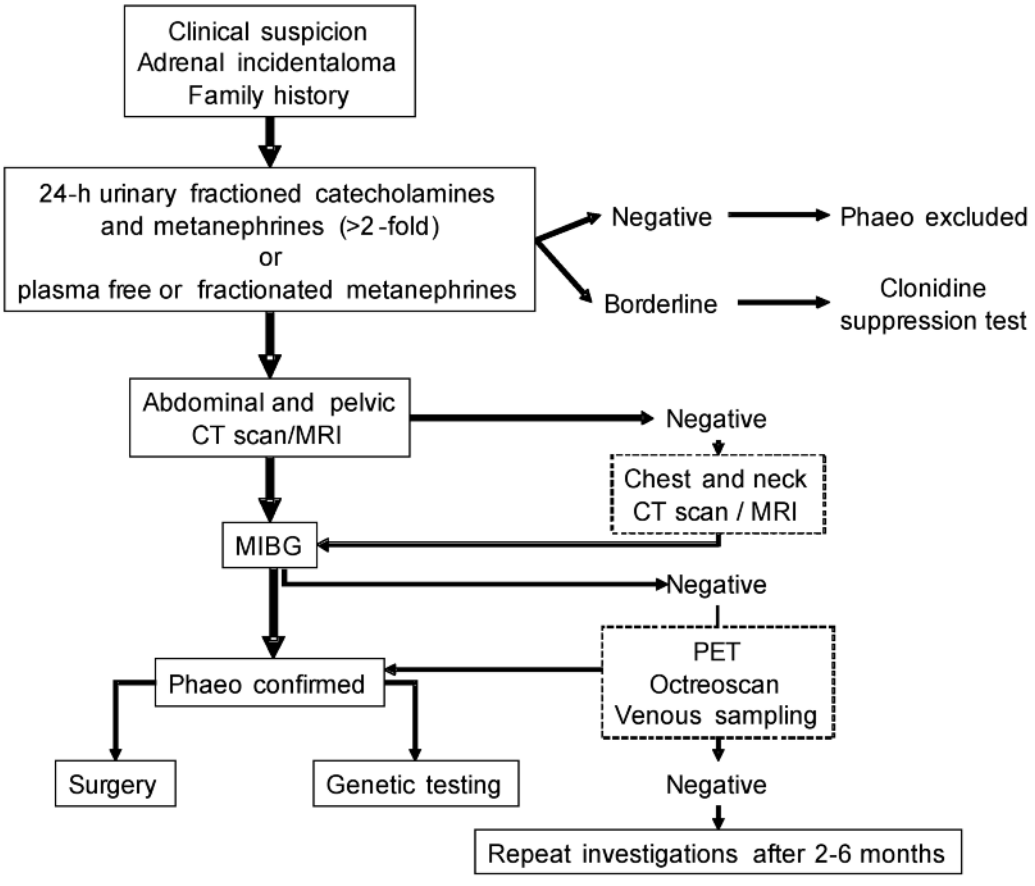

Fig. 1
Algorithm for the biochemical and imaging diagnosis of phaeochromocytoma / paraganglioma and its diagnosis

glucocorticoid coming from the adrenal cortex. Therefore, small phaeochromocytomas mainly secrete adrenaline whereas large phaeochromocytomas or paragangliomas rather produce noradrenaline. Dopamine secretion may also suggest malignancy. Finally, it is noteworthy that phaeochromocytomas may contain COMT that allow them to metabolize directly catecholamines and to secrete metanephrines and normetanephrines. This is usually the case of large phaeochromocytomas, the consequence being a lack of symptoms.

Increased concentrations of urinary or plasma concentrations of catecholamines and their metabolites will lead to suspect a phaeochromocytoma. However, the optimal test to confirm the diagnosis has been debated. Usually, most of laboratories rely upon 24-hour measurements of fractionated catecholamines (adrenaline, noradrenaline and dopamine) and of their metabolites (metanephrines, normetanephrines, VMA and HVA). Nevertheless, some studies have suggested that measurements of plasma metanephrines (free or fractionated) should be the test of choice for diagnosis of phaeochromocytoma. In one of them, performed at four referral centres, sensitivities and specificities of plasma free metanephrines were 99 and 89% respectively (23). Using receiver-operating-characteristic (ROC) curves, they showed that sensitivity and specificity were highest for plasma free metanephrines. Of note, despite a good specificity (95%), VMA had a poor sensitivity (64%). At the Mayo Clinic, a review of medical records from 1978 to 1996 revealed that the most reliable method for identifying a phaeochromocytoma was measuring combined 24-hour urinary total metanephrines and catecholamines (sensitivity 98% and specificity 98%). In a more recent study testing outpatients for two years (24), the same group found that the sensitivity of fractionated plasma metanephrines was 97% compared with a sensitivity of 90% for urinary total metanephrines and catecholamines. The specificity of fractionated plasma metanephrines was 85% compared with 98% for urinary measurements. Alltogether, it can be concluded that measurements of metanephrines have the best diagnostic performances. Regarding plasma or urine measurements, evaluation of plasma metanephrines provide the best sensitivity but lack specificity, especially

in elderly patients (the specificity of fractionated plasma metanephrines falling to 77% in patients older than 60 years) (24). Metanephrines are also normal in dopamine-secreting neoplasms because they are not direct metabolites of dopamine. Thus, some experts (5) now recommend measurements of 24-hour urine fractionated metanephrines as a screening test in low-risk patients but plasma measurements may be preferred in high-risk patients.

Interfering conditions and medications

Several clinical conditions or medications may interfere with catecholamine measurements. Catecholamines may be increased in situations of physical stress or illness such as heart failure, myocardial infarction, stroke, sleep apnea syndrome and withdrawal from ethanol. Advanced renal failure is another condition where results of urinary catecholamines and metabolites may be invalid. Plasma catecholamines or free metanephrines are also increased in patients with renal failure or under haemodialysis.

Regarding interferences in the dosage, most laboratories now measure catecholamines and their metabolites by high-performance liquid chromatography with electrochemical detection or tandem mass spectrometry. These techniques can avoid some interferences encountered with fluorometric analysis (e.g. in patients receiving labetalol, sotalol, alpha- methyldopa or imaging contrast agents). However, some drugs are still able to interfere with modern techniques. For instance, tricyclic antidepressants or other psychoactive drugs inhibiting catecholamine re-uptake may falsely increase catecholamine levels. However, selective serotonin re-uptake inhibitors do not interfere. Other interfering medications include levodopa, drugs containing catecholamines (e.g. decongestants) and amphetamines. Interestingly, a common drug such as paracetamol has been reported to increase levels of fractionated plasma metanephrines in some assays (4).

It is also noteworthy that several drugs with sympathetic activity or inhibiting the re-uptake or the metabolism of catecholamines can even provoke a clinical picture of pseudo-phaeochromocytoma.

Chromogranine-A

Chromogranine-A, a glycoprotein secreted by most phaeochromocytomas has been proposed as an alternative diagnostic test to catecholamines because its dosage is not affected by drugs commonly used for the treatment of phaeochromocytoma (3). Its diagnostic sensitivity is good (86%) but its specificity is poor (74%) (3, 25). This can be explained by the fact that its levels are increased in the presence of even moderate renal failure or of other neuroendocrine tumours. However, when combined with elevated plasma catecholamines in patients with normal renal function, its diagnostic specificity increases to 98% and its positive predictive values to 97% (3, 25). A recent study has even found a diagnostic sentivity of 100% when chromogranin measurements were combined with those of urinary catecholamines (adrenaline and noradrenaline) (26).

A role of chromogranin to distinguish benign from malignant tumours is controversial because some authors found high values in case of malignancy but others not (27, 28).

Other markers

As indicated above, phaeochromocytomas may produce many substances (e.g. ACTH, adrenomedulline, atrial natriuretic factor, erythropoïetine, neuropeptide Y, neurone-specific enolase, PTHrP, VIP, etc) (20, 21, 29). Among them, neuropeptide Y (NPY) has aroused some interest because its levels are increased in 85% of patients with phaeochromocytomas (30). However, its accuracy does not reach that of catecholamines and its metabolites. Neurone-specific enolase (NSE), when elevated may be a marker of malignancy.

Other biological findings, although less specific, may include a neutrophilic leucocytosis, a raised erythrocyte sedimentation rate, hypercalcaemia, diabetes or polyglobulia.

Pharmacologic tests

These tests, either suppressive or provocative, are rarely recommended because of the diagnostic accuracy of metanephrine measurements. Among the tests, the oral clonidine suppression test is probably the safest. Clonidine is a centrally acting α_2-adrenergic receptor agonist that suppresses the release of noradrenaline from sympathetic neurones. The test, carried out after an overnight fast in supine position reduces plasma noradrenaline by more than 50% in normal subjects but not in patients with phaeochromocytoma. Sensitivity and specificity of the test improve significantly with a measurement of normetanephrines that do not decrease in 96% of patients with phaeochromocytoma, compared with 67% for noradrenaline (27, 31). This test should be used to exclude false positive results when metanephrine levels are borderline. Intravenous pentolinium (not available in all countries) is an alternative suppression test worth mentioning.

Provocative tests, such as the glucagon stimulation test, are no longer used routinely, because they are potentially dangerous.

Genetic testing

As indicated above, the dogma that 10% of phaeochromocytomas are inherited is vanishing since two main

Table I

Characteristics of familial syndromes associated with phaeochromocytomas and paragangliomas

Syndrome	Gene	Predominant site of disease	Main secretion
von Hippel-Lindau	VHL	Adrenal	NA
Neurofibromatosis type 1	NF1	Adrenal	NA et A
Multiple Endocrine Neoplasia type 2	RET	Adrenal	A
Paraganglioma 4	SDHB	Chest - Abdomen	NA
Paraganglioma 1	SDHD	Head - Neck	NA
Paraganglioma 3	SDHC	Head - Neck	Non functional

A = Adrenaline ; NA = Noradrenaline.

studies, one published in 2002 (11) and the other in 2005 (12) reported mutations in 24 and 27.4% of cases. In 2006, the European Network for the Study of Adrenal Tumours (ENS@T) Phaeochromocytoma Working Group analysed the germline DNA from 642 patients with phaeochromocytoma and paraganglioma and identified a mutation in 25.9% of cases (13).

Six genes are subject to mutations : VHL for von Hippel-Lindau syndrome, NF1 for neurofibromatosis 1, RET for MEN2, SDHB, SDHD and SDHC for other familial syndromes (Table I). These three last genes encode subunits (B, D more rarely C) of mitochondrial succinate dehydrogenase (SDH). Their mutation is associated with three syndromes : paraganglioma-4 for SDHB, paraganglioma-1 for SDHD and paraganglioma-3 for SDHC (Table I). Patients with von Hippel-Lindau syndrome, neurofibromatosis-1 and MEN2 predominantly develop adrenal phaeochromocytomas. Their inheritance is autosomal dominant. Patients with SDHB mutations usually present with paragangliomas of sympathetic origin that are thoracic and abdominal. Phaeochromocytomas are less frequent in these patients. SDHB mutations are also inherited in an autosomal dominant manner. Head and neck paragangliomas of parasympathetic origin predominate in SDHD mutation carriers. Sympathetic paragangliomas or phaeochromocytomas are rare in these patients. Again, inheritance is autosomal dominant. Noteworthy, SDHD mutations are maternally imprinted. Mothers can transmit the mutation but only fathers transmit the disease (15). Finally, regarding patients with SDHC mutations, they often develop parasympathetic paragangliomas of head and neck, the syndrome being also dominant autosomal.

Diagnosis of a phaeochromocytoma or a paraganglioma raises the question of when and how genetic testing should be ordered, given the cost, the non-reimbursement and the absence of local specialized laboratories. The clinical approach should be the initial step : the family and past history, clinical examination searching for thyroid nodules, mucosa neuromas, a marphanoid habitus, neurofibromas, café-au-lait spots, Lish nodules or retinal angiomas. Blood could be sampled to measure calcitonin (for CMT detection) and calcium (in case of hyperparathyroidism). Then, genetic testing could be considered according to certain risk factors and patient characteristics, as suggested by the ENS@T genetic screening algorithm (Table II) (13). So, mutations should be suspected in young subjects (younger than 35 years), in patients with a family history or a syndromic presentation, extra-adrenal or multiple tumours, bilateral adrenal phaeochromocytomas and malignant tumours. Of note, mutations can also be found in patients with apparently sporadic presentation.

Localization of tumour

Once a diagnosis of phaeochromocytoma is made, a localization of the tumour is required (Fig. 1). Computed Tomographic (CT) scan and magnetic resonance imaging (MRI) are considered as the first-line imaging techniques. CT and MRI provide similar sensitivity (averaging 98 to 100%) for adrenal phaeochromocytomas but MRI seems slightly more sensitive (94% vs 90%) for extra-adrenal tumours (6). Unfortunately, specificity of both techniques is low (70%) because of the high incidence of incidentalomas. The abdomen and the pelvis should be explored first because most phaeochromocytomas (95%) are found in the abdomen and pelvis. If these investigations are negative, a CT of the neck and chest should be performed. If CT is negative, MRI could be the next option. The typical imaging phenotype of a phaeochromocytoma is an enhancement with intravenous contrast on CT and a high signal intensity on T2-weighted MRI. MRI should be preferred to CT in children and pregnant women in order to avoid radiation exposure.

After CT and MRI, functional imaging should also be considered to confirm the nature of the lesion and the absence of metastases or multifocal tumours. The most commonly used technique is ^{123}I-meta-iodo-benzylguanidine (^{123} I-MIBG). Sensitivity of this scintigraphy is 83-100% whereas its specificity is 95-100% (4). ^{123}I-MIBG is also superior to ^{131} I-MIBG, especially to detect metastases. It is noteworthy that several drugs may inter-

Table II

Criteria of a genetic testing according to the European algorithm (13)

	Screening for mutation	(First instance)	(Second instance)
Clinical diagnosis of neurofibromatosis type 1	No		
Family history or syndromic presentation	Yes	RET-VHL-SDHB-SDHD	
Age < 35 years	Yes	VHL-RET	SDHB-SDHD
Extra-adrenal or multiple tumours	Yes	SDHB-SDHD-VHL	
Bilateral phaeochromocytomas	Yes	RET-VHL	SDHB-SDHD
Malignant tumours	Yes	SDHB	VHL-SDHD
Apparently sporadic presentation	Yes	VHL-SDHB-SDHD	

fer with MIBG uptake (e.g. tricyclic antidepressants, labetalol, calcium channel blockers, phenoxybenzamine).

If MIBG scintigraphy is negative, positron emission tomography (PET) imaging and somatostatin-receptor scintigraphy (octreoscan) are other useful radionuclide techniques. PET imaging may use several tracers. ^{18}F-Fluorodeoxyglucose (^{18}F-FDG) is the most widely available and used in oncology. Nevertheless, it has been little studied in phaeochromocytoma. Its sensitivity is comparable to that of MIBG but its specificity is less because of its uptake by a variety of other neoplastic and non-neoplastic processes. Other new tracers used in the biosynthesis or the re-uptake of catecholamines are certainly promising and more specific of the adrenal medulla. They include ^{18}Fluoro-dopamine (18 F-DA), ^{18}F-Fluoro-dihydroxy-phenylalanine (^{18}F-DOPA),^{11}C-Hydroxy-ephedrine and ^{11}C-Epinephrine.

If PET scan is negative, octreoscan is recommended. Whereas octreoscan may be negative in patients with benign phaeochromocytoma, it would be better than MIBG to detect malignant or metastatic phaeochromocytomas (32). Finally, if all imaging have failed in a patient with biochemically proven phaeochromocytoma, venous sampling coupled with measurement of catecholamine or preferably free metanephrines could be carried out (33). If this technique is not available, a new work-up could be repeated after a few months.

Treatment

Preoperative management (4-6, 34)

After localization, the treatment of phaeochromocytoma is a surgical resection. Regarding the preoperative management, large, randomized, prospective and controlled studies are lacking. However, there is a consensus to start a pharmacological treatment 10-14 days before operation in order to control hypertension and to expand the contracted blood volume. A longer duration of preoperative treatment may be required in case of associated complications such as a recent myocardial infarction, a catecholamine-induced cardiomyopathy, vasculitis or uncontrolled diabetes. Volume expansion can be achieved by a high salt diet or IV fluid (saline or colloid). Blood pressure and heart rate should be monitored in hospital when treatment is started. The goal is a blood pressure of 130/80 mmHg or less while sitting and about 100 mmHg systolic while standing. Target heart rate should be 60-70 bpm sitting and 70-80 bpm standing.

Regarding the pharmacological approach, practices are wide-ranging. Adrenergic blockade, calcium channel blockers and angiotensin receptor blockers were all recommended. Nevertheless, α-adrenergic blockade remains the preferred initial choice in literature. The non-selective and long-acting α-blocker phenoxybenzamine is reported as the drug that is the most commonly used, but is no longer available in many countries. The initial dose is usually 10 mg once or twice daily, which is increased as needed to control hypertension. Other α-adrenergic blockers such as prazosin (Minipress®), terazosin (Hytrin®) and doxazosin can also be used. They are all selective, competitive and short-acting α_1-adrenergic antagonists. In our centre, we favoured these last years the use of terazocin, which proved to be fully satisfactory. An initial dosage of 1 mg/day is given and increased according to blood pressure measurements or possible side-effects.

β-adrenergic blockade can also be given to control tachycardia and arrhythmias but only after α-adrenergic blockade is effective. Indeed, administration of non-selective β-blockers alone would lead to the loss of β_2-receptor mediated vasodilation and the unopposed effects of α-adrenergic stimulation. β-blockers should be used cautiously because they can reveal a catecholamine-induced cardiomyopathy. Thus, the initial dose should be low.

Calcium channel blockers provide another option. Among these drugs, which include amlodipine, nifedipine, nicardipine and verapamil, nicardipine (Rydene®) is the most commonly used. At our institution, we give this drug to supplement adrenergic blockade when the control of blood pressure is inadequate. This obviates the need to increase the dosage of α-adrenergic blockade and reduces the risk of their side-effects.

Calcium blockers can also be used safely to control blood pressure when a phaeochromocytoma is suspected but a diagnosis not yet firmly established.

Catecholamine synthesis inhibitor (α-methyl-paratyrosine or metyrosine) should be used with caution because of its side-effects (sedation, diarrhoea, anxiety, galactorrhoea, urolithiasis...). This drug is an analogue of tyrosine that competitively inhibits tyrosine hydroxylase, the enzyme catalyzing the first step of catecholamine synthesis. Although some medical institutions give this drug routinely to all patients, several others consider it should be reserved to patients in whom other agents are ineffective or who have highly active tumours or when destructive therapy is planned (e.g. radiofrequency ablation of hepatic metastases).

Acute hypertensive crises may occur before or during surgery. They should be treated intravenously. The drugs usually used include phentolamine, nitroprusside, nicardipine, nitroglycerine and urapidil. Of interest, several reports have supported the efficacy of magnesium sulphate infusions to control haemodynamic disturbances during surgery (34-36). This beneficial effect has been attributed to a decrease in catecholamine release as well as to anti-arrhythmic and arteriolar vasodilator properties. Finally, ventricular and supraventricular arrhythmias can be treated with lidocaïne or short-acting β-blockers such as esmolol or labetalol.

Surgery

An experienced surgeon in conjunction with an experienced anaesthesiologist is required to perform such surgery. Nowadays, the laparoscopic approach which was first described by Gagner *et al.* (37) is preferred because it results in less postoperative pain, a shorter hospital stay, faster recovery and less cosmetic damage. In our initial series (including eight patients), we demonstrated the safety and the efficiency of laparoscopic adrenalectomy which could remove even large-sized lesions (more than 10 cm in diameter) (38). During surgery, we found that hypertension peaks could be induced by patient positioning on the operating table, peritoneal insufflation and/or tumour manipulation and occurred concomitantly with a release of catecholamines. The greatest instability was also observed in noradrenaline secreting phaeochromocytomas probably as a result of the more pronounced vasoconstrictive effect of this amine through binding to α-receptors (38, 39).

Postoperative management

Cardiovascular and metabolic monitoring in the intensive care unit may sometimes be necessary after operation. Hypotension may occur. It usually results from persisting action of antihypertensive drugs, a down-regulation of a high chronic exposition to catecholamines or incomplete α-adrenergic blockade and volume expansion. This should be treated with fluids and colloids and intravenous pressor agents if needed. It is noteworthy that removal of bilateral phaeochromocytomas implies a glucocorticoid coverage that should be started in the operating room. Hypoglycaemia can also occur postoperatively and should be monitored and corrected.

Malignancy

Malignant phaeochromocytomas are rare, 10% according to the 10% dogma. Patients with SDHB mutations have a higher risk of malignancy (4, 5). The distinction between a benign and a malignant phaeochromocytoma is difficult on biochemical and histological basis. It is usually admitted that the only clue of malignancy is local invasion or the presence of metastases (6, 40). Some studies have reported that the lack of expression of inhibin/activin beta-B-subunit or of NPY mRNA favours malignant diagnosis (41, 42). The prognosis of a malignant phaeochromocytoma is poor with a 5-year survival rate of less than 50% (5).

The first principle of treatment is tumour mass reduction, which can be achieved by surgical resection of primary tumour and metastases. Long-term pharmacological control of catecholamine-dependent symptoms is also indicated. Skeletal metastases may be treated with external radiotherapy or cryoablation. Regarding liver metastases, hepatic resection should be considered for localized lesions. Less invasive techniques could also been used, such as arterial embolization, chemoembolization, cryo- and radiofrequency ablation. Therapeutic doses of ^{131}I-MIBG may produce a tumour response in 30% of patients and a stabilization of disease in 57% (43). In selected cases, long-term octreotide may be another therapeutic option as well as radiolabeled octreotide (5, 44). In case of poor radionuclide uptake and response, chemotherapy should be considered. The most widely protocol combines cyclophosphamide, vincristine and dacarbazine (45). Other combination chemotherapy regimes have also been described with an improvement in some patients (6). Beneficial and additive effects have also been reported when chemotherapy is combined with ^{131}I-MIBG (46). Finally, the inhibition of heat shock protein 90, which is overexpressed in malignant phaeochromocytoma, has been shown to reduce cell proliferation in vitro. However, clinical studies are still required (6, 47).

Phaeochromocytoma and paraganglioma in pregnancy

Hypertension is a common problem during pregnancy and is usually due to pre-eclampsia. Phaeochromocytoma is extremely rare during pregnancy but provokes non-

specific symptoms that may resemble those of pre-eclampsia (48). Delayed or unmade diagnosis is however responsible for a high maternal and foetal mortality. The clues that should alert the clinician include paroxysmal or labile hypertension associating the characteristic triad (headache, sweating and tachycardia), postural hypotension, worsening of the supine position and a family or a past history of phaeochromocytoma, CMT or hyperparathyroidism (as a part of MEN 2A) (49-51, 5). Of note, the spells of hypertension in the supine position but not in the sitting or standing position are explained by the compressing effect of the gravid uterus on the tumour. Uterine contractions, foetal movements and the process of delivery may also cause a release of catecholamines (50). Myocardial ischemia, cardiomyopathy, encephalopathy and multiple organ failure have all been reported during pregnancy (51). Once a diagnosis of catecholamine-secreting tumour is suspected, the tests are the same as those performed in non-pregnant women. 24-hour catecholamines or plasma fractional metanephrines are unaffected by pregnancy. MRI is the preferred imaging technique because it does not expose the foetus to radiations. MIBG is contraindicated. Although the timing of surgery and delivery is still debated, some authors (5) recommend surgery during the first two trimesters of pregnancy. This surgery can be laparoscopic (possibly retroperitoneal) (52). If a phaeochromocytoma is diagnosed in the third trimester and the foetus is nearer to term, caesarean section and tumour resection could be combined (5). A caesarean section appears to carry less risk than vaginal delivery. Regarding the pharmacological treatment, data of literature strongly suggest phenoxybenzamine which is generally safe for the foetus (53). The disadvantage could be a perinatal depression and transient hypotension in some cases.

A last important issue to address is the psychological and ethical impact of a pregnancy in someone known to be member of a MEN 2A family, carrier of the proto-oncogen RET mutation and who plans to be pregnant (54-56). Clear discussion and counselling of patients and closely related family members should be organised in the presence of the multidisciplinary team. The risks for the baby and the mother, the possible transmission of RET mutation to progeny, the importance of a close follow-up during pregnancy should be explained. The potentials of recent technology (prenatal molecular diagnosis of RET mutation by amniocentesis, in vitro fertilization and the pre-implantation genetic diagnosis) should be presented.

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