REVIEW

Diagnosis of Pheochromocytoma

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SUMMARY

The purpose of this article is to give an overview on recent advances in the diagnosis, localization by imaging and treatment of pheochromocytoma. Pheochromocytoma is a mostly benign tumor (malignancy rate 10 - 15%) which arises from chromaffin cells with excessive catecholamine production and secretion. Most tumors are localized in the adrenals but 15 - 18% of the lesions are found extraadrenally (paragangliomas). Pheochromocytoma is a rare form of secondary hypertension; it can also be found as a feature of familial disease (e.g. von Hippel-Lindau disease, MEN type II) due to genetic mutations of several genes that have been identified recently. In familial pheochromocytoma molecular genetic analysis has improved the diagnostic modalities. In such patients the tumor can occur bilaterally and patients often remain normotensive until the tumor produces sufficient catecholamines to have hemodynamic effects. The extreme importance of recognizing this tumor is evident from the fact that it can be successfully removed in about 90% of the cases, whereas if unrecognized the tumor poses great risk of death or devastating complications. Diagnostic screening includes measurement of catecholamines and their metabolites (metanephrines) in plasma and/or urine. Furthermore, pharmacological testing (e.g. clonidine suppression test) may be indicated in patients with moderately elevated catecholamines or when the diagnosis is still uncertain. Several imaging techniques are applied to localize the tumor. Abdominal CT scan is still considered the “gold standard” since about 98% of the tumors lie infradiaphragmatically. Magnetic resonance imaging (MRI) and MIBG-scanning are other useful methods. Recently, positron emission tomography (PET) based techniques have also been developed. After the diagnosis is made tumor removal following pharmacological pretreatment is the decisive therapeutic measure. (Clin. Lab. 2002;48:5-18)

Abbreviations

Abbreviation | Description
-------------|------------------
A | adrenaline
COMT | catechol-O-methyltransferase
CT | computed tomography
DHPG | dihydroxyphenylglycol
DOMA | dihydroxymandelic acid
DOPAC | dihydroxyphenylacetic acid
EDTA | ethylenediaminetetraacetic acid
ELISA | enzyme linked immunosorbent assay
HPLC | high pressure liquid chromatography
MAO | monoaminooxidase
MEN | multiple endocrine neoplasia
MIBG | metaindoxybenzyguanidine
MN | metanephrine
MRI | magnetic resonance imaging
NA | noradrenaline
NMN | normetanephrine
NPY | neuropeptide Y
PET | positron emission tomography
PNMT | phenylethanolamine-N-methyltransferase
RIA | Radioimmunoassay
SD | Standard deviation
SPECT | single photon emission computed tomography
VHL | von Hippel-Lindau disease
VMA | vanillylmandelic acid

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Case report

A 50-year-old woman was referred to our outpatient clinic because of uncontrolled hypertension. She had a history of high blood pressure for 15 years which was well controlled with antihypertensive monotherapy until about 9 months ago. At that time the patient started to have blood pressure values around 165/105 mm Hg with systolic peak values of 210 mm Hg and she did not feel well. To rule out secondary causes of hypertension, diagnostic work-up was initiated including renal scintiscan, magnetic resonance imaging of the kidneys and adrenals without revealing any abnormality; routine laboratory tests were also unremarkable, except for urinary catecholamines which were slightly elevated. When we first saw the patient she was taking standard doses of an ACE inhibitor, a diuretic, a β-blocker and a calcium antagonist; despite this therapy her blood pressure was 180/95 mm Hg, with a regular heart rate of 78/min. Her weight was 71 kg at a height of 165 cm. Years ago lumbar spondylodesis had been performed resulting in reduced spine mobility. The physical examination was otherwise unremarkable except for a 1/6 grade systolic heart murmur at the apex. The renal sonogram revealed normally sized kidneys without any abnormal finding. Her kidney function was normal (plasma creatinine 0.5 mg/dL) without albuminuria, and serum potassium was low normal (3.5 mmol/L). Urinary total catecholamines (198 µg/24 hrs) were 2-fold above the upper limit (100 µg/24 hrs); plasma noradrenaline (451 ng/L) was slightly above the upper limit (350 ng/L), whereas plasma adrenaline was normal (45 ng/L, upper limit 50 ng/L). A MIBG-scintiscan with SPECT (Figure 1) was then performed which revealed a small adrenal tumor on the left side. After pretreatment with phenoxybenzamine for 10 days left adrenalectomy was performed without complications. Three weeks after surgery her blood pressure decreased to 135/90 mm Hg with a heart rate of 75/min; she was still taking a β-blocker and a small dose of potassium-sparing diuretic. This case demonstrates that pheochromocytoma may also occur in patients with long-standing essential hypertension.

INTRODUCTION

Pheochromocytoma is a mostly benign tumor arising from neuroectodermal chromaffin cells, which belong to the adrenergic (sympathoadrenal system); if unrecognized, it poses an enormous risk of death or serious complications (1). Especially, patients undergoing surgical procedures and pregnant women are at very high risk (2). In turn, surgical removal of the tumor is curative in up to 90% of cases. However, if it is not correctly diagnosed, the tumor is invariably fatal. The average pheochromocytoma is about 5 cm in diameter and 70% weigh less than 70 gms; some of them are very small or weigh as much as 4000 gms. Tumors are usually encapsulated and vascular and can be cystic (Figure 2) (3). The incidence of pheochromocytoma in Cau-
DIAGNOSIS OF PHEOCHROMOCYTOMA

Figure 3: Principle pathways of synthesis and metabolism of catecholamines; only metabolites which are important for diagnostic purposes are shown (redrawn from 11).

**COMT** = catechol-O-methyltransferase, **DOMA** = dihydroxymandelic acid, **DOPAC** = dihydroxyphenylacetic acid, **MAO** = monoaminooxidase, **PNMT** = phenylethanolamine-N-methyltransferase

Pheochromocytoma is about one case per 100,000 inhabitants and year, quite rare a disease altogether (4). Among unselected hypertensives, the prevalence ranges from 0.05 to 0.2%, so that pheochromocytoma is the underlying disorder in hypertension almost as frequently as primary hyperaldosteronism (approx. 0.5%) (5, 6). In patients with adrenal incidentaloma the prevalence is 4% (7). A peak is found between the second and fifth decade of life, but the disease is not uncommon among the elderly (3, 6).

These tumors produce an excess of the catecholamines adrenaline, noradrenaline, dopamine, metanephrines and vanillylmandelic acid which are released into the circulation. Release can occur permanently or periodically. Most tumors produce both noradrenaline and adrenaline, less often solely noradrenaline. Exclusively adrenaline or dopamine producing tumors seem to be rare; however, contradictory results have been reported in the literature. In one series of 19 patients with pheochromocytoma 6 were found to exclusively secrete adrenaline (8). Catecholamines exert their effects by stimulating specific cellular sites, namely alpha (\(\alpha_1, \alpha_2\)), beta (\(\beta_1, \beta_2\)) and dopaminergic receptors. As with other receptors, classification of these receptors and their subtypes is based on the rank order of potency of their responses to agonists and antagonists. Due to the varying pattern of excess catecholamines and their different effects on adrenoreceptors the resulting clinical picture may also be quite variable. Adrenaline causes hypermetabolism and tachycardia (via \(\beta_2\)-receptors) whereas noradrenaline induces peripheral vasoconstriction (via \(\alpha_1\)-receptors). Dopamine enhances myocardial contractility and has some diuretic and natriuretic action.

In sympathetic nerve endings, parts of the brain and in chromaffin cells catecholamines are synthesized from the precursor tyrosine through enzymatic degradation. The rate limiting enzyme is tyrosine hydroxylase which at first generates dopa, which is a substrate for the ubiquitous enzyme dopa-decarboxylase, generating dopamine. Dopamine-\(\beta\)-hydroxylase then catalyses the production of noradrenaline, which in the adrenal medulla - but not in peripheral nerve endings - is converted to adrenaline by phenylethanolamine-N-methyltransferase (PNMT) (Figure 3). In normals the relative contribution...
to the total catecholamine level in blood is 73% for noradrenaline, 14% for adrenaline and about 13% is dopamine (3).

In the tumor tissue the same biosynthetic pathway is operative; however, the activity of the enzymes involved may differ; thus, the distribution and secretion of the various catecholamines may also differ from tumor to tumor. Very rarely an exclusively dopamine-producing pheochromocytoma may occur, which is usually malignant (9). Some tumors also secrete other substances of neuroectodermal origin such as neuropeptide Y (NPY), enkephalins and chromogranin A and B. Neuropeptide Y is mostly undetectable in patients with ectopic tumors (paraganglioma) (10). The free catecholamines in the tumor tissue and in the circulation are being - besides other routes of elimination - rapidly degraded to a large number of metabolites via the enzymes monoaminoxidase (MAO) and catecholamine-O-methyltransferase (COMT). Important metabolites which can also be used for diagnostic purposes are 3-methoxy-4-hydroxymandelic (also called vanillylmandelic) acid (VMA) (derived from adrenaline and noradrenaline), homovanillic acid (from dopamine), metanephrine (from adrenaline) and normetanephrine (from noradrenaline). These metabolites are excreted in the urine (Figure 3). The deaminated metabolite dihydroxyphenylglycol (DHPG) is considered to be produced intraneuronally after reuptake of noradrenaline and DHPG plasma levels may therefore reflect the extent of neuronal traffic (23).

Localization

The distribution of the tumors in the body is shown in Figure 4. Up to 98% of all pheochromocytomas are found infradiaphragmally, with preponderant adrenal localization (80 to 90%). About 10% of the adrenal pheochromocytomas are bilateral (7, 11, 13). The relatively frequent incidence of pheochromocytomas among adrenal tumors should not be underrated. This was shown by a recently published Canadian study involving 121 patients with adrenal tumors, 16% of them presenting with pheochromocytoma, 46% with adenoma, and 29% with carcinoma (13). According to the literature, 15% (14) to 18% (15) of the pheochromocytomas are located extraadrenally, mostly in the sympathetic plexuses along the abdominal vessels, also termed paragangliomas. Localizations outside the abdominal cavity (e.g. in the urinary bladder or in the cervix) are rare (15). Pheochromocytoma of the urinary bladder typically presents with hypertensive crisis related to micturition. Ten to 15% of the pheochromocytomas are malignant with metastatic spread predominantly in the regional lymph nodes, but the liver, lung and bones may be affected as well. The malignancy rate is 29 to 40% with extraadrenal localization, compared with 2 to 11% in adrenal localization (15). As in many endocrine tumors there are no uniform definitive histologic criteria to distin-

Figure 4: Anatomic distribution of pheochromocytoma in 207 cases; the numbers represent percent of total (re-drawn from 12)

“Think of it”

This is by no means a trivial request, as a great number of pheochromocytomas are diagnosed only post mortem. In an autopsy study of the Mayo Clinic, Rochester, USA, carried out over a period of 50 years on a total of 40078 autopsies, the diagnosis of pheochromocytoma was made in 54 (31 females, 23 males) cases (17).

“Think of it, confirm it, find it and remove it”

Not all authors, however, believe that invasion of adjacent structures is a criterion of malignancy (15).

Three decades ago the preferred clinical strategy for patients with pheochromocytoma was aptly summarized by Ross with the dictum (16)

“Think of it”
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(76%) of these patients the diagnosis was not known at the time of death, and in 23 of these undiagnosed cases (55%), pheochromocytoma had retrospectively been the apparent cause of death. Similar results were published in the Swedish study by Stenström and Svärdssudd (18).

These researchers reported that in about 40% of the cases the diagnosis was made at autopsy, particularly in the elderly. Although the diagnostic possibilities, in particular imaging procedures have been significantly improved since these studies were performed, pheochromocytoma continues to be a diagnostic challenge. Even today, misdiagnosis is frequent with a large number of pheochromocytomas only being identified post mortem (19, 20). This is certainly due to the fact that the clinical manifestations of the tumor are extremely manifold, overlapping with a great number of different disorders. The symptomatology of pheochromocytoma has been compiled in the meanwhile „classical” work of Gifford et al. of 1964 (21). The triad „headaches, flushes and palpitations” is a predominant feature in the majority of patients, in both the paroxysmal and persistent type of the disease. Truncal sweating and pallor is also very common. Plouin et al. (22) computed in their study on a total of 2585 hypertensive patients (eleven pheochromocytomas among them) that the presence of this “Gifford triad” permits a diagnostic specificity and sensitivity > 90% when there is clinical suspicion of pheochromocytoma. This has to be viewed with some reservation, since determination of vanillylmandelic acid in the 24 hour urine collection was the only confirmatory test employed in this study, so that possibly other factors may have been responsible for the incidentally raised values (23).

Another likewise feared complication is “catecholamine-induced dilated cardiomyopathy”, usually resulting in death if not treated (26).

The changes in routine laboratory tests are noncharacteristic. Insulin release is suppressed by catecholamines; a diabetic constellation with hyperglycemia and secondary glucosuria is thus more frequent (27). The blood count of some of patients reveals a raised hematocrit (and/or raised hemoglobin) consistent with reduced plasma volume due to vasoconstriction. Mild proteinuria is more frequently seen and probably caused by increased venous lactate levels (23, 26).

Most pheochromocytomas are sporadic. In addition, there is a number of hereditary illnesses which may be associated with pheochromocytoma (Table 1). Advances in genetic mutation analysis have considerably improved the identification of such patients, allowing detection of pheochromocytoma at an early stage even before typical symptoms occur (1, 25, 28).

This includes some of the phakomatoses [von Hippel-Lindau disease (an autosomal dominant tumor predestination syndrome), neurofibromatosis type 1] as well as various syndromes of the multiple endocrine neoplasias (MEN type IIa, less common type IIb) and familial carotid Body tumors (3,28). The precise molecular mechanisms

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Figure 5: Ambulatory blood pressure profile of a 21-year-old woman with pheochromocytoma and von Hippel-Lindau disease (same patient as Figure 2) before, 1 week or 6 months following tumor removal (from 24).

Table 1: Hereditary forms of pheochromocytoma (1)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple endocrine neoplasia type II</td>
<td>RET oncogene</td>
</tr>
<tr>
<td>von Hippel-Lindau disease</td>
<td>von Hippel-Lindau tumor supressor gene</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>Neurofibromatosis type 1</td>
</tr>
</tbody>
</table>
Table 2: Most important differential diagnosis (adapted from (3))

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential hypertension</td>
</tr>
<tr>
<td>Other secondary forms of hypertension (renal</td>
</tr>
<tr>
<td>parenchymal, renovascular, other endocrine</td>
</tr>
<tr>
<td>hypertension, rare genetic forms, e.g. Liddle</td>
</tr>
<tr>
<td>syndrome, etc.)</td>
</tr>
<tr>
<td>Hypertensive crisis with monoamine oxidase</td>
</tr>
<tr>
<td>inhibitor therapy</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
</tr>
<tr>
<td>Anxiety, tension states, psychosis</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Paroxysmal tachycardia</td>
</tr>
<tr>
<td>Hyperdynamic circulatory state</td>
</tr>
<tr>
<td>Migraine and cluster headaches</td>
</tr>
<tr>
<td>Intracranial lesions (with or without increased</td>
</tr>
<tr>
<td>intracranial pressure)</td>
</tr>
<tr>
<td>Pre eclampsia and eclampsia</td>
</tr>
<tr>
<td>Carcinoid</td>
</tr>
<tr>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Mastocytosis</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
</tr>
<tr>
<td>Incidentaloma</td>
</tr>
</tbody>
</table>

Differential diagnosis

Differential diagnostic considerations would have to include a variety of disorders (“pheochromocytoma = the great mimic”). A recently published article in a textbook quotes 40 differential diagnoses (3). Essential hypertension is the most important differential diagnosis, especially in the paroxysmal or refractory clinical presentation. Other secondary forms of hypertension also need to be ruled out. In view of a similar clinical picture, it may also be difficult to discriminate against hyperthyroidism, although diastolic blood pressure elevation in hyperthyroidism is almost never found (31). One should also take into account a number of heterogeneous syndromes, which are frequently classed under the rather unclear general term “pseudopheochromocytoma”. This includes various anxiety syndromes, hyperkinetic heart syndrome, and other disorders. Paroxysmal disorders such as transitory ischemic attacks, carcinoid, hypoglycemia or intracranial tumors, etc. should be ruled out as well (for review see 3, 6). Table 2 summarizes the most important differential diagnoses.

“Confirm it”

Diagnostic exploration with regard to pheochromocytoma is required in:

- all patients with critical blood pressure elevation, particularly when this is associated with symptoms typical for pheochromocytoma (see above)
- all patients with resistant hypertension
- all patients with the incidental finding of an adrenal tumor (incidentaloma)
- in hypertensive or normotensive patients with the aforementioned familial disorders (periodical screening advised)

In many centers even hypertensive patients not meeting these criteria are subjected to a diagnostic workup for pheochromocytoma. In view of the considerable expenditure as to time, staff and funds, this procedure cannot be recommended for general application. In essence, this opinion is shared by the Deutsche Hochdruckliga (German League on Hypertension) (32). Established evidence of raised catecholamine concentration in either plasma or urine is of decisive diagnostic importance. The diagnosis of pheochromocytoma in most patients is straightforward when plasma catecholamine levels (norepinephrine, adrenaline) or urinary excretion of catecholamines and/or their metabolites are well above the levels for patients with essential hypertension or healthy subjects (23). Published data show that a nonstressed plasma total norepinephrine/adrenaline level of more than 2000 ng/L is diagnostic of pheochromocytoma, and the false “positive” rate of such a finding is extremely low (33, 34). The diagnostic problem with regard to pheochromocytoma is to separate pheochromocytoma pa-
Table 3: Sensitivity and specificity of various catecholamine/metabolite measurements in plasma and 24 h urine

<table>
<thead>
<tr>
<th>parameters</th>
<th>upper reference limit *</th>
<th>sensitivity (% -range)</th>
<th>specificity (% -range)</th>
<th>references</th>
</tr>
</thead>
<tbody>
<tr>
<td>plasma NA + A</td>
<td>950 ng/L</td>
<td>83 - 100</td>
<td>93 - 100</td>
<td>23,34,35,37</td>
</tr>
<tr>
<td>plasma NMN/MN</td>
<td>2.5 * / 1.4 nmol/L **</td>
<td>99 - 100</td>
<td>89 - 100</td>
<td>1,38</td>
</tr>
<tr>
<td>urinary NA + A</td>
<td>100 - 200 µg/24 h</td>
<td>67 - 100</td>
<td>77 - 95</td>
<td>36,42,53,62</td>
</tr>
<tr>
<td>urinary NMN + MN</td>
<td>1.8 mg/24 h</td>
<td>67 - 100</td>
<td>83 - 100</td>
<td>23,34,35,36,37</td>
</tr>
<tr>
<td>urinary VMA</td>
<td>8 - 11.0 mg/24 h</td>
<td>28 - 90</td>
<td>87 - 100</td>
<td>23,34,35,36,37</td>
</tr>
</tbody>
</table>

NA = noradrenaline, A = adrenaline, NMN = normetanephrine, MN = metanephrine, VMA = vanillylmandelic acid; # 95 or 97.5 % percentile or mean + 2SD
* 4-fold of upper normal limit; ** 2.5-fold of upper normal limit
Conversion factors: NA 0.005911 for nmol/L; A 0.005458 for nmol/L;
* 95 or 97.5 % percentile or mean + 2SD
§ review article

Patients with only moderate biosynthetic activity of the tumor from patients with unspecific stimulated sympathetic nervous system activity, i.e. patients with essential, neurogenic or renovascular hypertension. Furthermore, measurements of catecholamines and their metabolites in the plasma and urine may reveal normal values when the tumor only secretes periodically (35). In addition, pheochromocytomas do not always secrete sufficient catecholamines to produce positive test results or typical signs or symptoms. Therefore, commonly used investigations of urinary or plasma catecholamines and/or their metabolites and other biochemical tests, such as measurement of plasma chromogranin A levels, are not always able to reliably confirm or reject the diagnosis. Moreover, the biochemical approaches per se have several limitations. The fact that there are various testing methods may frequently hamper the diagnostic validity of the results since sensitivity and specificity of these tests may vary considerably. Several recent publications offer a synopsis of the varying data from the current literature with an assessment of their diagnostic validity (23, 35, 36, 37, 38). Table 3 (adapted from 39) attempts to display these heterogeneous data on specificity and sensitivity in an integrative fashion. The upper reference limits of the pertinent determinations (when available) refer to data obtained from hypertensive subjects and should not be viewed as “normal limits” per se (23). The definition of normal catecholamine levels is rendered difficult by the fact that under standardized conditions, essential hypertensives - whose differential diagnosis is being worked on - present with plasma noradrenaline levels which are significantly higher than in healthy subjects (23, 40). Moreover, these normal limits may vary depending on the laboratory and on the analytical method applied (e.g. spectrophotometry, fluorometry, thin-layer chromatography, HPLC, RIA and ELISA) (36). It appears that VMA determination in the urine may be less suited as a screening test for suspected pheochromocytoma since the sensitivity of this method in some testing series approximated merely 50%. In case of pathologically increased VMA secretion, this finding is very specific and thus highly indicative of pheochromocytoma (23, 34). As a rule, however, the other techniques, i.e. determination of plasma catecholamines and/or catecholamine or metanephrine/normetanephrine excretion in the urine, should be given preference. A recent study suggests that the determination of plasma metanephrines (determination with HPLC) provides 100% sensitivity for the detection of a pheochromocytoma compared to only 82% when plasma and urinary catecholamines were determined (38). It therefore appears that measurement of the plasma levels of normetanephrine and metanephrine has even higher sensitivity than other biochemical tests for the diagnosis of both familial and sporadic pheochromocytoma (1); a larger increase and a longer persistence of metanephrines than catecholamines in plasma may contribute to their greater diagnostic accuracy (41). To our knowledge, however, at present a commercial sensitive enough kit is not yet available for the determination of plasma metanephrines. Metanephrine is the major degradation product of adrenaline and increased levels may be the only guiding finding in the presence of high metabolic turnover (36). Therefore, when an exclusively adrenaline-producing pheochromocytoma is suspected (more commonly with bilateral adrenal localization or in familial disease) both urinary (or if possible plasma) adrenaline/noradrenaline and metanephrine/normetanephrine should be determined, since these tumors can be overlooked by solitary total determination (35, 42). A number of drugs can interfere with the measurement or affect the levels of catecholamines and their metabolites (increase: e.g. levodopa, methyl dopa, MAO inhibitors, benzodiazepines; decrease: e.g. fenfluramine, α-
**Table 4: Clonidine suppression test (34, 48)**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Moderately raised plasma catecholamine levels (noradrenaline + adrenaline 1000 – 2000 pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principle</td>
<td>( \alpha_2 ) stimulation effecting decline of neuronal noradrenaline release</td>
</tr>
<tr>
<td>Method</td>
<td>Clonidine 300 µg per oral route, measuring of plasma catecholamines before and 2 or 3 hours after application</td>
</tr>
<tr>
<td>Interpretation</td>
<td>Total catecholamine level decreased to &lt; 500 ng/L after 2 or 3 hours is not suggestive of pheochromocytoma</td>
</tr>
<tr>
<td>Risks</td>
<td>Minor, occasional hypotension and bradycardia</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>97%</td>
</tr>
<tr>
<td>Specificity</td>
<td>67%</td>
</tr>
</tbody>
</table>

**Table 5: Influence of drugs on clonidine receptors (51)**

<table>
<thead>
<tr>
<th>Weakens suppression</th>
<th>Without influence</th>
<th>Effects unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>( \alpha )-blockers</td>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>( \beta )-blockers</td>
<td></td>
<td>Calcium antagonists</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 6: Safety measures for the clonidine suppression test (50)**

- Avoid volume depletion before testing (hypotension)
- Discontinue \( \beta \)-blockers 48 hrs before testing (bradycardia)
- Avoid testing after a short-term period (2 - 3 days) of clonidine withdrawal (hypotension)
- Avoid testing in baroreceptor dysfunction due to bilateral carotid artery disease (hypotension)
- Avoid testing in severe atherosclerosis (cardiovascular/cerebrovascular accident)

In addition, other biochemical tests have been employed. This includes the ratio plasma noradrenaline/plasma DHPG, which appears to speak against noradrenaline-producing pheochromocytoma with levels <0.5 (45). Plasma levels of the proteins chromogranin A and B stored in the chromophil granules, which the tumor cells, along with catecholamines, release into the circulation can be determined (46). Plasma adrenomedullin levels were also found to be increased in adrenal pheochromocytoma (47). Presently, these tests do not seem to offer superior diagnostic accuracy compared to measurement of urinary/plasma catecholamines and/or their metabolites.

**Pharmacological testing**

Pharmacological testing is recommended in patients with only moderately elevated plasma or urinary catecholamines and when the diagnosis is still uncertain (3). Years ago, provocative tests were developed which are based on a pharmacologically induced (e.g. by histamine or tyramine) release of catecholamines in patients with the tumor. These tests bear some risk for the patient, and most of them are nowadays obsolete. One of these tests, however, the glucagon stimulation test, is still being used. Reportedly, the complication rate is smaller than with the other tests (34, 48). A more widely used test is the clonidine suppression test (Table 4); it is based on the fact that the imidazoline clonidine stimulates central \( \alpha_2 \)-imidazoline receptors, thereby decreasing the neuronal noradrenaline release. The noradrenaline/adrenaline release from the tumor is not affected since the tumor is not innervated and its secre-
Figure 6: Plasma noradrenaline + adrenaline concentrations before (pre) and 3 hrs after (post) oral application of 300 µg clonidine in 114 patients with suspected pheochromocytoma. Four of the 6 patients with a "positive" result had pheochromocytoma (P) (conversion factor 0.005911 for nmol/L) (redrawn from 51).

"negative test"; "positive test"

ation is not influenced by suppression of the sympathetic nervous system (Figure 6). The test is considered "positive" if the total plasma catecholamines (adrenaline plus noradrenaline) are not suppressed below 500 ng/L 2 to 3 hours after the oral administration of 300 µg clonidine (34, 49). Other definitions, however, have also been applied in subsequent publications. The test results can be affected by several antihypertensives (Table 5). The risks of the test are low provided certain safety measures are obeyed (Table 6). Patients with "positive" test results require further diagnostic work-up (see below) since the likelihood of pheochromocytoma is markedly increased (50, 51).

In the light of the various biochemical tests and newer molecular genetic methods that have become available the clinician must decide what tests in what sequence are most appropriate. However, opinions in that respect vary and it is therefore difficult to provide a general recommendation. In our clinics/institutions, the follow-

ing diagnosis making strategy has proven efficient (see also Figure 7):

- Catecholamine (noradrenaline/adrenaline) or metabolite (metanephrine/normetanephrine) secretion in 24-hour urine is checked twice at least. In case of a definitely pathologic finding (at least 100% in excess of the "normal range" for hypertensives), search for the site of the tumor is begun.

and/or

- Catecholamine plasma levels (noradrenaline/adrenaline) are determined under standardized conditions (i.e. decline in the supine patient after insertion of a cannula, 30 minutes of rest, 10 ml EDTA blood, immediate chilling, centrifugation at 4000 rpm for 5 min at 4 °C, plasma stored at - 20 °C until RIA; in some laboratories antioxidants are added as a plasma preservative, but stability studies indicate that this practice may not be necessary). In case of definitely pathologic values (i.e. noradrenaline + adrenaline > 2000 ng/L), search for the site of the tumor is begun.

and/or

- Future plan: measurement of plasma metanephrines concentration under standardized conditions.

- Clonidine testing is performed in patients with moderately raised "basal" plasma catecholamine levels (i.e. noradrenaline + adrenaline between 1000 and 2000 ng/L). In case of insufficient suppression (i.e. no decline of plasma adrenaline + noradrenaline to < 500 ng/L), search for the site of the tumor is begun.

- Future plans: molecular genetic testing for mutations of the RET or von Hippel-Lindau tumor suppressor gene will be offered to asymptomatic patients with suspected familial pheochromocytoma or in the sense of germline testing.

"Find it"

Diagnostic localization techniques have substantially improved since the days of Ross’ dictum. The most important techniques are listed in Table 7. Computerized tomography of the abdomen is still the “gold standard” since up to 98% of all pheochromocytomas are located infradiaphragmally, in fact, in the abdomen (3, 6) (Figure 8). Magnetic resonance imaging (MRI) is also being used to detect the tumor. This method is of particular advantage since it goes without exposure to radiation, thus bearing no hazard for pregnant women. In the T2-weighted image, pheochromocytomas possess signal
### Table 7: Routine imaging techniques

<table>
<thead>
<tr>
<th>Technique</th>
<th>Special advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal CT</td>
<td>Great experience / high safety</td>
</tr>
<tr>
<td>Abdominal MRI</td>
<td>No exposure to radiation, suited for pregnant women</td>
</tr>
<tr>
<td>Metaiodinebenzylguanidine (MIBG) scintiscan</td>
<td>Identification of additional manifestations and metastases</td>
</tr>
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### Table 8: Synopsis of the most important diagnostic methods

- Demonstrating of raised catecholamine/metabolite secretion in either urine or plasma
- Pharmacologic testing (clonidine suppression test)
- Abdominal CT scan or MRI, MIBG scintiscan
- Molecular genetic analysis for familial disease

### Figure 7: Proposal for diagnostic decision making for patients with suspected pheochromocytoma

intensity by comparison with other benign adrenal tumors, thereby facilitating a definite diagnosis in many cases already. Favorable results have also been reported for extraadrenal pheochromocytoma (15). The $^{131}$I- or $^{123}$I-metaiodinebenzylguanidine- (MIBG) scintiscan is based on nuclide uptake in the tumor tissue, which enables visualization of secondary manifestations, metastases or tumors in unusual locations. This diagnostic method is felt to be obligatory nowadays (52).

The relative diagnostic relevance of those various techniques has already been discussed in detail elsewhere (13, 15, 35, 53). The results of a recently published prospective comparative study demonstrate that sensitivity of CT and MRI was similarly high (23), so hardly any tumor was overlooked, whereas specificity was only about 70%. The reverse was true for the MIBG scintiscan, revealing only about 80% of the tumors, specificity being 100%. These data are largely consistent with others from the literature (52).

Besides these imaging techniques newer methods have become available, mostly based on positron emission tomography. Currently, several imaging radiopharma-
Figure 8: CT scan of right adrenal pheochromocytoma in a 21-year-old woman with von Hippel-Lindau disease (same patient as Figure 2).

Surgical removal of the tumor is the decisive therapeutic measure. Recently, minimally invasive techniques like posterior retroperitoneoscopic adrenalectomy have increasingly been applied for adrenal tumors (54). After the diagnosis has been made, pharmacologic pre-treatment of the patient is required to reduce the peri-operative risk. The objective of therapy is to improve blood pressure and to alleviate symptoms, thereby also reducing the risk of cardiovascular complications such as hypertensive crises or development/aggravation of malignant hypertension. Most authors advise initiation of oral α-blockade, e.g. by phenoxybenzamine (10 - 50 mg b.i.d.) at least 7 - 10 days prior to surgery (23, 55). Patients with tachycardia or arrhythmias (mostly supraventricular) should receive a β-blocker in addition, with cardioselective agents (e.g. metoprolol, atenolol) given preference over nonselective β-blockers. β-blockade should generally only be started subsequently to α-blockade, since particularly nonselective β-blockers may evoke hypertensive crises due to inhibition of vaso-dilating β2-receptors (3, 23). A recently published study has raised some doubt about the therapeutic value of pharmacologic preparation (56). In this study, 29 pa-
tients underwent surgery without preceding preparation while perioperative mortality remained unchanged. This surgical result is probably related to improved anesthesiologic perioperative monitoring (57). Pharmacologic preparation should nevertheless not be refrained from without compelling reason. Surgical mortality is rated from 0 to 3.5%, depending on the center (3). In view of its inoperability in most cases, treatment of malignant pheochromocytoma is significantly different from management of the benign form (58). Therapy is based on two principles:

- Suppression of the catecholamine effect. This is mostly achieved by administration of α- or β-blockers. Calcium antagonists are increasingly used for symptomatic management (3, 23)
- Suppression of catecholamine synthesis. Quite good experience has been gained here with the “false precursor”-α-methylparatyrosine (metyrosine), an inhibitor of tyrosine hydroxylase, which decreases catecholamine formation. Moreover application of radiotherapy by 131I-MIBG, which is taken up from most tumors and their metastases, has been going on for some years (59). After an initially favorable outcome, the long-term effect of internal radiotherapy is nowadays viewed with some reservation (3, 23) but may be indicated in selected patients (60). And palliative removal of the tumor - if possible - is always advisable to reduce tumor tissue mass. Conventional chemotherapy and/or radiotherapy will not result in improvement, except for rare cases (61).

**Prognosis**

Prognosis of pheochromocytoma is overall good. After removal of the tumor, blood pressure normalizes or significantly improves in about 75% of the patients (Figure 5). The 5-year survival rate in benign pheochromocytoma is in excess of 90%, versus a mean of just 44% in malignant pheochromocytoma. As these tumors are growing slowly, there have been reports on courses of more than 20 years (3, 6). In conclusion, medical advances in several areas (biochemistry, imaging, molecular genetics) have further improved the identification, diagnosis and treatment of many patients with sporadic or familial pheochromocytoma. Despite improved diagnostic and therapeutic procedures, however, the imperative “think of it” continues to be the most essential medical challenge, and any further measure for the benefit of the patient is derived there from.

**References**

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