

Pheochromocytoma and paraganglioma – an overview

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ABSTRACT

Pheochromocytoma and paraganglioma derive from chromaffin tissue that secretes catecholamines, which determine the characteristic clinical picture of the disease. Serious and potentially fatal cardiovascular complications require rapid diagnosis and treatment. The available biochemical tests are recommended not only to patients with characteristic clinical symptoms, but also to all patients with incidentally identified adrenal tumours. There is a growing incidence of diagnosed germline mutations associated with familial pheochromocytoma and paraganglioma in tumours originally identified as the sporadic form, and therefore current recommendations ever more often indicate the need for genetic testing in all patients with diagnosed pheochromocytoma or paraganglioma. Surgical treatment, which is the treatment of choice, brings very good results in the case of benign tumours, and even the malignant ones, provided they are operational. Unfortunately, there is no sufficiently good and efficacious alternative treatment for patients with unresectable or metastatic malignant tumours.

KEY WORDS: chromaffin cell tumour, pheochromocytoma, paraganglioma, germline mutations, clinical picture, diagnosis, treatment

INTRODUCTION

Chromaffin cell tumours are rare and usually benign neoplasms, belonging to the group of neuroendocrine tumours, which develop from the catecholamine-secreting chromaffin cells. They are usually observed in the adrenal medulla, taking on the name of *pheochromocytoma* (PCC), and less frequently extraadrenally, termed *paraganglioma* (PGL) there [1]. Most PGLs are hormonally active tumours developing from sympathetic ganglia. However, there are also PGLs located mainly in the region of head and neck, developing from the elements of the parasympathetic system, and usually hormonally inactive (HNPGGL, head and neck paraganglioma). An excess of circulating catecholamines leads to a typical clinical picture involving the following symptoms: cardiac palpitation, anxiety, headache, arterial hypertension, and hyperhidrosis. As there may be serious and potentially fatal cardiovascular complications in the course of the disease, it is considered a highly dangerous one, requiring urgent diagnostics and treatment. Hence, a comprehensive diagnostic procedure is recommended not only for the patients who manifest typical symptoms, but also for all those with incidentally diagnosed adrenal tumours (incidentalomas).

EPIDEMIOLOGY

Pheochromocytoma and paraganglioma are rare tumours, whose incidence ranges from 2 to 8 cases/million annually [1–3]. It is estimated that PCC is responsible for 0.1 to 0.6% of the cases of secondary arterial hypertension, and it constitutes around 4% of the incidentaloma cases [4–8]. In accordance with the World Health Organisation (WHO) definition of 2004, malignancy of chromaffin cell tumours is confirmed by a remote metastasis, i.e. another tumour located in a region, where there is no physiological presence of chromaffin cells [1]. No histological or molecular indicators of tumour malignancy have been identified to date [1, 9]. PCC is revealed to be malignant in 10 to 25% of cases, while PGL in as many as 20% up to 50–60% of cases [10, 11]. The most frequent metastatic locations are lymph nodes, bones, liver, lungs, and kidneys. Based on the published analyses of numerous pathological cases, malignancy risk factors for chromaffin cell tumours appear to be its size exceeding 5 cm, extraadrenal location, presence of germline mutation in the succinate dehydrogenase-coding genes, and in particular in the gene coding its β subunit (*SDHB*), and dopamine secretion [10, 11].

PCC and PGL usually develop in the fourth and fifth decade of life, while the familial forms are more frequently diagnosed in young patients (below the age of 40). They are mainly located within the abdominal cavity (90%), with PCC chiefly found in the medulla of one of the adrenals (90%), or more rarely bilaterally (around

10% of cases), whereas the extraadrenal PGL develops mainly in the ganglia of the autonomous nervous system (in the abdominal cavity often involving the coeliac, superior mesenteric, and inferior mesenteric ganglia, whereas in the mediastinum the aortic bifurcation region), and in other sites, where chromaffin cells are to be found, such as the heart or bladder [12, 13]. In children, on the other hand, the tumour is much more often located in both of the adrenals (25%) or outside of them (25%) [12].

As mentioned above, there is the sporadic and familial (hereditary) form of the chromaffin-cell tumour [12, 14]. Aetiology of the tumour is unknown in the former case, although some authors claim that it may be associated with previously occurring adrenal medulla hypertrophy [12]. The proportion of PCC/PGLs that are genetically determined (familial forms) is now considered to be ever higher, ranging from 30 to 41% of all cases [15, 16]. In the latter scenario PCC/PGL forms part of genetically determined syndromes of multiple endocrine tumours, such as (Table 1):

- neurofibromatosis type 1 – NF1, von Recklinghausen disease
- von Hippel–Lindau disease (VHL)
- multiple endocrine neoplasia type 2: MEN2A, MEN2B
- pheochromocytoma/paraganglioma syndrome – PCC/PGLs.

The above mentioned syndromes are caused by germline mutations in the following genes: for *NF1* – suppressor gene for NF1 tumours, for *VHL* – suppressor gene for VHL neoplasms, for MEN2 – *RET* protooncogene, as well as in the *SDHA*, *SDHB*, *SDHC* and *SDHD* genes coding the A, B, C, and D subunits of the succinate dehydrogenase (also known as the mitochondrial respiratory chain complex II), and in the *SDHAF2* gene (also referred to as *SDH5*), coding the SDH enzyme cofactor [17–22]. The result of mutations involving the SDH coding genes are hereditary PCC and PGL syndromes (PCC/PGLs). In 2010, two other genes were identified, whose mutation is responsible for PCC/PGLs, i.e. *TMEM127* and *MAX* [23, 24]. Depending on the type of mutation, PCC/PGL syndromes which develop as a consequence thereof are different in terms of their location (adrenal and extraadrenal), unifocality or multifocality, higher or lower secretory activity, type of secretory activity, and degree of malignancy risk. Malignant PCC and PGL usually involve the *SDHB* gene mutation [11, 25]. Due to a substantial proportion of germline mutations (30–41%), the need for genetic tests in all PCC and PGL patients is increasingly advocated [16]. The tests should all the more be recommended in the following cases: positive family history, young patient age (below 40), extraadrenal location of the lesion, bilateral PCC or multifocal PGL, tumour malignancy, and characteristic clinical picture for the aforementioned syndromes

TABLE 1.
Genetically conditioned syndromes involving PCC or PGL [12, 39].

Gene	Syndrome	Syndrome Manifestations
<i>RET</i>	MEN2A	medullary thyroid carcinoma, PCC, hyperparathyroidism, Hirschsprung's disease
<i>RET</i>	MEN2B	medullary thyroid carcinoma, PCC, mucosal neuromas and ganglioneuromas, marfanoid habitus
<i>NF1</i>	type I neurofibromatosis	peripheral neurofibromas, café au lait spots, iris hamartoma, bone structure disorders, PCC, other CNS tumours
<i>VHL</i>	von Hippel–Lindau disease	retinal angiomas, CNS hemangioblastoma, optic nerve gliomas, renal carcinoma, renal and pancreatic cysts, pancreatic neuroendocrine tumours, PCC, ear and epididymis cystic adenomas
<i>SDH</i>	PGL1/PGL5 familial syndromes	HNPGL, PGL, rarely PCC, malignant chromaffin-cell tumours mainly in PGL4 (<i>SDHB</i> mutation), probable association between the <i>SDHB</i> mutation and other tumours (papillary thyroid carcinoma, renal carcinoma, gastrointestinal stromal tumours – GIST)

[15, 16]. Early identification of the familial forms enables adequate follow-up and early detection of relapses or potential other endocrine tumours, as well as identification and monitoring of the other family members at risk from the disease.

Secretory activity of PCC and PGL, leading to an excess of catecholamines circulating in the body, determines the characteristic clinical picture of the disease. The secreted catecholamines are mainly adrenaline and noradrenaline, and much less frequently dopamine or its precursor dihydroxyphenylalanine (DOPA) [12]. Moreover, the tumours might secrete other substances, including chromogranin A (CgA), atrial natriuretic peptide, parathormone, calcitonin, adrenocorticotrophic hormone, corticoliberin, somatotropin, erythropoetin, endothelin 1, adrenomedullin, neuropeptide Y, and interleukin 6 [8, 12].

CLINICAL PICTURE

Clinical picture of the disease is determined by the direct impact of the secreted catecholamines on the body. It is very changeable and depends on the volume and type of the prevailing catecholamine (noradrenaline stimulates the α receptors more strongly, producing a greater constrictive effect on peripheral vessels, while adrenaline stimulates both the α and β receptors to a similar degree, causing a general adrenergic activation) [12, 14]. Moreover, other substances secreted by the tumour may also influence the clinical picture. Catecholamines strongly affect the cardiovascular system and metabolic processes, causing a compensatory reduction in the activity of the sympathetic nervous system, and increased activity of the parasympathetic one [12]. Thus, the clinical picture usually involves: tachycardia, pallor, headache, hyperhidrosis, elevated arterial pressure, and anxiety [14]. The symptoms often present suddenly, lasting for several minutes and receding spontaneously or setting in for an hour or longer. They may occur periodically, spontaneously or in association with certain circumstances (e.g. the food ingested or

the medications taken) [12, 14, 26, 27]. Patients may also present with non-specific symptoms, such as reddening, fever, nausea, emesis, abdominal pain, constipation, fatigue or weight loss [12, 14, 28]. Arterial hypertension may be persistent or paroxysmal, achieving high values, and leading to dangerous hypertensive crises. The ejection of catecholamines may cause not only sinus tachycardia, but also serious ventricular arrhythmias. Arterial hypertension as well as dysrhythmia constitute significant risks, leading to serious and not infrequently lethal complications – hypertrophic cardiomyopathy, takotsubo cardiomyopathy, cardiac failure, myocardial infarction, and stroke [14, 26, 28, 29]. Such complications may also result from the administration of some medications enhancing the secretion of catecholamines. A handful of cases of hypertensive crisis, cardiac ischemia, and severe multi-organ failure, including death, were described as following the administration of glucocorticosteroids in patients with (usually) undiagnosed PCC/PGL [27]. Such reactions were reported after dexamethasone (2 mg and more) administered during the suppression test as part of the adrenal incidentaloma diagnostic procedure, as well as after betamethasone and methylprednisolone. In those cases, PCC presence was confirmed, frequently accompanied by haemorrhagic and necrotic lesions within the tumour and its metastases. Administration of exogenous glucocorticosteroids resulted not only in an increased secretion and release of catecholamines from PCC cells, but most probably also the haemorrhage inside the tumour leading to a sudden and massive release of catecholamines [27]. Hence, it is recommended for the tests involving higher doses of dexamethasone, performed as part of the adrenal incidentaloma diagnostics, to be carried out once PCC/PGL has been ruled out, and for the patients with similar post-glucocorticosteroids complications to undergo a PCC/PGL-oriented diagnostic procedure [27].

In some PCC patients, arterial pressure remains normal or is significantly lower, causing syncope episodes or even shock (cases

of orthostatic hypotonia or the effect of hypotensive substances, such as DOPA or adrenomedullin, secreted by the tumour) [12, 14, 28]. High blood glucose values, stemming from the impact of excess catecholamines on glycogenolysis and gluconeogenesis, might erroneously suggest the diagnosis of diabetes [12]. Thus, in patients who do not present with other typical diabetes symptoms, such diagnosis should be questioned and verified. When the chromaffin-cell tumour is located in the urinary bladder, haematuria may be observed, and elevated arterial pressure during miction, together with other characteristic symptoms [13]. Since the clinical manifestations are so varied, chromaffin-cell tumour is often defined as one of the greatest imitators, which is why, according to many experts, the first treatment step to be taken is to remember about the disease, and make the correct diagnosis [14, 26].

A special case, and one which constitutes a serious clinical problem, is the development of a hormonally active PCC or PGL in pregnant women. The incidence of such cases is estimated as 1 in 50 000 [26]. Diagnostic difficulties mainly result from the fact that some of the typical PCC symptoms (arterial hypertension and headaches in particular) match the symptoms of preeclampsia, with the latter often misdiagnosed in such scenarios [12, 26]. Therefore, an analysis of the remaining symptoms, differentiating the two conditions, is essential. It should also be mentioned here that unlike in the typical PCC clinical picture, some pregnant women present with contrary symptoms – orthostatic hypotonia or incidents of sudden decrease in arterial pressure with symptoms of cardiovascular collapse. The cases which are especially dangerous, both for the mother and the child, are the ones which remain undiagnosed until the time of delivery. The risk of miscarriage as well as mother and child mortality is estimated as very high, i.e. 40 to 48% and 44 to 56% respectively [26]. Hence, sufficient attention should be directed to women who develop high arterial hypertension during pregnancy, resistant to treatment or showing a tendency for large fluctuations. Optimum biochemical diagnostics involves 24-hour urinary output of metoxycatecholamines, and MRI [12, 26]. PCC treatment in pregnant women is not significantly different from that in other groups of patients. Pharmacological preparation before surgical treatment is similar, and it appears that the safest drug for the child is phenoxybenzamine. Surgical treatment raises doubts, though, as to the optimum surgery time [12, 26]. Some specialists believe that the best solution is laparoscopic tumour resection before 24 weeks of gestation [12, 26]. When PCC/PGL is diagnosed at a later stage, caesarean section is the recommended mode of delivery. As far as the possibility simultaneous tumour resection and caesarean section is concerned, views on the matter are divided [12, 26].

BIOCHEMICAL TESTS

All patients with suspected chromaffin-cell tumours should undergo adequate biochemical tests. It applies both to patients manifesting paroxysmal symptoms suggesting PCC/PGL and those with changeable or treatment-resistant arterial hypertension, paradoxical arterial pressure changes during surgical procedures or under anaesthesia, patients with positive family history of familial chromaffin-cell tumours, and patients with adrenal incidentaloma, including those who do not present with the typical disease symptoms [14, 28, 30]. Biochemical tests performed to date include: serum and urine catecholamines (adrenaline, noradrenaline, dopamine), and their metabolites, metoxycatecholamines (metanephrine and normetanephrine), in serum and 24-hour urine sampling, as well as 24-hour urine vanillylmandelic acid (VMA). Release of catecholamines from tumour cells is quite changeable, their half-life is short, and additionally it is possible that they are metabolized inside the tumour (if its size is large), without being released into the bloodstream. Therefore, testing their concentration levels is not the recommended mode of action today [14, 26, 30]. It is much more useful to test the concentration of their metabolites, metanephrine and normetanephrine in serum and/or urine, and those are the tests of choice these days [14, 26, 30–32]. Serum metoxycatecholamines is the test exhibiting the highest sensitivity and specificity of 98% and 89–92% respectively [14, 26, 32]. 24-hour urinary fractionated metoxycatecholamines is an assay of comparable sensitivity and only slightly lower specificity, which is why, depending on their availability, the two tests are the most frequently used ones nowadays [14, 26, 31, 32]. It should be added here that the accuracy of measurements is undoubtedly affected by the testing method, with the most popular immunoenzymatic method being the least accurate one at the same time. Much more advanced and accurate methods, allowing for an ever greater elimination of false positive results, include liquid chromatography with electrochemical detection (LC-EC), high performance liquid chromatography with electrochemical detection (HPLC-EC), and the most accurate liquid chromatography with tandem mass spectrometry (LC-MS/MS), capable of determining the concentration of dopamine metabolite, 3-metoxytyramine [26, 32].

When performing the biochemical tests, one has to pay attention to the conditions in which they are carried out. It is generally known that different factors may affect the test results. Elevated results of catecholamine and catecholamine metabolite release are reported after significant exercise, ethanol and some medications (paracetamol, labetalol, sotalol, tricyclic antidepressants, amphetamine derivatives, benzodiazepines, methyl dopa and chlorpromazine), while lowered ones are observed after methyl-

glucamine (component of radiological contrasting agents), reserpine, and some foodstuffs (nuts, bananas, citrus fruit, black currant, coffee, black tea – as they all contain methyltyrosine, as well as some sweets, as they contain vanilin) [12, 14]. Moreover, factors such as stress and severe pathological conditions may also contribute to false positive results (due to the enhanced activity of the sympathetic system) [12, 14].

Pharmacological tests were applied in the past, when the more accurate and safer biochemical tests were not available. They consisted in monitoring the patient (heart rate, arterial pressure) after the administration of a certain drug. The most popular pharmacological test involves clonidine, and it is applied very rarely, as an adjunctive test, when the clinical presentation is dubious or there is no access to biochemical tests [12, 14]. Provocative stimulation tests with agents such as glucagon, histamine, and naloxone are no longer used.

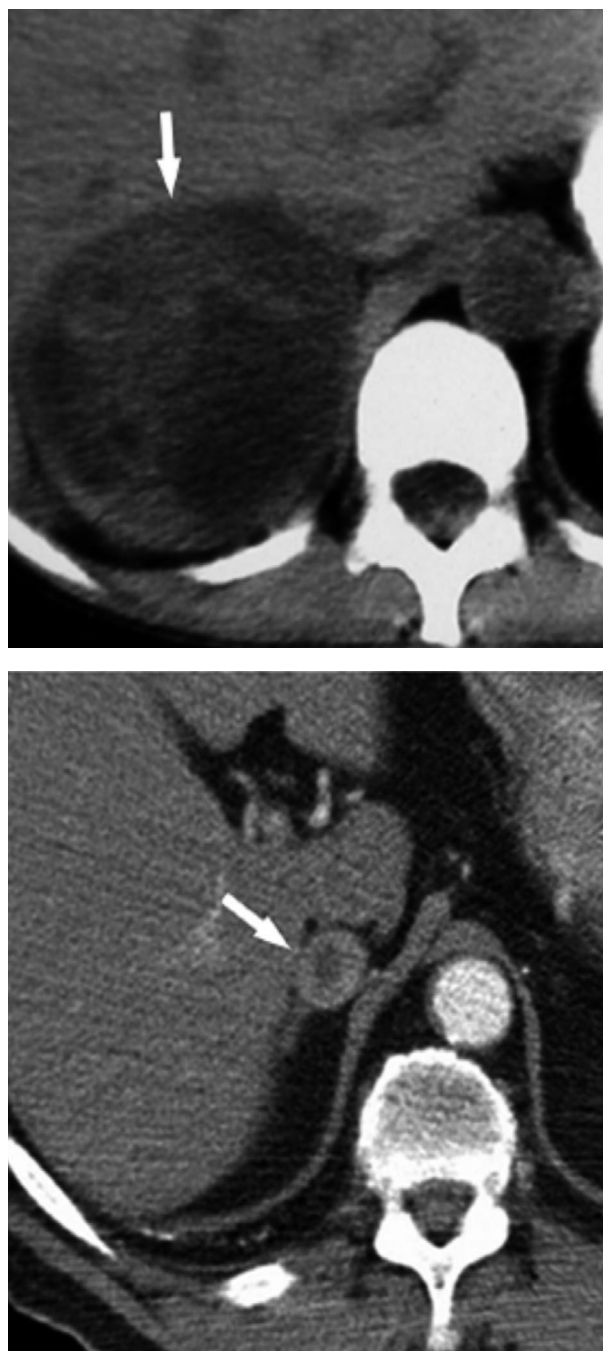
TUMOUR LOCALIZATION

Positive results of biochemical tests indicate the need for localizing PCC/PGL. Imaging diagnostics at our disposal includes: ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), scintigraphy and positron emission tomography (PET). The most easily available ultrasound examination may be enough to confirm tumour presence, especially within the adrenals, depending on the size and location of the tumour as well as the expertise of the technician. Frequently, though, ultrasound alone is insufficient, and more accurate examinations are required. CT and MRI have the sensitivity of 90–100%, and specificity of 70–80%, which enables tumour localization in most of the cases [14, 26]. CT imaging is now considered the test of choice.

Many tumours are found already at the stage of CT imaging, but it may prove insufficient in the case of very small lesions, and ones with extraadrenal location [12, 14, 26, 30]. In such scenarios MRI is the alternative, recommended for very small and extraadrenal lesions, as well as in children, pregnant women, and all those allergic to contrasting agents. Additionally, MRI enables initial differential diagnosis (in T2-weighted scans, PCC stands out with the strongest signal of all adrenal solid tumours) [12, 14, 26, 33].

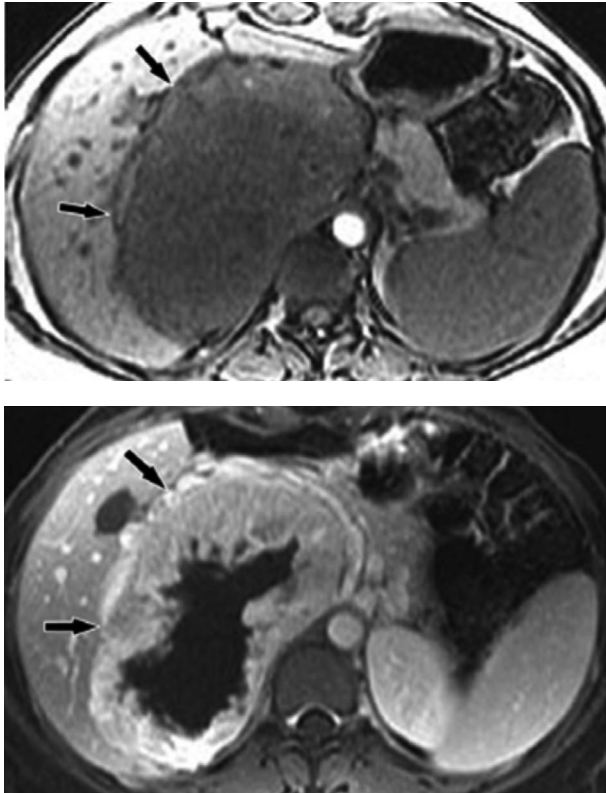
When tumour localization is still difficult or multiple, extraadrenal and metastatic tumours are suspected, other imaging examinations may be performed, i.e. scintigraphy and PET. Iodine-tagged ^{123}I -metaiodobenzylguanidine scintigraphy (MIBG) has 80–95% sensitivity and a high specificity of 95–100% (thanks to the specific uptake of the MIBG tag by the tumour chromaffin cells) [26, 34]. Thus, it may be very useful in the above mentioned cases, as well as in preoperative management aimed at an exclusion of multiple lesions or metastases, following an earlier

FIGURE 1.
Pheochromocytoma – CT scans.



diagnosis of PCC, and also during the qualification of patients for ^{131}I -MIBG treatment in the case of malignant tumours [12, 14, 26]. Still, when comparing MIBG scintigraphy to other imaging technologies, its relatively lower sensitivity is more and more often pointed out, especially with reference to metastatic and extraadrenal tumours, as well as the fact that the degree of MIBG uptake by tumour cells may be affected by some medications. Nevertheless, scintigraphy remains a very useful and

FIGURE 2.
Pheochromocytoma – MRI scans.



widely accessible diagnostic tool [14, 26, 34]. As neuroendocrine tumours, PCC and PGL may demonstrate expression of somatostatin receptors, a yet another examination may prove useful, i.e. indium- (octreotide) or technetium-tagged (tetrotilde) scintigraphy, using somatostatin analogues (SSA) [12, 34]. The technique enables visualization of even very small tumours, and in particular those with extraadrenal location, provided there is SS2 receptor expression, to which the radiopharmaceuticals applied show the greatest affinity [12]. That limiting factor renders the examination less sensitive in comparison with the other imaging techniques (around 75–90%). On the other hand, the tool permits the qualification of patients suffering from malignant PCC/PGL for yttrium- or lutetium-tagged SSA radioisotope therapy [12, 34]. Another examination, which may be treated as an alternative or complementary one to the previously mentioned imaging techniques, exhibiting very good sensitivity and specificity is PET with the use of radiopharmaceuticals and tracers that are specific for the adrenal medullary cells. It is especially useful in combination with CT, and can be helpful, when other imaging methods fail [12, 14, 26, 31, 34]. Radioactive tracers used in the diagnostics of chromaffin-cell tumours include: fluorine-tagged dopamine, DOPA and fluorodeoxyglucose ($[^{18}\text{F}]\text{DA}$, $[^{18}\text{F}]\text{DOPA}$, $[^{18}\text{F}]\text{FDG}$),

carbon-tagged hydroxyephedrine ($[^{11}\text{C}]\text{HED}$), and gallium-tagged somatostatin analogues ($[^{68}\text{Ga}]\text{SSA}$). The tests attain very high sensitivity in the diagnostics of PCC and PGL, especially in comparison with MIBG scintigraphy, and in particular in the cases of metastatic PCC/PGL, which has been proven in the paper by V. Ruffini and collaborators, analysing the results of as many as 329 different publications [14, 26, 34]. However, access to those diagnostic tools is still largely limited.

One more method of examination, performed in exceptionally difficult diagnostic situations, is testing the presence of methoxycatecholamines in venous blood drawn directly from the adrenal veins. In practice, however, the method is very rarely applied [26].

TREATMENT

The treatment of choice is PCC/PGL resection. In the case of PCC, the preferred option is laparoscopic adrenalectomy, but the final decision on the method of surgery lies with the surgical team. Arguments for open/classical adrenalectomy include the following: uncertain tumour location, suspicion of tumour invasiveness, reoperation due to disease recurrence, tumour size > 8 cm, haemorrhagic diathesis or lack of experience in the laparoscopic mode of surgery [12, 26]. In the case of bilateral PCC, and in children in particular, adrenal cortex-sparing operation is sometimes recommended in order to prevent a lasting deficiency of glucocorticosteroids, with the necessary condition being no risk of lesion malignancy (the predisposing mutations need to be ruled out) and disease recurrence [14, 26]. The patient has to be adequately prepared for the surgery, so that factors such as preoperative stress, anaesthesiological agents or physical irritation of the tumour during resection do not result in a sudden release of catecholamines, leading to serious and life-threatening cardiovascular complications [12, 14, 26, 35]. Patient preparation involves the lowering and control of arterial pressure with the help of α -blockers (phenoxybenzamine, doxazosin, prazosin or terazosin, or with the calcium channel blockers – derivatives of dihydropyridine), slowing down of the heart rate in tachycardia (only selective β_1 -blockers, and only once the α receptors have been saturated), as well as adequate fluid and sodium supply, preventing potential hypovolaemia and orthostatic hypotonia upon tumour resection [35]. In some healthcare centres, metyrosine, a drug inhibiting the hydroxylation of tyrosin involved in catecholamine synthesis, is also administered, as it is very efficacious in leading to a haemodynamic stabilization, but at the same time can trigger neurological side effects [35].

After the surgery, further close monitoring of the patient is indispensable, as are appropriate instructions. A sudden decrease in the level of the secreted catecholamines together with the up to

36-hour effect of α -blockers and β -blockers (provided they have been administered), and a decrease in cortisolemia as a result of adrenalectomy, may cause hypotension, bradycardia, symptomatic hypoglycaemia, and dyselectrolytemia [35]. Hence, postoperative follow-up requires rigorous control of vital signs and biochemical parameters, and an adequate response algorithm.

Cases of malignant PCC or PGL which remain inoperable or have developed metastatic lesions require alternative treatment options, apart from conservative symptomatic treatment. The applied chemotherapy regimen – cyclophosphamide, vincristine and dacarbazine (CVD) – brings along only short-term remissions [26, 36]. The best documented method, which is a palliative one by and large, is radioactive iodine-tagged MIBG (^{131}I -MIBG). Partial remissions are described following the use of that method alone, as well as in combination with CVD chemotherapy, but disease progression is observed relatively quickly during patient follow-up [12, 14, 26, 31]. The potential impact of an increased radioiodine dose on the efficacy of treatment is now discussed [26].

Other methods under debate these days involve the use of promising SSA, tagged with radioactive yttrium or lutetium [31, 37]. Research is also carried out on tyrosine kinase inhibitors (growth factor receptors), such as: sunitinib, axitinib or dovitinib [24, 37]. Temozolomide, an alkylating dacarbazine derivative, in combination with the so called LB1 molecule, a serine/threonine protein phosphatase 2A (PP2A) inhibitor, is also looked into as a potential treatment option for malignant PCC/PGL [37, 38]. Other currently researched agents include inhibitors of the heat shock proteins

(HSPs), which play an important part in the development of malignant PCC, and whose expression is significantly higher in the malignant PCC cells as compared to the benign ones [37].

The remaining methods which bring along some benefits (slowing down disease progression and reducing the symptoms) involve different procedures aimed at reducing tumour mass: cytoreduction surgeries, ablation treatments, embolization, and cryotherapy.

SUMMARY

Chromaffin-cell tumours occur relatively rarely, and are usually benign, with highly characteristic symptoms. However, they still remain a great challenge in terms of the diagnostic and therapeutic process. They may give rise to dangerous, life-threatening cardiovascular complications, which is why they require a swift diagnosis and treatment. The proportion of diagnosed familial cases of chromaffin-cell tumours, which are genetically conditioned, is going up now, extending the scope of medical services to include patient follow-up and search for other components of the individual familial syndromes, as well as examination and follow-up of the patient's family members. Additionally, the methodology of biochemical and imaging tests is developing continuously, delivering ever more accurate diagnostic tools. Still, inasmuch as the patients suffering from benign chromaffin-cell tumours can count on being cured, there is no efficacious treatment on offer for those with malignant lesions, which prompts us to carry on research in the field.

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