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METHODS OF PARACLINIC DIAGNOSIS OF CATECHOLAMINE SECRETING TUMOURS, ESPECIALLY OF PHEOCHROMOCYTOMA

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Summary
Catecholamine tumoral syndrome is caused by lesions of the medulosuprarenal cromafin tissue (pheochromocytoma or pheochromocytoblastoma) or of the neural crest (paraganglioma), from the ganglionar cells (ganglioneurinoma or ganglioneuroblastoma) or from the sympathetic nervous cells (sympathogonia – sympathoblastoma and sympathoblasts – neuroblastoma), tumors that excessively secrete cathecolamines (adrenaline and noradrenaline), but also neuropeptides. Indications for testing are associated with the clinical context. Because the pheochromocytoma means a heterogeneous group of secretory tumours, there is no analysis achieving the 100% accuracy. The diagnosis can be established by hormonal dosages for basal determinations and by dynamic tests or through nonspecific tests. Imagistic explorations like computer tomography, abdominal and pelvic MRI can localise the tumour. Plasma and urinary metanephrines dosage are the first intention tests because have a higher accuracy compared to catecholamines or other metabolites. Considering the low prevalence of catecholamine secreting tumours, we considered it necessary to systematise diagnostic possibilities.
Keywords: *pheochromocytoma, plasma metanephrines, high blood pressure.*

Rezumat
Sindromul catecolaminic tumoral este determinat de formaţiuni ale ţesutului cromafin medulosuprarenal (feocromocitom sau feocromocitoblastom) sau ale crestei neurale (paragangliom), din celulele ganglionare (ganglioneurom sau ganglioneuroblastom) sau din celulele nervoase simpatice (simpatogonii - simpatoblastom şi simpatoblaști - neuroblastom), tumori care secretă în exces catecolamine (adrenalină şi nordarenalină), dar şi neuropeptide. Indicaţiile de testare sunt asociate contextului clinic. Deorece feocromocitomul reprezintă un grup heterogen de tumori secretante, nu există o analiză care să atingă acurateţea de 100%.

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Diagnosticul poate fi stabilit prin dozări hormonale pentru determinări bazale și prin teste dinamice sau teste nespecifice. Explorările imagistice precum computer tomografia, RMN abdominal și pelvin permit localizarea formațiunii. Măsurarea metanefrinelor plasmatice şi urinare sunt testele de primă intenţie deoarece au acurateţe diagnostică mai bună decât catecolaminele sau alţi metaboliţi. Având în vedere prevalenţa redusă a tumorilor secretante de catecolamine, am considerat necesară o sistematizare a posibilităţilor diagnostice.
Cuvinte cheie: *feocromocitom, metanefrine plasmatice, hipertensiune arterial.*

Introduction

Catecholamine tumoral syndrome is caused by lesions of the medulosuprarenal cromafin tissue (pheochromocytoma or pheochromocytoblastoma) or of the neural crest (paraganglioma), from the ganglionar cells (ganglioneurinoma or ganglioneuroblastoma) or from the sympathetic nervous cells (sympathogonia – sympathoblastoma and sympathoblasts – neuroblastoma), tumors that excessively secrete cathecolamines (adrenaline and noradrenaline), but also neuropeptides. Some synthesised neuropeptides are also present in normal medulosuprarenal (MSR) (metenkephalin, β-endorphin, neuropeptide Y), others do not (vasoactive intestinal polypeptide (VIP), calcitonone, somatostatin, adrenocorticotropic hormone (ACTH), erythropoietin etc.). They can be located in various regions: medulosuprarenal, the Zuckerkandll organ (paraaortic area between the emergence of the lower mesenteric artery and the bifurcation of the abdominal aorta), the base of the skull, the pericard, the thoracic paravertebral space, the presacral abdomen, the bladder, the pancreas, the thyroid, the testicles, etc. Because of the multicentric origin, the malignant behaviour is difficult to establish only on histological criteria, and metastasis has to be demonstrated[1].

Annual occurrence is 1.55 to 4 cases/million. The occurrence of pheochromocytoma in the general population complies with "the rule of 10": 10% are bilateral or multiple, 10% are ectopic (extra-adrenal), 10% are malignant, 10% are family-related - in which case 50% are malignant, 10% occur in children. However, still many patients remain undiagnosed, the prevalence of catecholamine tumoral syndrome being

0.05% in - anatomopathological studies. Pheochromocytoma occurs at any age, but the highest frequency is between 30-50 years. In adults, the disease affects men and women equally[2].

Clinical presentation

The catecholamine tumoral syndrome clinical presentation is represented by a string of events related to the structure of the tumour, so its functional profile: primary secretion of catecholamines, intermediate metabolites, neuropeptides, etc. The main clinical presentations are:

1. Paroxysmal HBP - about 50% of cases; can be severe;
2. Paroxysmal attacks; sudden onset, lasting from minutes to hours, headache, sweating, tachycardia, chest pain, pallor, nausea;
3. Can be induced by certain drugs: opioids, anaesthetics, glucagon, monoamine oxidase inhibitor (MAOI);
4. Cardiac indications: tachycardia, bradycardia, arrhythmia; heart failure; hypertensive encephalopathy; acute myocardial infarction; sudden death. Recently it has been proven that patients with catecholamine tumoral syndrome have a higher risk for major cardiovascular events than **patients with** primary high blood pressure (HBP), probably due to the prolonged exposure to toxic effects of tumoral catecholamines.
5. They frequently form metastases at the lung, lymph nodes, bones and liver[3].

Biological investigations

Indications for testing are associated with the clinical context. Because the pheochromocytoma means a heterogeneous group of secretory tumours, there is no analysis achieving the 100% accuracy.

Hormonal dosages:

Basal determinations - dosages are usually made by high performance liquid chromatography (HPLC): urinary dosages - bladder removals are measured per 24 hrs of catecholamines and metabolites (urinary free catecholamines, urinary metabolites: total metanephrines - metanephrine (MN) and normetanephrine (MTN), vanillylmandelic acid (VMA), plasma dosages: plasma catecholamines, plasma free metanephrines, serum cromogranin (CgA) - a protein stored and released together with catecholamines in the adrenal medulla and sympathetic neuronal vesicles.

Dynamic tests: suppression (phentolamine and glucagon) or stimulation (glucagon, thyramine histamine - rarely used because of their high risk);

Nonspecific tests: carbohydrate intolerance, increased blood sugar; increased haematocrit; increasing free fatty acids; hypercalcemia;

Max Schottelius is the one who made the first description of pheochromocytoma. He described the classic elements of the tumour, as well as brown colouring occurring after exposure to Mueller fixative containing chromate. This colour change results from oxidation of catecholamines and lies in the name of pheochromocytoma, meaning a dark chromate-positive tumour[4].

Histology - immunohistochemistry, as well as cromagranine-associated tissue biopsy, support the diagnosis[5].

Imaging investigations

Computer tomography and MRI of the abdomen and pelvis are the most common methods to discover the location of the

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tumour. Both methods have similar sensitivities (90% -100%) and specificities (70% - 80%) . Computer tomography exposes more detailed images compared to MRI. Additional imaging methods may be needed if the CT or MRI scan does not locate the tumour. *Iodine-131* scintigraphy - metaiodobenzylguanidine (MIBG) associated with CT presents anatomical and functional images with good sensitivity (80% - 90%) and specificity (95% - 100%). Other imaging alternatives may be Indium-111-octreotide scintigraphy and PET F18-fludeoxyglucose, both of which may be associated with CT for better image quality[6].

The presence of the tumour must be first time demonstrated biochemically. These tests should enable the clinician to determine expeditiously the diagnosis. The question was which of these tests ensure the accuracy of the diagnosis.

Catecholamine metabolising

Semi-life of catecholamines is very short, and their action ends quickly. Free hormones are removed through several mechanisms:

- urinary elimination-5%;
- cell reuptake which is at the same time a mechanism of inactivation and restoration of reserves;
  - → catabolism following two main paths:
  - → controlled methoxylation at the level of liver by catechol-O-methyltransferase -(COMT) resulting in metanephrine (MN) and normetanephrine (MTN);
  - → oxidation under the action of monoamine oxidase (MAO); the resulting dihydroxymandelic aldehyde is methoxylated to obtain vanillylmandelic acid[5,7].

Recommended tests

Plasmatic and urinary MTN dosage are the first intention tests because have a higher accuracy compared to cathecolamines or other metabolites. It is proven that the dosage of plasmatic and urinary catecholamines is not safe enough, the tumour often discharging in episodes or even negligible in asymptomatic patients. Acute metanephrine dosing can be attributed to continuous intratumoral production and release of metanephrines in circulation. This secretion is independent of the great variability of tumour catechol release or sympathoadrenal excitation. By comparing the various biochemical tests it was found that the plasma or urinary dosage of metanephrines has a great sensitivity for the diagnostic compared to other traditionally used tests. There are important differences concerning the performance of biochemical tests between sporadic and hereditary

illness, specificity being better and sensitivity lower in hereditary group. Screening in patients with hereditary predisposition leads more often to detection of small tumours, which release small quantities of catecholamines which might be insufficient to produce signs and symptoms. In contrast, sporadic diseases are typically suspected on the basis of signs and symptoms caused by catechol excess produced by large tumours, which are more easily detected[8].

Diagnosis of tumours secreting catecholamines put considerable problems yet, only 6% of patients being clinically diagnosed. Anatomopathological -studies at autopsies have shown that the disease is not recognised in 20%-75% of patients alive, half of them dying because of it.

A study was conducted on 31 patients, 17 with pheochromocytoma and 14 with histological evidence of other adrenal tumours, for whom plasma metanephrines, plasma catecholamines and urinary catecholamines were dosed. These dosages were done before surgery, during the surgery (before the incision of the skin when handling the tumour and after the tumour was separated from the circulation) and 1-3 months after the surgery. MTN dosage and urinary catecholamines prove a sensitivity of 100%, 82% respectively, for the diagnosis of pheochromocytoma. The level of plasma catecholamines and not of MTN, was influenced by changing posture and stress during surgery. It was concluded that the dosage of plasma MTN is the most effective determination in the diagnosis of the disease, the variability of the results being linked to external factors[9].

In March 2002 a study was conducted to determine which biochemical method is more accurate for the diagnosis of pheochromocytoma. The aim was to determine the test or the aggregation of tests that can provide the most accurate information for the diagnosis of catechol tumours.

This study took place between the years 1994-2001, was a cohort study, conducted in four reference centres and included 214 patients whose diagnosis of pheochromocytoma was confirmed and 614 patients who were not diagnosed with a adrenal tumour. Plasma free MTN, plasma catecholamines, urinary catecholamines, MTN and divided urinary MTN and urinary VMA were measured. Sensitivity for plasma MTN was 99% [95% interval of safety (96%-100%)] and for divided urinary MTN 97% [92% IS (95%-99%)] were greater than for 84% plasma catecholamines [95% IS (78% to 98%)], 86% urinary catecholamines [95% IS (80% -91%)], 77% total urinary metanephrines [95% IS (68%-85%)], 64% urinary vanillylmandelic acid [95% IS (87%-92%)].

Specificity was greater for 95% urinary VMA [95% IS (93%-97%)] and 93% total urinary MTN [95% IS (89%-97%)], intermediate for 89% plasma MTN [95% IS (87%-92%)], 88% urinary catecholamines [95% IS (85%-91%)] and 81% plasma catecholamines [95% IS (78%-84%)] and low for 69% divided urinary MTN [95% IS (64%-72%)]. As a conclusion: dosage of plasma MTN is the best test, which should be the first intention in the diagnosis of the tumour[10].

Another study was carried out between the years 1999-2001 in two university hospitals from Switzerland and two institutions from France, where a retrospective analysis of the biochemical diagnosis of pheochromocytoma was done. 46 cases with histologically confirmed diagnosis and 181 cases with possible tumour, but with

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negative investigations were included. The aim of the study was to assess the diagnostics performance through the dosage of single plasma free MTN or combined with free and divided MTN in the urine in 24 hours, in patients without renal dysfunction. Sensitivity and specificity were compared after each performed dosage and the results are the following: The plasma free MTN and free and divided urinary MTN had the same sensibility — 96% (86%-99%), 95% (85%-99%) and 95% (84%-99%), together with similar specificity 89% (83%-94%), 91% (84%-95%) and 86% (80%-91%). All three tests are equivalent in pheochromocytoma diagnosis and may be conventionally associated, two for confirmation or exclusion of the tumour[11].

For the correct interpretation of the biochemical tests in catecholamine secreting tumours, account should be taken of certain factors that may affect the results: exercise, posture, food, stress, hypoglycemia and medication.

False-positive results

- Diet
  Many foods that contain significant amounts of biogenic amines may give false-positive results: bananas, pineapple, nuts and cereals. Plasma and urinary MTN are not affected, but the free 3-methoxytyramine concentration may increase significantly after ingestion of foods rich in amines, so food restriction is required when dosing this metabolite.
- Medication
  The effects of drugs cause changes due to pharmacodynamic and pharmacokinetic interference, influencing the secretion, metabolism and excretion of catecholamines and its metabolites. Paracetamol, one of the most frequently used medications interferes with the dosage of plasma free MTN if the dosing method is by HPLC-ECD (the combined electrochemical detection with high performance liquid chromatography).

Labetalol, buspirone, mesalamine and sulfasalazine may also influence test results. Examples: sympathicomimetic medication (ephedrine, amphetamine, cocaine, caffeine and nicotine) - increase the release of adrenaline and noradrenaline; drugs that inhibit norepinephrine reuptake: serotonin-NA reuptake inhibitors (venlafexine), selective serotonin inhibitors; tricyclic antidepressants; MAOI (blocks the conversion of noradrenaline (NA) in adrenaline (A)). Certain antihypertensives may alter test results: calcium channel blockers - dihydropyridine, $\alpha_1$blockers (doxazosinum), non-selective α blockers - phenoxybenzamine - blocks α_2 receptors, causing the increased release of NA associated with reflex increase of

sympathetic activity, L-DOPA (levodopa), used in the treatment of Parkinson's disease - increases the concentration of 3-metoxytyramina (metabolite of dopamine) and MTN[12].

False-negative results

Normal value of plasma free MN or divided urinary MN exclude the diagnosis of secretory tumour. Exceptions are small tumours (less than 1 cm), usually clinically asymptomatic, dopamine producing tumours, tumours in which NA and A are not synthesised or metabolised in NMT and MN. 3-methoxytyramine testing should be considered in patients with atypical presentations, who are suspected of paraganglioma and who have normal urinary and plasma values of MN. Moreover, there were found patients with mutations in SDHx, which can present silent biochemical tumours. The silent biochemical phenotype in small tumours with mutations in the SDHB reflects a defect in catecholamine synthesis, due to the absence of the tyrosine hydroxylase, an enzyme which catalyses the first step in catecholamine biosynthesis. Other potential mechanisms which give false-negative results would be the accumulation of catecholamines analogues in secretory granules. Therefore, the screening of SDHB mutation tumours should not be limited only to tests showing catechol excess, including as an additional test the dosage of chromogranin A (a non-specific neuroendocrine secretory protein) and imaging studies[8,13].

As we stated before, false-positive results in the diagnosis of pheochromocytoma still remain a problem. For this there were studies reassessing the association between the medicines and false-positive results using additional tests, including the clonidine suppression test. This study included 208 patients with confirmed pheochromocytoma and 648 patients whose diagnosis of tumour was excluded. The clonidine suppression test was performed in 48 patients with tumour and in 49 without tumour. Administration of tricyclic antidepressants and phenoxybenzamine led to 41% false-positive increases in plasma MTN and to 44%-45% false-positive urinary and plasma increases of NA. Elevated levels were predictive for the diagnosis of pheochromocytoma. The lack of decrease and increase in plasma levels of NA and NMTN after clonidine suppression test confirms with greater specificity the diagnosis of the tumour. However, 16 of the 48 patients had normal or low values of NA after administration of clonidine. In contrast, plasma NMTN remained elevated in all, indicating a safer diagnosis by testing NMTN than NA. It should be noted that in people with suspected pheochromocytoma and positive biochemical tests, the medication determining errors should be removed the first time, the clonidine test helping us in the accuracy of the diagnosis[14].

Clonidine suppression test

Indications: pheochromocytoma evaluation when plasma NA level is between 1000-2000 pg/ml and/or when plasma MN is 4 times higher compared to the reference range.

The test is useful for differentiating pheochromocytoma patients from other causes determining elevated NA and MTN values; it is performed with the patient in supine position to prevent orthostatic hypotension; dry mouth or drowsiness may occur; 0.3 mg clonidine is administered (this being the dose for a patient weighting 60-80 kg), adjusting the dosage according to weight-4.3 µg/kg up to a maximum of 0.5 mg.

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Interpretation - 3 hours after taking clonidine, one of the criteria below supports the diagnosis:

1. The lack of NM suppression is higher than 40% and the NM level over the upper normal limit; 96% sensitivity, 100% specificity;
2. Increased plasma concentration of the NM above the limit of reference range; 96% sensitivity, 96% **specificity;**
3. Increased plasma concentration of the NA above the limit of reference range; 71% sensitivity, 94% specificity;
4. NA suppression is less than 50%; 81% sensitivity, 82% specificity;

Details: the test can associate hypotension in patients with normal hypertension; dosage of urinary and plasma and MTN of catecholamine may interfere with the administration of certain medications - linking with imaging tests can eliminate the need for testing; what medication should be avoided: tricyclic antidepressants and phenoxybenzamine; selective α_1 blockers do not interfere with the test and can be used in hypertension control; β-blockers, calcium channel blockers, diuretics may affect plasma NA level, but have no significant influences on the NA; patients with relatively low levels of catecholamine (under 1000 pg/ml) can have false-positive results if they use in the diagnostic the criterion number 4; measurement of plasma NM after suppression test increases sensitivity and specificity of the diagnosis towards the dosage of plasma NA; the test cannot be used for patients with elevated plasma MTN because clonidine has a minimal effect on them, nor in dopamine producing tumours, in this case being useful the dosage of plasma and urinary dopamine[15].

Currently there are no certain biomarkers for malignant pheochromocytoma and paraganglion. A study was done proposing to examine whether measurement of catecholamines and metabolites can be useful for this purpose. In the study 365 patients with paraganglion were enrolled, 105 having metastases and 845 patients without tumour.

Eighteen catecholamines and metabolites were analysed, taking into account the size of the tumour, its location and the mutations of the B sub-unit of succinate dehydrogenase (SDHB). Plasma methoxytyramine was 4.7 times higher in patients with metastases than in those without metastases, difference independent of the tumour size and association with growth of 1.6 up to 1.8 of plasma MN and NMN concentration. The increase in plasma methoxytyramine was associated with mutations in the SDHB and with the presence of extraadrenal tumours, being increased also in patients with no mutations in the SDHB, but also in those with adrenal tumour metastases. Increased risk of

malignancy associated with mutations in the SDHB reflects large tumours with extraadrenal location, but there are also independent markers for adrenal tumour metastases. The values of methoxytyramine over 0.2 nmol/l or tumour sizes over 5 cm indicate an increase in the probability of the existence of metastases, particularly in association with the extraadrenal locations[16].

To determine genetic mutations of SDHx numerous studies were done, trying to figure out the most efficient method for their detection. It is known that in 35% of patients diagnosed with pheochromocytoma and paragangliom, there are mutations in the B subunit (SDHB) and D subunit (SDHD). In genetic diseases, a quality human DNA for study is essential to be obtained. So far blood tests are favoured, by obtaining leukocyte DNA, however the high quality leukocyte DNA can be also taken from saliva. At the annual Conference of the Society for Endocrinology in San Diego-USA (5-8 March 2015), a study was presented, aiming at determining the SDHB and SDHD mutations in patients with pheochromocytoma and paragangliom, using saliva tests. The study was conducted at the National Institute of Health Bethesda, USA, where they collected blood and saliva samples simultaneously from 15 patients: 6 known with SDHB mutations, 4 with SDHD mutations and 5 with negative genetic screening for any SDHx mutation.

Quality of saliva DNA was similar to that of DNA in blood; saliva DNA concentration was 455 ng/µl, the blood of 400ng/µ L; the purity of the saliva was lower than that of blood, indicating the existence of several contamination proteins. All saliva samples were genotyped successfully. It can be concluded that the saliva DNA is a good alternative for genomic extraction, due to the high concentration and acceptable purity and can be used as an alternative screening for SDHx mutations. Furthermore, the saliva test is non-invasive, the saliva sample collection being taken also at the patient's house[17].

The latest studies have demonstrated a significant correlation between genes involved and location of the tumour, as follows:

- For unilateral pheochromocytomas: succinate dehydrogenase complex, subunit B or D (SDHB or SDHD), VHL and RET;
- For bilateral pheochromocytomas: SDHB, VHL, RET, NF1, MYC associated with factor X (MAX) and TMEM127;
- Pheochromocytomas associated with sympathetic paraganglioms: SDHB, SDHC, SDHD, RET, VHL, MAX and HIF2A;
- Pheochromocytomas associated with head and neck paraganglioms: SDHD, SDHB, SDHC, TMEM127 and VHL[18].

Adrenal incidental formation is a tumour of the adrenal glands that is accidentally discovered in a patient undergoing imaging investigations for reasons other than adrenal glands. The prevalence is of 2.3% and is increased to 6.9% in patients over 70 years of age. The vast majority of incidental formations are benign and non-secretory, but the investigations are necessary to rule out malignant or secretory tumours.

In order to establish a diagnosis for an adrenal nodule which is unexpectedly discovered we must answer 3 questions:

1. Is the lesion malignant? And, if so, is it adrenocortical carcinoma or metastasis?
2. Is the lesion a pheochromocytoma?
3. Is the lesion an adrenal adenoma? Is it silent or secretory?[19]

Often the management of these tumours

includes biochemical hormone follow-up over a number of years, which induces an important financial and emotional discomfort to patients what turn out to be healthy. The opinion about the long-term biochemical follow-up of these patients has been recently changed. However, the records are unclear. It has been hypothesised that the long-term biochemical follow-up in patients with initially normal screening may increase the sensitivity in the discovery of secretory tumours.

Starting from that premise, a survey was conducted, aiming at all incidental formations found in a single Centre of Endocrinology in Stockholm-Sweden, from 2006 to 2010. It was a retrospective cohort study which included 294 patients. According to the recommendations of the Swedish Guide of Endocrinology, the initial assessment of patients was related to hormones and imaging. Hormonal investigations included the dosage of cortisol and catecholamine secretion in all patients. In patients with HBT or hypokalaemia, they added the determination of aldosterone and serum renin activity. All information, including biochemical screening and imaging characteristics of the tumour at the initial evaluation and subsequent visits were recorded in the records of the patients. The carried out biochemical investigations were as follows: dosage of aldosterone, plasma renin activity (PRA), plasma MTN, urinary catecholamines (urine collected in 24 hours) and plasma cortisol. From the imaging point of view, the lesions were classified as benign if they were smaller than 3 cm and had radiological features of adenoma and hyperplasia and if larger, those with more than 3 cm in size, with stationary size development in the last 24 months. As a result: 94% of incidental formations were benign and non-secretory; There was no case of adrenal carcinoma or adrenal metastases; any patient with negative biochemical initial tests has not developed any hormonal secretion during the study. In conclusion, these patients do not require a long-term biochemical follow-up after discovering the incidental formation[20].

However, about 15% of the incidental formations grow in size during the follow-up. It is known that malignant tumours can keep the same size large periods of time. In patients with known malignancy, the probability that a node is malignant is 25%-36%. In the general population with no malignancy confirmed the prevalence is less than 0.5%.

To do this, a strategy to characterise these nodules, at minimal cost, without invasive testing is important. Imaging tests, namely computer tomography (CT) and nuclear magnetic resonance, help us in this regard. CT imaging follow-up of adrenal masses is

controversial. The American Endocrinology Guidelines suggest that, for nodules larger than 4 cm, a repeated CT scan without contrast dye should be performed every 3-6 months and thereafter annually for the next two years. If the tumour mass increases or becomes active due to hormones, adrenalectomy should be performed, the same indication being recommended for tumours larger than 4 cm[19].

Recent studies demonstrated a link between the brown adipose tissue and pheochromocytoma. Thus, the brown adipose tissue was detected by 18F-FDG PET/CT in 27.4% of patients with pheochromocytoma, while in 6.1% of people with no record of pheochromocytoma an activation of brown adipose tissue was demonstrated[21].

Considering the low prevalence of catecholamine secreting tumours, we considered it necessary to systematise diagnostic possibilities. Analysing the data presented in the studies with those of the current endocrinology guidelines, I consider that in the initial biochemical diagnosis it is more effective to dose the plasma metanephrines. According to the foregoing, the diagnosis of catecholamines secreting tumours requires compliance with a protocol, starting from the biochemical one associated with other investigations according to the clinical data of the each case.

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