ANALELE UNIVERSITĂȚII "DUNĂREA DE JOS" GALAȚI
MEDICINĂ
FASCICULA XVII, ANUL VIII, 2009

THE PHEOCHROMOCYTOMA – MANAGEMENT

Laura Iconaru, M. Dobrescu, Diana Paun,
Gherlan Iuliana, Ruxandra Hristea, Sabina Oros,
Adina Dragomir, Anca Dragutescu,
Constantin Dumitrache

"C.I.Parhon" National Endocrinology Institute, Bucharest, Romania
UMF " Carol Davila" , Bucharest, Romania

laura.iconaru@yahoo.com

RESUME

Le phéochromocytome est une tumeur à cellules chromaffines produisant des catécholamines en excès et située dans 90 % des cas dans la médullosurrénale. C'est une maladie rare qui peut apparaître durant la grossesse. Seulement 500 cas de phéochromocytome ont été publiés dans la littérature. Cette maladie associée à la grossesse présente un risque de mortalité maternelle de 17 % et de mortalité fœtale de 26 %.Le diagnostic repose sur la clinique (signes d'appel), la biologie (diagnostic positif) et la radiologie (diagnostic topographique). Cliniquement, plus de 100 symptômes ont été rattachés au phéochromocytome, mais aucun d'eux n'est spécifique .Certains regroupements syndromiques, le caractère paroxystique des symptômes ainsi que leur association à l'hypertension artérielle sont évocateurs. La triade céphalées/palpitations/sueurs abondantes" est retrouvée dans près de 90% des phéochromocytomes. Les autres symptômes sont moins évocateurs: douleur constrictive abdominothoracique ascendante, anxiété, tremblements, pâleur et troubles digestifs. La survenue des symptômes est généralement explosive et leur durée n'excède pas quelques dizaines de minutes. Les circonstances favorisantes sont la prise d'alcool contenant de la tyramine, l'augmentation de la pression abdominale (grossesse), l'absorption de certains médicaments (sulpiride, métoclopramide, antidépresseurs tricycliques). Un amaigrissement est souvent retrouvé dans les formes à sécrétion permanente. L'hypertension artérielle est constante au cours de l'évolution. Elle est le plus souvent permanente, mais peut seulement accompagner les autres symptômes. Les caractères souvent retrouvés sont: la variabilité des symptômes, la résistance aux traitements classiques et l'hypotension orthostatique en dehors de tout traitement médicamenteux. Devant ce tableau, il faut systématiquement chercher les signes d'autres tumeurs appartenant aux néoplasies endocriniennes multiples (NEM).

MOTS CLES*: phéochromocytome, hypertension artérielle, management*

1. Introduction

The pheochromocytomas are tumours of neuroectodermal origin that originate in the chromaffin cells of the adrenal medullary, the majority being sporadic and only 10% being associated to familial diseases: MEN, the von Hippel Lindau disease, the von Recklinghausen neurofibromatosis or the familial pheochromocytomas in genetically isolated syndromes. Although they represent a rare cause of

secondary arterial hypertension – it was encountered at less than 1% of the patients tested for hypertension – their diagnosis is important for the risks which may occur as a result of underdiagnosis - they can prove fatal for women in labour or patients undergoing surgery. Although the incidence may appear to be rather insignificant, the medical attitude towards this type of patients can lead to a rapid surgical healing in around 90% of the case, taking into account the fact that the untreated tumour has a fatal evolution through the complications induced by the catecholamines: malignant AHT, hart failure, myocardial infarction, strokes, ventricular arrhythmias, and metastasis. Also, the prognostic is good provided that the treatment be adequate and the diagnosis be given at an early stage [1-3].

Several studies carried out on autopsies have shown that half of the pheochromocytomas have not been diagnosed until the post-mortem examination, which comes to enforce the fact that this type of disorder is frequently unrecognised.

Being present at 90 to 100% of the patients, the arterial hypertension (AHT) is the most frequent clinical manifestation of the pheochromocytomas, however it may take several forms: sustained AHT (tumours continuously secreting catecholamines), AHT-like culminating points, accompanied by the classic triad – cephalalgia, transpiration, paleness – in the incidental catecholamine discharges or normal blood pressure, lacking in associated symptoms in spite of the high catecholamine levels, by the decrease in the sensibility of the adrenergic receptors caused by the excessive chronic stimulation.

The pheochromocytoma frequently associates other cardio-vascular conditions, such as:

-Acute myocardial infarction caused by a coronary spasm, the brutal stimulation of the beta receptors or the influx of the calcium ion through the sarcolemma membrane toxically influencing the myocytes and thus determining necrosis lesions;

-Over-ventricular or malignant ventricular arrhythmias;

-Late diagnosed long-term dilated cardiomyopathy cases: when compared to the medical literature, the histological and ultrastructural study of the cardiac biopsy has shown necrosis strips at the cardiocyte level, accompanied by the supercontraction of the sarcomeres, resulting in myofibrolysis;

- Hypertrophic cardiomyopathy, as a result of the norepinephrine-induced AHT;

-Cerebral infarction and extremity gangrenes through the vascular spasm;

-EKG modifications – left ventricular hypertrophy elements, over or under-aligned ST segment, U wave inversion, sinusal tachycardia or other rhythm disorders, such as the over-ventricular tachycardia [4-7].

In some of the patients, the myocarditis-like lesions with focal necrosis areas have been followed by fibrin deposits and platelet aggregations in the pulmonary arterioles.

The patients displaying persistent AHT symptoms can develop nephropathies and hypertensive retinopathy.

The main causes of death are: acute myocardial infarction, cerebral embolisms, arrhythmias, renal disorders, aortic dissection aneurysm and irreversible shock. The sole efficient treatment of the pheochromocytoma is the exclusion of the catecholamines source through the surgical ablation of the pre-existing tumoural formation, followed by a well-driven drug treatment for the prevention and control of the AHT paroxysm attacks and/or hypotension, due to the fact that this therapeutic procedure associates a morbidity risk of over 40% and a mortality risk of 2 to 4%.

Taking into account the hypertensive crisis and/or arrhythmia risk, even if the patient has been normotensive and asymptomatic in the postoperatory

stage, the preoperatory preparation implies a tight collaboration between the specialists and aims at blocking the effects of the secreted catecholamines. At present, there is no consensus regarding the specific therapy and the preferred medication for the preoperatory preparation, the recommended therapy being very heterogeneous.

The nonselective alpha blocker therapy or selective alpha 1 therapy is generally recommended for the AT control. Traditionally, the nonselective alpha blocker therapy with phenoxy-benzylamine is convenient for its two main actions:

- the nonselective alpha-adrenergic blockage;

-it enables the expansion of the intravascular volume, while reducing the frequency and the intensity of the intraopertory AT fluctuations.

-*The advantages of the phenoxy-benzylamine* are considered to be: its long-term action, allowing the administration in two daily doses and the fact that it induces a non-competitive blockage by covalently bonding the receptor – thus preventing the action of the catecholamines in the preoperatory preparation period.

-*The disadvantages* are numerous and dominated by the orthostatic hypo AT and tachycardia.

Several postoperatory complications may be attributed to this type of affection, especially the prolonged postoperatory hypotension, although the drug's administration is halted 24 to 48 hours prior to the surgery [8].

Several medical teams experienced favorable results regarding the use of selective alpha 1 blockage (Prazosine, Terazosine, Doxazosine).

Their use may eliminate certain disadvantages of the phenoxy-benzylamine, considering the fact that they selectively block the post-synaptic alpha 1 receptors and therefore do not lead to reflex tachycardia; moreover, their action takes less time, allowing a more rapid recovery of the postoperatory hypo-AT.

The beta blocker – adrenergic in the pheochromocytoma

The use of beta-blockers in the postoperatory treatment of the pheochromocytoma is necessary for:

- limiting the symptoms and signs brought by the increase in the circulating epinephrine level – especially tachycardia or arrhythmias – most obvious in patients with epinephrine and dopamine predominantly secreting tumours;

- blocking the excessive synaptic cardiac activity, as a result of the pre-synaptic alpha 2 receptors' suspension by using alpha-blocker drugs is not always necessary in patients already treated with doxazosine, excepting the ones with epinephrine secreting-tumours.

Consequently, if the phenoxy-benzylamine is the blocker of the alpha-adrenergic receptors traditionally used in fighting the catecholamine-induced vasoconstriction, the association of the beta-adrenergic blockers is advised in order to fight the catecholamine-induced arrhythmias, but also the reflex tachycardia associated to the alpha-blocker therapy. However, the isolated administration of beta-blockers in pheochromocytoma patients is contra-indicated, because the beta-blocker does not prevent and may even amplify the effects of the catecholamines at the alpha-receptors level.

Selective antagonists of the beta-1 receptors are used (atenolol, metoprolol, bisoprolol), a preferable alternative being the alpha+beta nonselective blockers, such as labetalol and carvedilol [9].

The calcium canals blockers are frequently used for the AT control in pheochromocytoma patients. They act by relaxing the arteriolar smooth muscle and decreasing the peripheral vascular resistance, as a result of the inhibition of the EN mediated intracellular calcium secretion and/or the calcium's transmembranary flux in the vascular smooth muscle. In this case, the advantage consists of

them not producing remote hypo-AT or orthostatic hypo-AT. They can be used for the postoperatory AT control, in the oral administration for the hypertensive intraoperatory fluctuations and they can also prove to be useful in patients with normotensive-induced hypertension crisis.

The surgery consists in a uni or bilateral suprarenalectomy, using the traditional or the laparoscopic method.

Concerning the benign tumours, the patients' prognostic is extremely positive.

Nonetheless, the laparoscopic surgery may induce unwanted effects that must also be taken into consideration:

-hemodynamic changes and excessive catecholamine secretion during the pneumoperitoneum's production in any laparoscopic intervention, which can be worsen by the pheochromocytoma;

-palpating the abdomen can trigger the secretion of catecholamines in the pheochromocytoma;

-the dissection of the intra-abdominal organs during the laparoscopy, although less traumatizing, can lead to the secretion of catecholamines;

-the moment of the vascular sutures corresponding to the tumour (the adrenal vein) is crucial for the success of the procedure;

-the manipulation of the tumour – even when made with the utmost care – usually produces an abrupt hemodynamic feedback, the norepinephrine-secreting tumours of certain patients causing a predominantly presser feedback, followed by the abrupt increase of the AT. These cases claim the use of phentolamine 2 mg iv and labetalol 5 mg iv, nicardipine iv, administered right before having started to manipulate the tumour [10];

-the tachycardia in patients with epinephrine (and dopamine) secreting tumours is usually fought with atenelol or labetalol 20 mg iv;

-in the patients having been treated with phenoxy-benzylamine, the severe postoperatory hypo-TA may be accompanied by a persistent complication, in spite of having filled the vascular bed (Dextrane) and the increase in the central venous pressure or the administration of alpha-1 agonists (Phenilephrine, Metoxamine, Norepinephrine).

This unfavourable evolution does not take place at the Doxazosine-type alpha 1 blockers. The patients treated with Phenoxybenzamine need a postoperatory high liquid charge, frequently reaching a positive hydric balance with obvious edemas.

Following the surgery, the patients will be closely monitored throughout all their lives, especially the familial cases and the extra-adrenal tumour cases, by:

-evaluating the serum and urinary catecholamines;

-determining the calcitonine level;

-examining the cervical region for the medullary thyroridian carcinoma.

The AHT postoperatory persistence may be caused by:

-the presence of tumour remains or of other tumours;

-the inadequate suture of the adrenal artery;

-excess of fluid;

-simultaneous essential AHT.

The postoperatory hypo-AT persistance may be caused by :

-hemoragy;

-the sudden increase in the venous capacity;

-an inadequate volemic balance;

-the prolonged effect of the alpha-adrenergic blocker (especially the Phenoxybenzamine)

.

2. Patients and methods

Our study has been carried out on a number of 30 patients who have been diagnosed with pheochromocytoma at the suprarenal, gonadic and

bone pathology department of the C.I. Parhon National Endocrinology Institute and have been monitored preoperatory ever since having been diagnosed, having then undergone the uni or bilateral suprarenalectomy at the surgical clinic of the Floreasca Emergency Hospital and being transferred postoperatory back to our clinic.

3. Results

1. The majority of the pheochromocytoma cases are sporadic, yet 10% are familial and usually associated with other MEN affections, the von Hippel Lindau disease, the von Recklinghausen neurofibromatosis, or take the form of familial pheochromocytomas in genetically isolated syndromes.

Regarding our patients, the disease is sporadic in *75%* of the cases, the rest of *25%* being MEN-related pheochromocytomas; the diagnosis for the patients displaying familial forms has been given by associating specific MEN disorders, their familial occurrence and in 2 of the patients, with the aid of a mutational study of the RET proto-oncogene, which uncovered the existence of mutations of the cysteinic domain of the 634 codon, mutations that are usually and characteristically associated to the increased predisposition to a pheochromocytoma (figure 1).

2. The hereditary tumours usually appear at earlier ages than the sporadic ones, which grants the age at the time of the diagnosis an increased importance, taking into account the genetic screening seeking the specific mutations; recent studies suggest that all the pheochromocytoma patients under the age of 50 must undergo a genetic test.

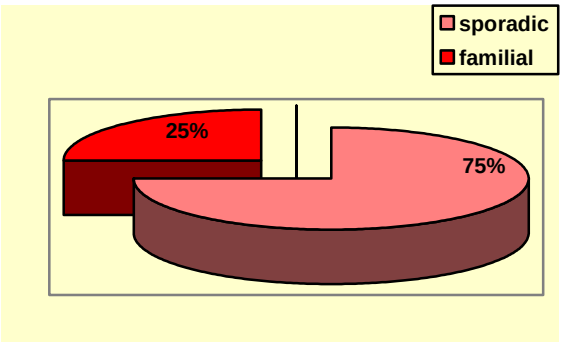

Figure 1. *The pheochromocytoma type: sporadic/familial*

Our patient lot also reveals the fact that an increased percentage of the patients (40%) are under the age of 50 at the time of the diagnosis, which imposes the genetic screening, especially when considering that the latest studies show that the vast majority of the sporadic pheochromocytoma cases associate germinative mutations (figure 2).

Consequently:

-at the time of the diagnosis,15% are between 20 and 30 years of age, all of them displaying familial forms of the disorder;

-10% are between 30 and 40 years of age;

-15% are between 40 and 50 years of age;

-30% are between 50 and 60 years of age;

-30% are over 60 years old.

3. The presence of the symptoms and signs determined by the catecholamine excess remains the main reason for the initial suspicion of the pheochromocytoma and it reflects the metabolic and hemodynamic actions of the catecholamines produced and secreted by the tumours. The symptom diversity may reflect variations in the nature and type of secreted catecholamine, as well as the co-secretion of other neuropeptides, such as: the VIP, CRH, the Y neuropeptide, FNA, the somatostatine etc.

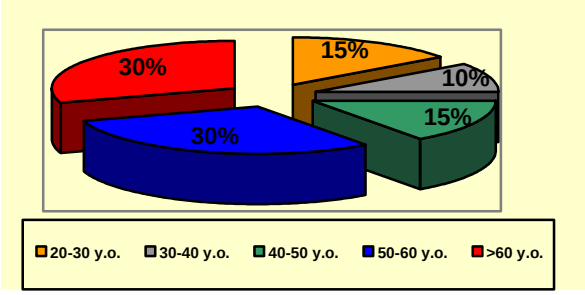

Figure 2 . *The distribution of the patients by the age criteria*

Concerning our patient lot, the distribution has been as follows (figure 3):

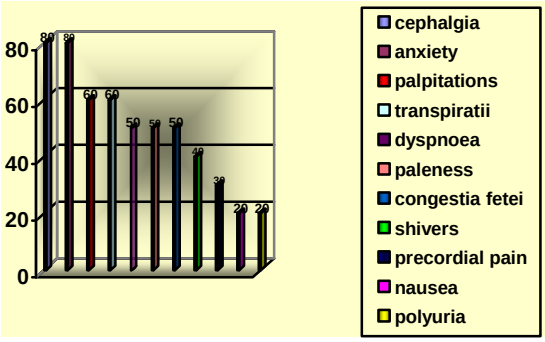

Figure 3 . *The main symptoms associated to the AT fluctuations*

4. The main clinical manifestation of the disease is the fluctuation of the blood pressure – a generally sustained AHT or a paroxysm-like behavior at a normal or constantly increased AT (especially at MEN patients), nonetheless, the pheochromocytoma may also cause arterial hypotension, usually alternating between low blood pressure and high blood pressure phases.

The AT fluctuations in our patient lot have been the following:

-25% had *constantly increased AT levels*, nonresponsive to the anti-hypertensive treatments undergone until the date of the diagnosis;

-72% displayed *hypertensive attacks* of high systolic and diastolic AT values – at the time of the attacks, the AT of all these patients surpasses the value of 200/ 110 mmHg, with a maximum value of 280/150 mmHg in one of the MEN patients also suffering from bilateral adrenal tumours;

-one single patient, suffering from the sporadic form of the disease, displayed an alternation of high blood pressure and low blood pressure phases.

It should also be noted that 75% of the patients with familial disease forms have paroxysm-like hypertensive attacks and only 25% have constantly increased blood pressure levels.

5. All the patients of the study lot have undergone tests in order to measure the *plasmatic and/or urinary MN and NMN* in order to confirm the pheochromocytoma diagnosis.

- Concerning the patients who have been tested for MN and NMN plasmatic and urinary levels, correlations of the two determination types have been found in 62% of the subjects with high plasmatic and urinary metabolites values.

- 25% of the subjects have only been tested for the plasmatic values of the metabolites, half of them displaying increased levels of both of the metabolites and the other half only displaying an increase in the plasmatic MN level.

- 35% of the patients have only been tested for the urinary MN and NMN values and suggestive increases for a positive diagnosis have only been found in the MN case (60% of the patients) and both MN and NMN increases in 30% of the patients; 10% of the patients had and increase only in the urinary NMN levels. It should be taken into account that all the patients have adrenal catecholamine-secreting tumours.

The MEN patients are generally prone to having increased plasmatic and urinary MN values. This statement is not confirmed by our test lot, considering the fact that 75% of the subjects had increased plasmatic and urinary MN and NMN levels and only the rest of 25% proving to have an increased MN level.

We have also discovered a correlation between the presence of *the bilateral adrenal tumours*, noticed in 50% of the MEN patients and one patient with both the sporadic form of the disorder and the *postoperatory increased urinary and plasmatic MN and NMN values*. Moreover, a correlation has been made between the *urinary value of the metabolites* and the presence of *the constant increasing AT pace* – high values of both urinary MN and NMN in all these patients.

Concerning the patients suffering from AHT attacks, the correlations could not be made only based on the levels of the plasmatic metanephrines, excepting the hypothesis of them being measured during the AHT crisis.

6. The fluctuations of the glycemic levels have resulted in changes that ranged from the alteration of the glucose tolerance to mellitus diabetes, a diagnosis based on the oral glucose tolerance in 50% of the patients, 40% of whom presented mellitus diabetes specific modifications.

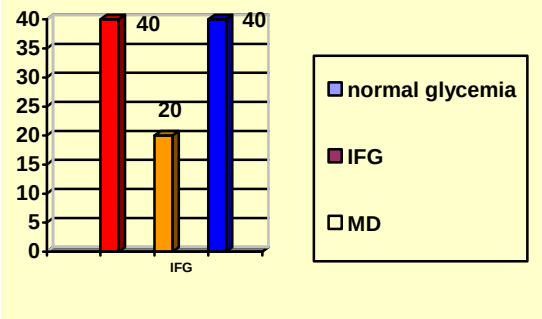

Image 4 . *The modification of the glucidic profile in the test lot*

Regarding the majority of the patients, the changes of the glucidic levels have only been reversed after the resection of the tumour, with only 2 of the patients being tested positive for mellitus diabetes postoperatory, nonetheless, they had already been diagnosed with the insulin-dependent type II MD (figure 4).

7. Regarding the MEN patients, the tumours are adrenal, benign and in one third of the cases, bilateral.

In all our *familial pheochromocytoma* patients, *the tumours were adrenal* and their *benign nature* has been confirmed of the postoperatory histopathological exam; *in 50% of the subjects*, the catecholamines-secreting tumours were bilateral and therefore the bilateral suprarenalectomy was required.

In all the subjects, the location of the tumour has been determined by running abdominal ultrasound examinations and CT scans; one single patient, whose AT levels have been high and constant postoperatory was directed towards the MIBG scintigram.

- bilateral adrenal tumours have been found in 20% of the patients and familial forms of the disease in 50% of them;

- the majority of the unilateral adrenal tumours can be found on the right side – 60%.

At the time of the diagnosis, all the *tumours* were *considerable in size* – ranging from more than 2 cm to 8 cm. No correlations have been established between the size of the tumours and the catecholamines' level.

8. The patients have undergone a cardiologic and EKG preoperatory consult and have been reevaluated in the postoperatory phase.

Regarding the examined patients, the EKG modifications were:

-rhythm disorders – sinus tachycardia, arterial or ventricular extrasystoles which are correlated to the symptoms described by the patients – palpitations in 80% of the subjects.

-HVS elements in 25% of the patients, correlated to the presence of the spontaneous or effort-induced angor;

-ST segment and T wave modifications in 40% of the patients;

-a single patient presented an inferior myocardial infarction sequel, also associating HVS elements and subepicardial ischaemia;

-during a THA attack caused by an EKG with HVS modifications, a 21 year old MEN patient developed a sinus tachycardia and a post-tachycardiac ST – an ST over-fluctuation of 3 mm in V2, V3 and signs of anteroinferior ischaemia, parietal hypokinesia, all discovered while undergoing a cardiac ultrasound test; the EKG aspect has rapidly normalized postoperatory, which comes to stress upon the toxic direct effect of the catecholamines.

The patients presenting persistent AHT symptoms may develop hypertensive nephropathy and retinopathy.

- 30 % of the patients of the study lot display modifications of the ophthalmologic exam, suffering from secondary retinopathy due the high levels of blood pressure, while another part of the patients display a postoperatory postretinopathy sequela maculopathy AHT.

- 30% of the test lot’s subject had a high level of the serum creatinine at the time of the diagnosis, only reaching normal values after the surgical resection of the tumour.

- 2 of the patients had an ischaemic cerebral embolism history.

9. *The medication administered preoperatory* was comprised of *efficiently blocking the alpha and beta receptors with* Carvedilol (Dilatrend), in a 12.5 by 25 mg/ day dose, not necessarily associated with *calcium blockers.*

Regarding the AT level control pre and periopertory, the response of the test subjects to this type of therapy has been positive.

The medical management was mainly focused on the preparation of the patient for the surgical resection of the tumour. One of the targets was the pharmacologic blockage of the effects of the catecholamines before the surgery, generally starting from the highly-debated problem of finding alternatives to the long-term complete nonselective alpha-blocker therapy and finding out if the alternatives confer the much needed safety and efficiency.

Although the use of the phenoxy-benzylamine alpha-blocker has proven to be the most documented so far from the pharmacologic point of view, the clinical practice has proven several major disadvantages; moreover, there have been claims according to which the preoperatory phenoxy-benzylamine treatment does not prevent the intraoperatory induced AHT by the manipulation of the tumour, consequently facing the risk of hypertensive attacks, regardless if the patient has or has not been administered alpha-blocker.

Regarding the preoperatory preparation of the patients, we resorted to the double association: a calcium blocker and an alpha adrenergic + beta (carvedilol) blocker, which has not only proven to be efficient, but also safe, without inducing the nonspecific blocker associated side effects, complete and prolonged with phenoxy-benzylamine. The beta-blocker action of the carvedilol has efficiently controlled the tachycardia and other rhythm disorders. Certain resistant AHT cases required the association of IEC and/or At II inhibitors.

The preoperatory preparation period for our patients has been brief, ranging from 7 to 15 days, displaying no correlation between it and the intraoperatory complications.

10. All the patients have undergone either a laproscopic (75%) or traditional (25%) uni or bilateral suprarenalectomy.

In two of the cases, the laparoscopic initial adrenalectomy required a conversion to the subcostal traditional procedure, as a result of certain intraoperatory complications:

-at the moment of the pneumoperitoneum procedure, one patient develops, severe rhythm disorders (TPSV, ventricular tachycardia), thus requiring electric defibrillation and the conversion of the surgery to the traditional subcostal right laparotomy;

-at the moment the tumour was mobilised ,another patient develops TPSV, atrial and ventricular fibrillation, requiring electric defibrillation and the conversion of the surgery to the traditional subcostal right laparotomy.

These two cases enforce the recent theories which have stated that the pneumoperitoneum may induce complications the anaesthetic management of the pheochromocytoma patients; the laparoscopic adrenaline is associated to the catecholamines secretion and hemodynamic modifications during the pneumoperitoneum procedure and the manipulation of the tumour; the increase in the intra-abdominal pressure during the conventional pneumoperitoneum is an important trigger factor for the catecholamine secretion.

An AT increase is also produced, but its level remains constant throughout the manipulation of the tumour.

The duration of the surgical procedure varies from 50 to 100 minutes, the bilateral suprarenalectomies usually requiring a greater period of time.

The average postoperatory hospitalization time ranges from 5 to 7 days.

11. *The postoperatory evolution* has been favorable both regarding the AT levels and the associated clinical symptoms and also the serum MN and NMN levels, having reached normal values after the resection of the catecholamines-secreting tumours in all except one of the patients, whose levels are still high; for this particular case, a MIBG scintigrame has been recommended, in order to determine the eventual secondary locations of the tumour.

4. Conclusions

The pheochromocytoma is a disorder characterised by unpredictable manifestations and diagnosis, its most frequent effects occurring during a surgical procedure usually treating other disorders and inducing possibly lethal circumstances.

Although the majority of the cases are sporadic, a relatively high percentage can generate germinative mutations, which leads to the necessity of genetic testing, especially at young ages or in case of either bilateral extra-adrenal or multiple tumours and last but not least, in case of a malignant tumour.

Along with several independent others, our study proves that measuring the metanephrine levels in the urine or plasma (MN and NMN) provides a greater diagnosis sensibility than the determination of the plasmatic catecholamines. The current recommendations for the initial testing of the pehochromocytoma include the measuring of the metanephrine levels fractioned in the urine and plasma.

The pharmacologic treatment and diagnosis aiming to control the catecholamine secretion and its consequences, as well as the surgical and anaesthetic management are still of an extreme importance.

The preoperatory association of the therapy with the calcium canals blockers and the alpha1 + beta blockers proves to be efficient for the preoperatory control and provides safety for the intra and postoperatory evolution, assuring a minimal morbidity and a null mortality in the reported cases.

The preoperatory alpha-blocker treatment does not prevent the hypertensive crisis during the intraoperatory tumour manipulation. The peroperatory preparation period in the reported cases has been of 7 up to 15 days, with the majority of the studies proving that a prolonged peroperatory preparation period proves not to be more efficient in the prevention of the intraoperatory complications.

Regardless of all its advantages, the laparoscopic surgery cannot diminish the problems imposed by the intraoperatory management.

The pheochromocytoma patients must be treated by a multidisciplinary team, which should include an

endocrinologist, a cardiologist a surgeon and an anaesthesiologist.

The patients must be monitored for the rest of their lives, especially in the familial cases or the ones with extra-adrenal tumours.

References

1.Henry M. Kronenberg, Shlomo Melmed, Kenneth S. Polonsky, P.Reed Larsen, Williams Textbook of Endocrinology, 11 th edition, 2008, editura Saunders.

2.David G. Gardner, Dolores Shoback, Greenspan Basic and Clinical Endocrinology, eighth edition,2007, editura McGraw Hill.

3.Karel Pacak,Preoperative Management of the pheochromocytoma patient J. Clin. Endocrinol. Metab., Nov 2007.

4.James G. Boyle, D. Fraser Davidson, Colin G. Perry, and John M. C. Connell,Comparison of Diagnostic Accuracy of Urinary Free Metanephrines, Vanillyl Mandelic Acid, and Catecholamines and Plasma Catecholamines for Diagnosis of Pheochromocytoma, J. Clin. Endocrinol. Metab., Dec 2007.

5.Alicia Algeciras-Schimnich, Carol M. Preissner, William F. Young, Jr., Ravinder J. Singh, Plasma Chromogranin A or Urine Fractionated Metanephrines Follow-Up Testing Improves the Diagnostic Accuracy of Plasma Fractionated Metanephrines for Pheochromocytoma, J. Clin. Endocrinol. Metab., Jan 2008.

6.Germline NF1 Mutational Spectra and Loss-of-Heterozygosity Analyses in Patients with pheochromocytoma and neurofibromatosis type1,J. Clin. Endocrinol. Metab., Jul 2007.

7.Salvatore Alesci, Shiromi M. Perera, Edwin W. Lai, Christina Kukura, Mones Abu-Asab, Maria Tsokos, John C. Morris, and Karel Pacak Adenoviral Gene Transfer in Bovine Adrenomedullary and Murine Pheochromocytoma Cells:Potential Clinical and Therapeutic Relevance, Endocrinology, Aug 2007.

8.Christian G. Ziegler, Flavie Sicard, Peter Lattke, Stefan R. Bornstein, Monika Ehrhart-Bornstein, Dehydroepiandrosterone Induces a Neuroendocrine Phenotype in Nerve Growth Factor-Stimulated Chromaffin Pheochromocytoma PC12 Cells, Endocrinology, Jan 2008.

9.Karagiannis, V Athyros - Pheochromocytoma: an update on genetics and management, Endocrine – Related Cancer, 2007; 14(4) 935 – 956.

10. K. Pacak - Preoperative management of the pheochromocytoma patient, J. Clin. Endocrinol. Metab., November 1, 2007; 92(11): 4069 – 4079.

Expert Consensus Document on Beta – adrenergic receptor blockers, European Herat Journal, 2004, 25(15): 1341 – 1362