

## Paraganglioma and cyanotic congenital heart disease: The role of tisular hypoxia<sup>☆</sup>



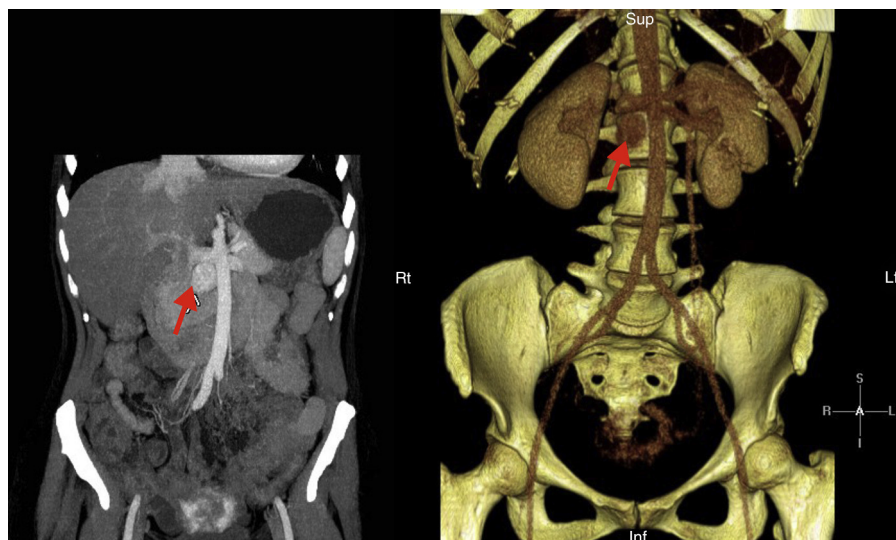
### Paraganglioma asociado a cardiopatía congénita cianótica: papel de la hipoxia tisular

Cyanotic congenital heart disease (CCHD) refers to a group of heart diseases which occur after birth, affect 1/1000 live newborns, and are associated with systemic hypoxia. The incidence of congenital heart disease ranges from 12 to 14/1000 live newborns.<sup>1</sup> The different congenital cardiac defects may cause increased pulmonary vascular resistance and pulmonary hypertension, so that approximately 8% of all congenital heart diseases and 11% of those with left-to-right shunts develop Eisenmenger's syndrome, characterized by progressive pulmonary vascular involvement and cyanosis resulting from systemic-pulmonary communication which causes shunt reversal. Eisenmenger's syndrome is the most common cause of CCHD in adults.<sup>2</sup>

Pheochromocytoma (PC) and paraganglioma (PG) are neuroendocrine tumors arising from chromaffin tissue which have a low incidence in the general population and a 0.2–0.6% prevalence in patients with high blood pressure. In more than 30% of cases, the occurrence of these tumors has been reported to be related to genetic changes.<sup>3</sup> Some publications have reported the coexistence of both conditions, and a potential pathogenetic association has been postulated.

We report the case of a 41-year-old female patient diagnosed in childhood with congenital heart disease consisting of single double-chambered left ventricle with L-malposition

of the great vessels and severe pulmonary hypertension in the Eisenmenger situation, with significant cyanosis and compensatory erythrocytosis, treated with sildenafil and bosentan. The diagnosis was made at five months of age and cardiac reconstruction surgery was rejected. The patient complained of HBP, asthenia, palpitations, and chest discomfort, and decompensated heart failure was found. Catecholamine hypersecretion was suspected, and hormone testing was performed with the following results: metanephrine level in 24 h urine 215  $\mu\text{g}/24\text{h}$  (NV < 341) and normetanephrine level 2491  $\mu\text{g}/24\text{h}$  (NV < 444). An imaging study consisting of abdominal CT showed a retroperitoneal mass 3 cm  $\times$  2 cm in size with a high contrast uptake in the interaortocaval space consistent with PG (Fig. 1). Adrenal gland scintigraphy with iodine-<sup>123</sup>MIBG and merging with CT images showed an area with pathological radiotracer uptake at the interaortocaval space coinciding with the lesion visualized by CT and consistent with the clinically suspected diagnosis. No distant lesions were shown. A molecular study was performed by sequencing encoding exons and exon-intron binding regions of genes: SDHD, SDHC, SDHB, VHL, SDHAF2, MAX, and TMEM127. No changes were found. After adequate alpha blockade with doxazosin, and under close cardiological monitoring, the patient underwent surgery. Histological examination of the surgical specimen revealed PG. No capsular or lymphovascular invasion was found. Immunohistochemistry revealed intense and diffuse expression for chromogranin, synaptophysin, and S100 staining in sustentacular areas; Ki-67 proliferation index: 1%. After surgery, urinary normetanephrine level was within the reference range, BP normalized, and there was an evident clinical improvement.



**Figure 1** Abdominal image showing high uptake in the described lesion (arrow).

<sup>☆</sup> Please cite this article as: Oleaga-Alday A, Goñi-Goicoechea F, Calles-Romero L, Pérez de Ciriza-Cordeu M, Paja-Fano M. Paraganglioma asociado a cardiopatía congénita cianótica: papel de la hipoxia tisular. *Endocrinol Nutr.* 2015;62:413–414.

An association of hypoxia and genetic syndromes related to the presence of PC and PG (SDHx, von Hippel-Lindau, HIF2A) has been reported in recent years. Most of these syndromes lead to an aberrant activation of signaling pathways activating the synthesis of hypoxia-induced factors (HIF), responsible for the pathogenesis of PC and PG.<sup>4</sup> It has been suggested that exposure to chronic hypoxia in patients with CCHD may increase the risk of developing PC and PG.<sup>5</sup> The reported patient was diagnosed in childhood, so that the course of the disease involved a prolonged cyanosis. On the other hand, as regards the biochemical phenotype, only norepinephrine production was found. The value of the biochemical phenotype as a guide for performing the genetic study in patients with PC/PG has been reported in recent years. This has made it possible to differentiate two groups (clusters 1 and 2) with different signaling pathways altered. In cluster 1, associated with errors in abnormal HIF activation, an increased expression of angiogenic factors leading to tumor occurrence is seen. This cluster is characterized by having a noradrenergic phenotype with normal epinephrine secretion.<sup>6</sup> Cluster 2 comprises a group of tumors caused by mutations in the rearranged during transfection (RET) proto-oncogene, the neurofibromatosis type 1 (NF 1) gene, and the TMEM127 gene with an adrenergic phenotype and predominant epinephrine secretion. The result of the genetic study performed in our patient ruled out a genetic predisposition. A diagnosis of PC/PG in these patients may be difficult to suspect due to the overlapping of symptoms. However, catecholamine hypersecretion may worsen the clinical picture, and it is therefore important to remember that the presence of PC/PG should be ruled out in patients with CCHD with a worsening of cardiac function.

## References

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## Minimally invasive parathyroidectomy in patients with previous thyroid surgery<sup>☆</sup>



### Paratiroidectomía mínimamente invasiva en pacientes con cirugía tiroidea previa

Minimally invasive parathyroidectomy (MIP) has been shown to be similar to bilateral neck examination in terms of efficacy and morbidity, with a level of evidence 1b<sup>1</sup> (4 randomized, controlled trials). Prior neck surgery, particularly prior thyroid surgery (PTS) in patients with primary hyperparathyroidism (PHP), is considered by most surgeons to be a contraindication for MIP on the grounds that fibrosis and adhesions caused by prior surgery may cause a distortion of tissues and structure location and make access through a

minimal incision difficult, as well as being associated with greater morbidity. The purpose of this letter is to review the use of MIP in the literature in patients with PHP and PTS, and to report the results of two patients who met these conditions and underwent surgery at our department.

Sixty-two patients with PHP underwent surgery from September 2010 to November 2014. The initial surgical approach was MIP and intraoperative PTH monitoring (IOPM) in 55 patients and direct bilateral neck exploration in seven patients.

The criteria for performing MIP included the surgical indication of PHP; no family history of PHP; unilateral gland disease located by at least one imaging test, if disagreement favored the result of scintigraphy; and adequate information to each patient based on his/her history. A history of prior neck surgery and PTS were not considered as reasons for exclusion.

Four patients (6%) had PTS. Two patients had undergone contralateral hemithyroidectomy, and although MIP was performed with an excellent outcome and they could be considered as having PTS, they were excluded from this study to avoid any addition of confounding factors. Thus, patients with surgery ipsilateral to adenoma location were

<sup>☆</sup> Please cite this article as: de la Plaza Llamas R, Ramia Ángel JM, Kühnhardt Barrantes AW, Gonzales Aguilar JD, Valenzuela Torres JC. Paratiroidectomía mínimamente invasiva en pacientes con cirugía tiroidea previa. *Endocrinol Nutr.* 2015;62:414–416.