

abnormalities. No calcifications in basal ganglia were found in computed tomography (CT) of the head. Bone densitometry showed osteopenia in the femoral head with a T-score of -1.1 .

The patient was advised to avoid treatments with calcium or vitamin D due to possible adverse effects, given the absence of symptoms.

Given the family history and genetic findings, it was decided to study the patient's son. The calcium and PTH levels detected were in the normal range (9.82 and 22.6 pg/mL respectively). The genetic study showed that he was not a carrier of the mutation identified in the family.

We report a novel mutation in the CaSR gene in two family members with asymptomatic hypocalcemia. Biochemical findings support the diagnosis of ADH, and confirm the pathogenic role of the mutation. Virtually every family with ADH has its own mutation. They are often heterozygous missense mutations.

A finding of hypocalcemia not associated with undetectable or greatly decreased PTH suggests a diagnosis of hypocalciuric hypercalcemia.⁷

There is a clear consensus against routinely treating asymptomatic patients. Treatment should be reserved for patients with clinically evident hypocalcemia. In these cases, calcium supplements and/or oral vitamin D should be administered at the lowest possible dose. The goal is to maintain the lowest serum calcium level that allows for symptom control.

Funding

The authors state that they have received no funding for the conduct of this study.

References

1. Thakker RV. Calcium sensing receptor: role in health and disease. *Indian J Endocrinol Metab.* 2012; Suppl. 2:S213–6.
2. Toka HR, Pollak MR. The role of the calcium-sensing receptor in disorders of abnormal calcium handling and cardiovascular disease. *Curr Opin Nephrol Hypertens.* 2014;23:494–501.
3. Raue E, Pichl J, Dörr HG, Schnabel D, Heidemann P, Hammersen G, et al. Activating mutations in the calcium sensing receptor: genetic and clinical spectrum in 25 patients with autosomal dominant hypocalcaemia – a German survey. *Clin Endocrinol (Oxf).* 2011;75:760–5.
4. Thakker RV. The calcium sensing receptor: and its involvement in parathyroid pathology. *Ann Endocrinol (Paris).* 2015;76:81–3.
5. Álvarez-Hernández D, Santamaría I, Rodríguez-García M, Iglesias P, Delgado-Lillo R, Cannata-Andía JB. A novel mutation in the calcium sensing receptor responsible for autosomal dominant hypocalcemia in a family with two uncommon parathyroid hormone polymorphisms. *J Mol Endocrinol.* 2003;31:255–62.
6. Nakajima K, Yamazaki K, Kimura H, Takano K, Miyoshi H, Sato K. Novel gain of function mutations of the calcium-sensing receptor in two patients with PTH-deficient hypocalcemia. *Intern Med.* 2009;48:1951–6.
7. Pearce SH, Williamson C, Kifor O, Bai M, Coulthard MG, Davies M, et al. A familial syndrome of hypocalcemia with hypercalciuria due to mutations in the calcium sensing receptor. *N Engl J Med.* 1996;335:1115–22.

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2173-5093/

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Pituitary adenoma associated with pheochromocytoma/paraganglioma: A new form of multiple endocrine neoplasia[☆]



Adenoma hipofisario asociado a feocromocitoma/paraganglioma: una nueva forma de neoplasia endocrina múltiple

Dear Editor:

Multiple endocrine neoplasia (MEN) syndromes are characterized by the presence of tumors affecting two or more

endocrine glands. Pituitary adenoma (PA) and pheochromocytoma/paraganglioma (Pheo/PGL) are common tumors in MEN type 1 and 2 respectively. The presence of both tumors in a patient is exceptional and was first reported by Iversen in 1952.¹ Advances in genetics have suggested a possible common pathogenetic mechanism in which mutations of genes encoding the enzyme succinate dehydrogenase (SDH) could be involved.^{2,3} In 2015, Xekouki et al. confirmed the existence of this association called "the three P association" or 3PAs: pituitary adenoma with pheochromocytoma/paraganglioma.⁴ Three cases of this association, one of them partially described previously, are reported below.⁵

Case 1

This was a 54-year-old male with no remarkable family history and with high blood pressure. Bilateral adrenal

[☆] Please cite this article as: Guerrero Pérez F, Lisbona Gil A, Robledo M, Iglesias P, Villabona Artero C. Adenoma hipofisario asociado a feocromocitoma/paraganglioma: una nueva forma de neoplasia endocrina múltiple. *Endocrinol Nutr.* 2016;63:506–508.



Figure 1 Coronal MRI image, a post-gadolinium T1 SE sequence, showing a 15 × 16 × 11 mm sellar lesion corresponding to case 2.

incidentalomas were diagnosed based on ultrasound examination for erectile dysfunction. Abdominal computed tomography (CT) showed a right adrenal mass 6 cm in size and a 2 cm nodule in the left adrenal gland. Urinary catecholamine levels were 3488 nmol/d (normal range: 116–699), and metaiodobenzylguanidine (MIBG) scintigraphy showed bilateral uptake. There were also acromegalic features, the serum IGF-1 level was 46.4 nmol/L (normal range: 8.1–32.8), and the serum GH level was not suppressed after an oral glucose tolerance test (OGTT). Pituitary magnetic resonance imaging (MRI) revealed a 7 mm sellar lesion. Bilateral adrenalectomy and subsequent transsphenoidal surgery were performed, and a pathological study diagnosed pheochromocytoma and pituitary adenoma with immunohistochemistry positive for GH and prolactin respectively. A genetic study of *RET*, *VHL*, *SDHB*, and *SDHD* was negative.

Case 2

This was a 38-year-old female with a deletion affecting *SDHB* exon 1. The index case was her brother, who had undergone surgery for functioning para-aortic paraganglioma. She was initially assessed for menstrual changes and galactorrhea, and was diagnosed with macroprolactinoma (Fig. 1). Treatment was started with cabergoline 1 mg/week, which resulted in symptom disappearance and the normalization of serum prolactin. The patient had no high blood pressure or adrenergic symptoms, and serum and urinary catecholamine levels were normal. Because of her family history and the presence of the same deletion as her brother, a CT scan of the neck, chest, and abdomen was performed, showing a right 11 mm nodule in the right side of the neck and a hyper-vascular mass 35 × 20 mm in size in the mediastinum. In OctreoScan®, the lesions expressed somatostatin receptors, which were consistent with paraganglioma. The mediastinal lesion was unresectable because it was too close to vascular structures. Because of the positive findings in scintigraphy

and based on its efficacy in some cases,⁶ treatment was started with somatostatin analogs. The assessment of the therapeutic response is pending. The genetic tests performed on her mother and sister were positive.

Case 3

This was a 56-year-old female with no remarkable family history, high blood pressure, and frequent hypertensive crises. The plasma norepinephrine level was 31,656 pg/mL (normal range: <300) and the urinary norepinephrine level was 2336 µg/d (normal range: <76). Abdominal CT and MRI revealed a 4 cm mass in the right adrenal gland and a 1 cm nodule in the left gland. MIBG scintigraphy showed right adrenal uptake. Bilateral adrenalectomy was performed at another hospital, and a pathological examination found a right pheochromocytoma and a normal left adrenal gland. The patient had phenotypic traits of acromegaly, a serum GH level of 17.9 ng/mL (normal range: <5), a serum IGF-1 level of 839 ng/mL (normal range: 94–483), and no serum GH suppression after OGTT. Pituitary MRI revealed a microadenoma, and transsphenoidal resection was therefore performed. Blood chemistry showed hypercalcemia (corrected calcium, 11.3 mg/dL) and a serum parathormone level of 87 ng/mL (normal range: <65) suggesting primary hyperparathyroidism. Neck ultrasound disclosed a right 16 mm nodule and a left 6 mm nodule consistent with parathyroid glands, and ⁹⁹Tc-sestamibi scintigraphy was negative. As the patient was asymptomatic, with calcium levels less than 11.5 mg/dL, and had no other criteria for surgery, watchful waiting was decided upon. A study of *RET*, *MEN-1*, and *VHL* showed no mutations.

Enzyme *SDH* is a protein complex of the mitochondrial membrane involved in the Krebs cycle. *SDH* consists of four subunits, *SDHA*, *SDHB*, *SDHC*, and *SDHD*. Changes in those genes inhibit the hydroxylation of hypoxia-inducible factor 1- α and cause an accumulation of succinate, which is related to a state of tissue pseudohypoxia and tumorigenesis.⁷ In addition to Pheo/PGL, *SDH* gene mutations have been identified in patients with Carney-Stratakis syndrome, renal carcinoma, or Cowden-like syndrome.^{8,9}

In a review of all reported cases of PA and Pheo/PGL,² mutations related to Pheo/PGL or PA were identified in 21 out of 72 patients. No genetic change could be shown in 23 patients, but there were elements suggesting a hereditary syndrome such as multiple Pheo/PGL, a family history of PA or Pheo/PGL, or an association with another endocrine disease. The remaining 28 patients were found to have no mutation or any other element suggesting hereditary disease. In the latter subgroup, a genetic study was available for only approximately half of the patients.²

Dénes et al.¹⁰ published in 2015 a genetic analysis of 39 patients with PA and Pheo/PGL. These authors detected 11 germinal mutations in five different genes: 5 *SDHB*, 1 *SDHC*, 1 *SDHD*, 2 *VHL*, and 2 *MEN1*. No mutation was found in 20 patients.

In patients with 3PAs and *SDH* mutations, PA is usually larger and locally aggressive or refractory to treatment. Most PAs secrete GH or prolactin or are non-functioning. Pheo/PGLs are often bilateral or multiple and have a trend to recurrence.⁴

The coexistence of bilateral pheochromocytoma and acromegaly suggests a pathogenic relationship between the tumors. An extension of the genetic study is currently ongoing to detect, among others, a *MEN1* mutation or a large deletion in *MAX*, a gene recently involved in cases of Pheo/PGL, where no evidence exists of other known mutations. This could possibly explain the lack of an apparent family history.¹¹ The second patient had a macroprolactinoma, which is uncommon in women of childbearing age and corresponds to the PA phenotype of patients with 3PAs. In case 3, the concurrence of three endocrine diseases suggests a relationship between them, and although they would be within the clinical spectrum of this new association, they could also correspond to MEN type 4. As regards the heterogeneity of the genetic study, it should be noted that the patients attended three different hospitals, and most tests, including the genetic study, were performed before the most recent findings regarding the 3PAs association were available.

In conclusion, the current evidence suggests that *SDH* mutations are related to pituitary tumorigenesis and a specific tumor phenotype. Patients with multiple Pheo/PGLs, an affected relative, or genetic *SDH* changes are predisposed to the development of pituitary tumors. In such cases, clinical, hormonal, and radiographic pituitary assessment is required. In the light of our current knowledge, a genetic study should first include the *SDHB* gene, and then all other subunits of succinate dehydrogenase, *VHL*, and *MEN1*. If the results of this study are negative, a test for *MEN4* should be performed.

References

- Iversen K. Acromegaly associated with pheochromocytoma. *Acta Med Scand*. 1952;142:1–5.
- O'Toole SM, Dénes J, Robledo M, Stratakis CA, Karbonits M. 15 years of paraganglioma: the association of pituitary adenomas and pheochromocytomas or paragangliomas. *Endocr Relat Cancer*. 2015;22:T105–22.
- Xekouki P, Pacak K, Almeida M, Wassif CA, Rustin P, Nesterova M, et al. Succinate dehydrogenase (SDH) D subunit (SDHD) inactivation in a growth-hormone-producing pituitary tumor: a new association for SDH? *J Clin Endocrinol Metab*. 2012;97:E357–66.
- Xekouki P, Szarek E, Bullova P, Giubellino A, Quezado M, Mastroyannis SA, et al. Pituitary adenoma with paraganglioma/pheochromocytoma (3PAs) and succinate dehydrogenase defects in humans and mice. *J Clin Endocrinol Metab*. 2015;100:E710–9.
- Lisbona Gil A, Robledo M, Fernández Riestra A, Alonso Rodríguez C. Acromegalia, hiperparatiroidismo primario y feocromocitoma. *Endocrinol Nutr*. 2006;53:382–6.
- Van Hulsteijn LT, van Duinen N, Verbist BM, Jansen JC, van der Klaauw AA, Smit JW, et al. Effects of octreotide therapy in progressive head and neck paragangliomas: case series. *Head Neck*. 2013;35:E391–6.
- Selak MA, Armour SM, Mackenzie ED, Boulahbel H, Watson DG, Mansfield KD, et al. Succinate links TCA cycle dysfunction to oncogenesis by inhibiting HIF- α prolyl hydroxylase. *Cancer Cell*. 2005;7:77–85.
- McWhinney SR, Pasini B, Stratakis CA. Familial gastrointestinal stromal tumors and germ-line mutations. *N Engl J Med*. 2007;357:1054–6.
- Ni Y, Zbuk KM, Sadler T, Patocs A, Lobo G, Edelman E, et al. Germline mutations and variants in the succinate dehydrogenase genes in Cowden and Cowden-like syndromes. *Am J Hum Genet*. 2008;83:261–8.
- Dénes J, Swords F, Rattenberry E, Stals K, Owens M, Cranston T, et al. Heterogeneous Genetic background of the association of pheochromocytoma/paraganglioma and pituitary adenoma: results from a large patient cohort. *J Clin Endocrinol Metab*. 2015;100:E531–41.
- Burnichon N, Cascón A, Schiavi F, Morales NP, Comino Méndez I, Abermil N, et al. MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. *Clin Cancer Res*. 2012;18:2828–37.

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2173-5093/

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