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(CASE REPORT)

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# Bilateral macro nodular adrenal hyperplasia causing primary hyperaldosteronism and Cushing syndrome

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## Abstract

The coexistence of primary hyperaldosteronism and Cushing's syndrome in the same patient is an uncommon situation.

We report the case of a 35-year-old female patient with resistant hypertension since the age of 30 years in whom exploration revealed a combination of primary hyperaldosteronism and ACTH-independent Cushing syndrome in the context of bilateral macro nodular adrenal hyperplasia.

G protein-coupled receptors aberrantly expressed in the adrenal cortex appear to have a central role in hormone hypersecretion and cell proliferation in this disease. However, other molecular mechanisms - such as mutations in Gsp or ACTH receptors, and adrenal paracrine hormone secretion may also be involved in this disease.

A good understanding of this rare and heterogeneous disease entity has contributed to a more accurate assessment of patients with PBMAH, improving earlier diagnosis and offering new therapeutic and potentially preventive strategies.

**Keywords:** Primary bilateral macro nodular adrenal hyperplasia (PBMAH); Cushing's syndrome; Autonomous cortisol secretion; Aberrant receptors; ARMC5

## 1. Introduction

Primary hyperaldosteronism (PAH) is characterized by hypertension, whether or not associated with hypokalemia, and is thought to affect 10% of hypertensive patients. It is mainly due to an adenoma or hyperplasia. Subclinical cortisol adenomas are benign tumors producing cortisol in an autonomous way that can slow down the corticotropic axis and the contralateral adrenal gland to varying degrees.

Primary hyperaldosteronism and Cushing's syndrome are two endocrine pathologies that may cause secondary hypertension (hypertension), possibly associated with hypokalemia. They often occur separately. Their coexistence in the same patient is an uncommon situation, which can be seen in the context of adrenal lesion.

Primary bilateral macronodular adrenal hyperplasia (PBMAH ) accounts for <1% of cushing's syndrome causes (1).Primary aldosteronism (PA) characterized by autonomous aldosterone hypersecretion constitutes mainly two subtypes, aldosterone-producing adenoma (APA) and bilateral idiopathic hyperaldosteronism (IHA). PA is currently considered to be a more common disease causing secondary hypertension than previously believed; its prevalence among hypertensive patients has been reported to be 5-15% (2). However, to date only a few cases of PA with Cushing's

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Syndrom due to a primary bilateral macronodular adrenal hyperplasia co-secreting aldosterone and cortisol have been reported (4, 6-8).

## 2. Case report

We report the case of a combination of primary hyperaldosteronism (basal Aldosterone 1035 pmoL/L, Renin 9.6 mIU/L, RAR 108 and clinical and biological ACTH independent cushing syndrome: CLU = 333 ug/24h (4.5 times normal), negative dexamethasone minute braking test (cortisol=17.7), , ACTH braked at 1, 3 pg/mL with the presence of multiple bilateral adrenal nodules > 1 cm in diameter with benign looking adrenal cortex hyperplasia on CT, nor-iodo-cholesterol scintigraphy and adrenal vein catheterization not performed. In a 35-year-old patient, hypertensive for 5 years with moderate hypokalemia, the patient is taking an antihypertensive quadritherapy including a spironolactone with improvement of the blood pressure figures and normalization of the hypokalemia.

Therefore, the diagnosis of bilateral macronodular adrenal hyperplasia with aldosterone-cortisol cosecretion was retained and a bilateral surrenalectomy in 2 times was indicated.

In the absence of catheterization of the adrenal veins and a nor-iodo-cholesterol scintigraphy, the left adrenalectomy was performed in a first step (size criterion), the anatomo-pathological study confirmed the diagnosis of BMAH.

## 3. Discussion

Bilateral macronodular adrenal hyperplasia (PBMAH) is a very rare cause of endogenous ACTH-independent cushing syndrome (<2%).

PBMAH has a characteristic imaging appearance of multiple bilateral macronodules (>10 mm) with hyperplasia and adrenal cortex.

Pathophysiologically, the expression of aberrant membrane receptors in the adrenal cortex plays an important role. In most cases, PBMAH is a sporadic disorder, although familial cases have been described.(9)

Recent studies have shown an association between germline/somatic mutations of the tumor suppressor gene ARMC5 in about 50% of cases.(10).

### 3.1. Genetic causes of PBMAH

In the majority of cases PBMAH appears to be sporadic. Several reports of familial clustering have been published with an autosomal dominant pattern of transmission.(11–15) The prevalence of familial forms of AIMAH is not yet known, as systematic familial screening has not been conducted. In recently studied families with PBMAH, aberrant hormone receptors have been identified in their adrenal tissues (see later section), but the genes implicated have not yet been identified.(16–17).Bilateral adrenal enlargement was found in 21% of a series of 33 patients with multiple endocrine neoplasia type-1 syndrome (MEN-1). In a large kindred of MEN-1, the prevalence of bilateral macronodular adrenal hyperplasia was 6%. No sporadic somatic mutation of the Menin gene has been identified in adrenocortical tissue in AIMAH. Bilateral adrenal nodules have also been found in patients with familial adenomatous polyposis (FAP), but a somatic point mutation of the APC gene was not found. In one report, AIMAH was identified in a patient with hereditary leiomyomatosis and renal cell cancer disorder due to a mutation in the fumaratehydratase gene (FH).

Adrenal adenomas are generally monosecretory. However, a mixed secretion can be observed in some cases, in our case, it is a hypersecretion of aldosterone and cortisol. Such a functional data seems important in a context of primary hyperaldosteronism because an associated hypercorticism, even infraclinical, leads to an increase in bone and metabolic morbidity with a risk of postoperative adrenal insufficiency in ignorance of the diagnosis. Some studies have found a 10% frequency of cosecretion, thus justifying the systematic search for cortisolichypersecretion in the presence of primary hyperaldosteronism.

Bilateral laparoscopic adrenalectomy is the main treatment for BMAH (18), In 45 bilateral adrenalectomies for BMAH, no surgery related death was noted. Because bilateral laparoscopic adrenalectomy requires lifelong steroid replacement and may induce adrenal insufficiency crisis, unilateral adrenalectomy was proposed in selected cases. Remission was achieved by unilateral adrenalectomy in patients with mild Cushing's syndrome. A study (15) reported a 93% success rate from unilateral adrenalectomy with a median follow-up of 69 months; two patients experienced transient

symptoms of hypocortisolism. UFC more than two times the upper limit of normal and marked asymmetry of adrenal enlargement are the best predictors of unilateral adrenalectomy effectiveness (18).

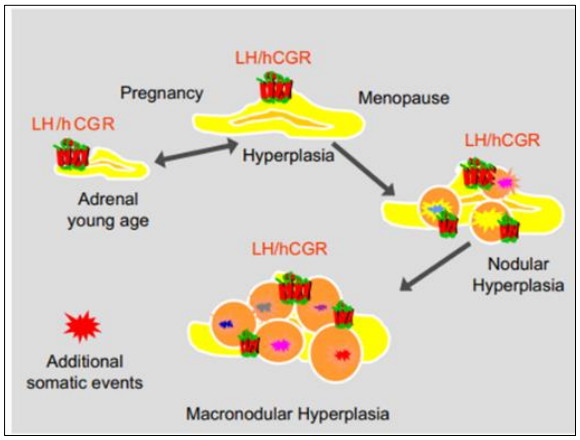


**Figure 1** Hypothesis of sequential genetic events leading to AIMAH

**Table 1** Principal genes associated to BMAH (18)

| Gene | Locus | Action | Type of mutation |
|---|---|---|---|
| *ARMC5* | 16p11.2 | Causes apoptosis and adrenal cell death | Germline and somatic |
| *MEN-1* | 11q13 | Regulation of cell proliferation and differentiation | Germline |
| *APC* | 5q12-22 | Prevention of β-catenin accumulation | Germline |
| *PDE11A* | 2q31-35 | Catalyzes the hydrolysis of cAMP and cGMP | Germline inactivation |
| *GNAS* | 20q13.1 | Stimulates cAMP production | Somatic during embryogenesis |
| *MC2R* | 18p11.2 | Regulates cortisol production and adrenal growth | Somatic |
| *FH* | 1q42.1 | Involved in Krebs cycle (mytocondria) and amino acid metabolism (cytosol) | Germline |

*ARMC5*, armadillo repeat containing 5; *APC*, adenomatous poliposis coli; *GNAS*, stimulatory G-protein alpha subunit; *MC2R*, melanocortin 2 receptor; *MEN1*, multiple endocrine neoplasia 1; *PDE11A*, 11A phosphodiesterase isoform.

## 4. Conclusion

The coexistence of primary hyperaldosteronism and cushing's syndrome in the same patient is an uncommon situation, which can be seen in the context of an adrenal lesion, including an adrenal nodule secreting both hormones: aldosterone and cortisol; the presence of a bilateral lesion such as the primary bilateral macronodular adrenal hyperplasia (PBMAH) is even more rare.

Thus justifying the systematic search for cortisolichypersecretion in the presence of primary hyperaldosteronism.

In recent years, several new findings have contributed to a better understanding of the heterogeneity of pathogenesis in PBMAH. Aberrantly expressed G-protein-coupled receptors in the adrenal cortex appear to have a central role in the hormonal hypersecretion and cell proliferation in this disease. However, other molecular mechanisms can also be implicated in this disease.

The appropriate surgical management of PBMAH remains controversial. Bilateral adrenalectomy results in lifelong steroid dependence. And is best reserved for patients with severe Cushing's syndrome. Unilateral adrenalectomy may be considered in selected patients.

The molecular and genetic findings identified recently should allow making early diagnosis and identify new targets to develop personalized pharmaceutical therapy. It is likely that other genes implicated in the development of BMAH will be identified. Genetic screening should allow identifying mutation carriers. Longitudinal follow-up of larger cohorts of patients in an international collaborative effort should define the natural history and indications for intervention therapies in these patients.

## Compliance with ethical standards

*Acknowledgments*

Thanking the patient for consent to describe her clinical case for the purpose of continuing education.

*Disclosure of conflict of interest*

The authors declare that they have no conflict of interests.

*Statement of ethical approval*

The present research work does not contain any studies performed on animals/humans subjects by any of the authors.

*Statement of informed consent*

Informed consent was obtained from the patient included in the study.

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