Bilateral adrenal incidentalomas: diagnostic and therapeutic approach

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Adrenal incidentalomas are adenomas discovered during investigation of non-adrenal disorders. They are more common in obese, hypertensive and diabetic individuals, and their prevalence increases with age, reaching 10% in individuals over 70 years. Adrenal incidentalomas can be bilateral in up to 15% of cases, with a prevalence of 0.3-0.6% in the general population. A group of Canadian researchers, coordinated by André Lacroix, recently reviewed this clinical problem (1).

ETIOLOGY
While most unilateral adrenal incidentalomas are non-secreting adenomas, most bilateral lesions are secondary to metastases, macro-nodular hyperplasia, pheochromocytomas and congenital (ACTH-dependent) adrenal hyperplasia.

Adrenal Metastases
Bilateral adrenal metastases usually originate in the kidney, the lung, the gastro-intestinal tract and the breast. Less commonly, they may be due to melanoma, thyroid carcinoma, bladder cancer, liver cancer or sarcomas. More rarely they may result from bilateral adrenocortical carcinomas or lymphomas. All patients with a history of cancer and bilateral incidental adrenal masses with suspicious imaging need adrenal biopsy (after exclusion of pheochromocytoma). The test has a sensitivity of 87% and a specificity of 100% (2). It is also important to consider the possibility of adrenal insufficiency requiring treatment, particularly when surgery is contemplated.

Bilateral Macro-Nodular Adrenal Hyperplasia (BMAH)
This definition excludes Primary Pigmented Nodular Adrenal Hyperplasia (PPNAH) (where the nodules are <10 mm), and hyperaldosteronism due to bilateral hyperplasia (which usually has clinical manifestations). BMAH is characterized by multiple adrenal nodules over 10 mm. The disorder, once called ACTH-Independent Macro-Nodular Adrenal Hyperplasia (AIMAH), is associated with incomplete cortisol suppression following 1 mg Dexamethasone Suppression Test, and varying degrees of hypercortisolism. Cortisol secretion in these patients is regulated by abnormal G protein-coupled receptors, responsive to a variety of agents (vasopressin, serotonin, LH/BhCG, β-adrenergic agonists, angiotensin II and glucagon), which stimulate the transcription pathway normally reserved to ACTH. The hypercortisolism, however, is not really ACTH-independent, as ACTH is also produced within the adrenal gland and causes autocrine and paracrine stimulation, which led to the more appropriate current definition. In some particularly severe cases, mutations have been described in the genes PRKACA and GNAS, causing a constitutive activation of the steroidogenic pathway, and in the gene ARMCS, responsible for adrenal tumorigenesis.

Bilateral Pheochromocytomas
They are usually syndromic and associated to MEN-2A and 2B, Von Hippel-Lindau syndrome, neurofibromatosis type 1, or to mutations of the gene MAX (3). Genetic studies in these patients are more important than in unilateral adrenal incidentalomas.

Congenital Adrenal Hyperplasia
These disorders derive by different enzymatic deficits affecting the adrenal steroidogenic pathway. 21-hydroxylase is most commonly involved. The compensatory increase in ACTH may cause adrenal nodules, uni- or bilateral, in over 80% of these patients. Similar findings may be detected in ACTH-dependent Cushing syndrome, particularly in elderly individuals with long-standing disorder.
Other Causes
Adrenal myelolipomas are usually unilateral. Infections (tuberculosis, histoplasmosis and blastomycosis) and infiltrative disorders (amyloidosis for example) may cause bilateral adrenal enlargement and adrenal insufficiency. Bilateral adrenal hemorrhage may be secondary to trauma, sepsis (Waterhouse-Friderichsen syndrome), anticoagulation therapies, and anti-phospholipid antibody syndrome. In these patients may be necessary to repeat imaging to rule out underlying malignancy.

BIOCHEMICAL AND GENETIC INVESTIGATIONS
The diagnostic approach, like in unilateral incidentalomas, aims to verify whether the lesions are hormonally active or cancer (2). It is also important to consider whether the masses on the two sides are discordant in terms of hormonal activity or underlying pathology, which may require selective catheterization of the adrenal veins or more advanced imaging.

Pheochromocytoma and hypercortisolism must be excluded in all patients, by measuring plasma and/or urine metanephrines and morning cortisol response to overnight suppression with 1 mg of dexamethasone. A subclinical hypercortisolism is often first suspected in presence of adrenal incidentaloma, particularly if bilateral. Current guidelines suggest that post-dexamethasone serum cortisol levels between 51 and 138 nmol/L (1.9–5.0 μg/dL) should be considered as evidence of ‘possible autonomous cortisol secretion’ and cortisol levels post dexamethasone >138 nmol/L (>5.0 μg/dL) should be taken as evidence of ‘autonomous cortisol secretion’. While these patients may not present the clinical phenotype of a florid Cushing, they are at increased risk of cardiac and skeletal problems, and all-cause mortality (4), and they require clinical and biochemical follow-up, and at times, surgery.

Primary aldosteronism must be considered in hypertensive patients (with or without hypokalemia) and the aldosterone/rein ratio evaluated after suspension of medications and substances interfering with the test.

In the presence of abnormal imaging and possible hyperandrogenism in a woman or gynecomastia in a man, it is recommended to measure total testosterone, DHEAS, androstenedione and estradiol.

In all patients with bilateral adrenal incidentalomas it is also important to consider hypoadrenalism and congenital adrenal hyperplasia (in particular the form secondary to deficit of 21-hydroxylase, which may be asymptomatic in men). 17-OH-progesterone, cortisol and ACTH should be measured in the morning, with a Synacthen test when required.

Patients with BMAH have a high prevalence of mutations of the gene ARMCS, which is associated with large macro-nodulation, severe hypercortisolism and possible presence of other tumors (meningiomas in particular), which suggest a possible new multineoplastic syndrome (5). Taking into account the clinical severity and the autosomic dominant nature of the mutation, it is likely that the screening for ARMCS, currently limited to third level centers, be in the future extended to family members of the index case to allow earlier diagnosis.

A recent French multi-centric study (6) highlighted a 5% incidence of heterozygous mutations of the gene NR3C1, which codifies the receptor for the glucocorticoids. These patients presented with bilateral adrenal incidentalomas, low-level resistance to glucocorticoids, hypertension and biochemical hypercortisolism, but no clinical Cushing. This finding is of importance in the differential diagnosis of subclinical Cushing and pseudo-Cushing. These patients do not benefit from surgery while they may derive advantage from anti-aldosterone drugs (in consideration of the picture of pseudo-hyperaldosteronism).

TREATMENT
Cancer
In the presence of bilateral adrenal metastases surgery offers a limited therapeutic option, in consideration of the poor general status and of the prognosis. Patients with lymphoma may benefit from chemotherapy.
BMAH
Surgery in BMAH must be individualized. In the presence of florid hypercortisolism (24h urine free cortisol over 3-4 times upper normal level) bilateral adrenalectomy is usually the intervention of choice. In the presence of moderate hypercortisolism (24h urine free cortisol less than 2-3 times upper normal range) it is usual to recommend a unilateral adrenalectomy, with or without partial contralateral adrenalectomy, as there is proof of benefit in reduction of hypercortisolism related comorbidities, also in cases with abnormal dexamethasone suppression test (7,8). The choice of which adrenal to remove depends on the size of the lesions, and the difference between the two glands in captation of radiotracer (selenium or iodine-cholesterol), and secretion of cortisol on catheterization of the adrenal veins (using catecholamines as criterion of adequate catheterization). In these patients, post-surgical follow up is important, both to confirm that the hypercortisolism does not relapse, and to rule out supervening hypoadrenalism.

Bilateral pheochromocytomas
Bilateral adrenalectomy is usually the treatment of choice. In some hereditary cases with low risk of malignancy (MEN-2, Von Hippel Lindau) it is possible to consider unilateral adrenalectomy plus partial contralateral adrenalectomy with cortical sparing, thus avoiding hypoadrenalism.

Other causes
Primary aldosteronism due to bilateral hyperplasia is usually treated with anti-aldosterone drugs (spironolactone et al).
In cases due to infection, infiltration or hemorrhage the treatment is that of the underlying disorder supplemented by therapy of hypoadrenalism if present.

CONCLUSIONS
Bilateral adrenal incidentalomas are not rare, and their management must be adapted to the multiple possible etiologies. BMAH has various clinical manifestations, and requires genetic counselling. Best practice in terms of follow up and surgery are still debated. There is a growing literature, which may soon lead to clinical guidelines to assist the management of these patients.

REFERENCES