

## MANAGEMENT OF ENDOCRINE DISEASE

# Differential diagnosis, investigation and therapy of bilateral adrenal incidentalomas

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## Abstract

The investigation and management of unilateral adrenal incidentalomas have been extensively considered in the last decades. While bilateral adrenal incidentalomas represent about 15% of adrenal incidentalomas (AIs), they have been less frequently discussed. The differential diagnosis of bilateral incidentalomas includes metastasis, primary bilateral macronodular adrenal hyperplasia and bilateral cortical adenomas. Less frequent etiologies are bilateral pheochromocytomas, congenital adrenal hyperplasia (CAH), Cushing's disease or ectopic ACTH secretion with secondary bilateral adrenal hyperplasia, primary malignancies, myelolipomas, infections or hemorrhage. The investigation of bilateral incidentalomas includes the same hormonal evaluation to exclude excess hormone secretion as recommended in unilateral AI, but diagnosis of CAH and adrenal insufficiency should also be excluded. This review is focused on the differential diagnosis, investigation and treatment of bilateral AIs.

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## Introduction

Adrenal incidentaloma (AI) is a mass larger than 1 cm in diameter discovered incidentally on imaging not performed for suspected adrenal disease (1). Adrenal lesions detected on screening imaging for patients with cancer or hereditary syndromes are outside of this definition. Advances in imaging techniques raised the prevalence of AI to 4.4% in radiological series compared to autopsy

data (1–8.7%) (1, 2, 3, 4, 5). The prevalence is higher in patients with obesity, diabetes or hypertension (6) and is increasing with age reaching 7–10% in individuals older than 70 years old (7, 8, 9). Although the majority of AIs are unilateral tumors bilateral AIs are found in up to 15% of cases (10, 11). Thus, the prevalence of bilateral AI can be estimated to be 0.3–0.6% in the general population.

### Invited Author's profile

**Isabelle Bourdeau** is Professor of Medicine in the Division of Endocrinology at Centre hospitalier de l'Université de Montréal (CHUM) and researcher at CHUM research center since 2004. In 2005, she established a new clinic focusing on genetics of adrenal tumors at CHUM. She is the National Delegate/PI for Canada of the American-Australian-Asian Adrenal Alliance (A5). As a clinician-scientist she performs translational research in adrenal diseases. Her research interests include genetics of adrenal tumors and the role of Wnt/beta-catenin signaling in adrenocortical tumor development.



Approach to unilateral AI has been discussed extensively in the past two decades (1, 9, 12, 13, 14), but no attention was devoted to bilateral AI. We will review here the etiologies, the investigation and management of bilateral AI focusing on adult population.

## Etiologies

The causes of unilateral or bilateral AI vary depending whether recruitment was from endocrinology clinics or from surgical series where adrenal cancers and secreting tumors are overrepresented leading to overestimation of the real prevalence of malignancy. A recent study confirmed the conclusions of a meta-analysis demonstrating that malignancy rate is low being 0.6–1.4% for adrenocortical carcinomas and 0.2–2.2% for metastasis in true AI being referred to endocrinology; benign non-secreting tumors represent more than 80–85% of AI (11, 15). We will describe below various etiologies of bilateral AIs that are summarized in Table 1.

The distribution of etiologies of bilateral AI differs from that of unilateral AI; two studies including 887 and 202 patients found that the most common causes of bilateral AI were metastasis, primary bilateral macronodular

adrenal hyperplasia (BMAH) (Fig. 1A) and bilateral cortical adenomas (16, 17). Other causes of bilateral AI include bilateral pheochromocytomas (Fig. 2), congenital adrenal hyperplasia (CAH), Cushing's disease or ectopic ACTH secretion with secondary bilateral adrenal hyperplasia (17, 18, 19, 20) (Table 1).

## Adrenal metastasis or malignancies

In a study involving 208 patients with AI including 172 unilateral AI and 36 bilateral AI, 19 (9%) patients had metastatic adrenal lesions and among them ten had bilateral adrenal lesions (21). The primary cancers leading to adrenal metastases in this study included kidney, bronchogenic carcinoma, colon, stomach and breast cancers (21). Bilateral adrenal metastases were also described in melanoma, thyroid cancer, sarcomatoid hepatocellular carcinoma and bladder cancer.

For patients with adrenal lesions with malignancy or who are at high risk for malignancy, adrenal biopsy may be indicated for staging work-up. Moreover, although recurrences most frequently occur locoregionally, in few patients, they may present with only distant unilateral or very rarely bilateral adrenal metastases that may be synchronous or metachronous. The overall sensitivity of adrenal biopsy for malignancy is of 87% with a specificity of 100% (14). Bilateral metastasis may lead to adrenal insufficiency due to neoplastic infiltration of the adrenal glands as described in patients with small-cell lung cancer (22).

Very rare case reports of bilateral adrenal gland metastasis were reported in patients with renal cell

**Table 1** Differential diagnosis of most common causes of bilateral adrenal incidentalomas.

### Extra adrenal lesions

- Kidney, pancreas and spleen lesions
- Technical artifacts

### Adrenal lesions

#### Tumoral

#### Adrenal tumors and hyperplasias

- Bilateral macronodular adrenal hyperplasia
- Adenomas
- Pheochromocytoma
- Adrenocortical carcinoma
- Congenital adrenal hyperplasia
- Glucocorticoid resistance syndrome
- ACTH-dependent hyperplasia
- Cushing's disease
- Ectopic ACTH Cushing's syndrome

#### Non-adrenal tumors

- Metastases
- Lymphoma
- Myelolipomas

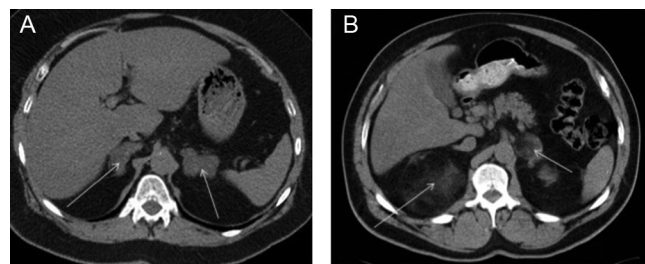
#### Infections

- Tuberculosis
- Histoplasmosis
- Blastomycosis

#### Infiltrative

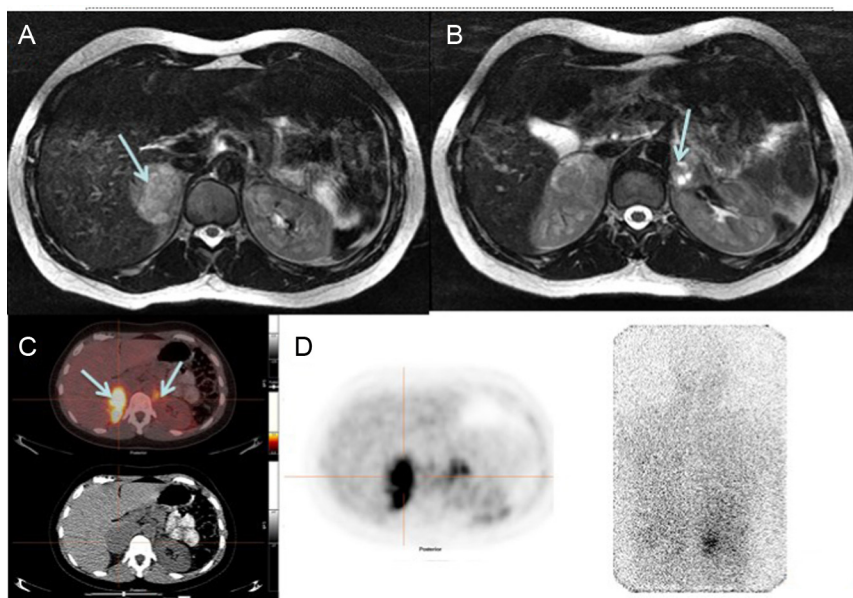
- Amyloidosis

#### Adrenal hemorrhage



**Figure 1**

CT scan imaging of bilateral adrenal lesions. (A) Classical findings of bilateral macronodular adrenal hyperplasia. (B) Bilateral adrenal myelolipomas (right: 10.7×9.5 cm and left: 3.9×4.3 cm) showing classical features of myelolipomas with well-defined fat attenuating in the lesions. The arrows are pointing to the adrenal glands.

**Figure 2**

Bilateral pheochromocytomas in a 28-year-old woman. (A) MRI showing a 4.7×4.4 cm right adrenal mass and a 2.9×2.9 left adrenal mass (B). The masses are hypointense on T1-weighted image, and in both lesions, there are areas of hyperintensity on T2-weighted images. (C) Both adrenal lesions showed uptake at FDG-PET with a SUVmax of 5.4 on the right side and 4.6 on the left side. (D) MIBG was positive only on the right adrenal gland. Diagnosis of bilateral pheochromocytomas was confirmed at pathology after bilateral adrenalectomies.

carcinoma. Surgical resection of metastases is the only therapeutic option for these patients. Both bilateral adrenalectomies and total adrenalectomy on one side and partial adrenalectomy on the contralateral side to preserve adrenal hormonal function were reported (23, 24).

Other less frequent neoplastic causes of bilateral AI include the rare bilateral adrenocortical carcinomas and lymphoma. A recent French cohort of 28 patients with adrenal lymphoma reported a prevalence of bilateral adrenal lymphoma of 71% (25). The initial symptoms were a worsening general state, weight loss and abdominal pain associated with classical biological features of lymphoma such as increased LDH,  $\beta$ 2microglobulin, CRP or ferritin levels. Importantly, adrenal insufficiency was found in 8 of 11 patients (73%) with bilateral lymphoma (25). Patients with adrenal lymphoma do not undergo adrenalectomy as they are treated with systemic chemotherapy.

### Bilateral macronodular adrenal hyperplasia

Bilateral adrenal hyperplasia can either present as macronodular (nodules >1 cm) or micronodular (nodules <1 cm). The micronodular form includes primary pigmented nodular adrenal disease (PPNAD) that is most often not associated with dominant adrenal nodules except for rare cases (26). For this reason, PPNAD does not usually present as AI, and it will not be further discussed in this review. Similarly, we will not discuss extensively primary aldosteronism, which is secondary to bilateral adrenal hyperplasia in approximately 60% of cases as they

may have normal-appearing adrenal glands on CT and are rarely investigated in the course of evaluation of AIs (27).

BMAH is suspected when there is bilateral AI with incomplete suppression to 1 mg dexamethasone overnight test. Cortisol secretion is in part regulated by the expression of multiple aberrant G protein-coupled receptors (GPCRs) in zona fasciculata cells including those for vasopressin, serotonin, luteinizing hormone/human chorionic gonadotropin,  $\beta$ -adrenergic agonists, GIP, glucagon and angiotensin II (28). These GPCRs led to the activation of cyclic AMP/protein kinase A (PKA) signaling pathway in a similar fashion to the pathway activated by ACTH receptor consequently leading to the transcription of steroidogenic factors. GPCRs were identified in 80% of patients with overt or mild hypercortisolism (28). Several simultaneous aberrant receptor responses were demonstrated in half of the patients with BMAH: vasopressin and serotonin being the stimuli leading to the highest number of aberrant responses *in vivo* (29, 30, 31, 32, 33). The presence of aberrant responses was less frequent in patients with unilateral adenomas and overt hypercortisolism (29) probably due to the high frequency of mutations in the catalytic subunit of PKA (*PRKACA*) in those patients (34). The concept of ACTH-independent cortisol secretion was challenged after the demonstration of paracrine and autocrine production of ACTH in tissues of BMAH regulating cortisol production (35, 36).

On unenhanced CT, both adrenal glands are enlarged usually with multiple nodules (Figs 1A and 3), but diffuse adrenal enlargement without nodules is also seen. Attenuation higher than 10 HU was also described (37).



Time (minutes)	Cortisol (nmol/L)	17(OH)P (nmol/L)
-15	650	8,3
0	596	10,0
30	1515	43,4
60	1707	49,7

**Figure 3**

Adrenal CT scan of a 69-year-old man who presented with bilateral incidentalomas. The left adrenal gland has two nodular lesions of 3×2 cm and 1.6×1.3 cm (11 HU), whereas the right adrenal gland has a nodule of 1.8×0.8 cm. All nodules were stable in size from 2006 to 2017. The hormonal investigation was normal. Including the 1 mg dexamethasone suppression test. The 250 µg cosyntropin test showed overproduction of serum cortisol and 17-hydroxyprogesterone supporting the diagnosis of bilateral macronodular adrenal hyperplasia.

In contrast-enhanced imaging, nodules can have marked enhancement, and there might be enhancement of the periphery of the glands. An asymmetric appearance is possible and may be confused with a unilateral disease. On MR, relative to the liver, glands are usually hypointense on T1-weighted images and hyperintense on T2-weighted images (38).

In limited studies using 2-(fluorine 18) fluoro-2-dexoxy-D glucose positron emission tomography/CT

(PET/CT) imaging, uptake in the macronodular adrenal glands of BMAH was higher than the liver, with maximum standardized uptake value (SUV max) >3.1 (3.3–8.9), thus reaching level usually seen in malignant tumors (37, 39) although BMAH is well recognized as a benign disease. These findings need to be confirmed in larger series.

## Pheochromocytomas

Bilateral adrenal pheochromocytomas are more likely associated to a hereditary cause compared to unilateral pheochromocytomas (40). Bilateral adrenal pheochromocytomas may be found in association with multiple endocrine neoplasia type 2A and type 2B, von Hippel–Lindau syndrome and have been reported in patients with neurofibromatosis type 1 as well (41). More recently, germline mutations of the tumor suppressor susceptibility gene, *MAX* (MYC-associated factor X), were identified in a large cohort of pheochromocytomas and paragangliomas with a prevalence of 1.12% (42). Among the 19 patients harboring a pathogenic germline *MAX* mutations, 11 had developed bilateral pheochromocytomas (42). Thus, caregivers should look for underlying genetic syndromes and offering a genetic counseling to patients with bilateral pheochromocytomas knowing that the probability to identify a germline genetic cause is higher than that in unilateral pheochromocytoma. Pheochromocytomas are hypervascular, then they have intense enhancement during the arterial phase of CT scan. Similarly, in MRI, they show hyperenhancement following injection of gadolinium and classically they are hyperintense on T2-weighted images (43).

## Congenital adrenal hyperplasia

In patients with CAH, chronic elevation of ACTH leads to adrenal tumors in 82% of cases. The occurrence of 21-hydroxylase-gene mutation (CYP21) in patients with unilateral AI and bilateral AI was found at similar frequency with a prevalence of 16.1% and 21.1% respectively (44). A meta-analysis of 36 publications on CAH and adrenal tumors suggested that bilateral AI may predict CAH; one-third of biochemically confirmed CAH had bilateral AI and this frequency was increased to 50% in the subgroup of patients with genetically confirmed CAH, which is much higher than the expected prevalence of 15% of bilateral AI (45). Nodular adrenal hyperplasia



occurs in ACTH-dependent Cushing's syndrome particularly in older patients and those with a longer standing disease (46).

### Other causes of bilateral AI

Among the less frequent causes of bilateral adrenal lesions are adrenal myelolipoma (Fig. 1B), benign tumors composed of mature adipose cells and hematopoietic tissue. They may be diagnosed incidentally, due to mass effect symptoms or rarely hormonal-secreting symptoms if there is a compound associated hormone-secreting tumor in the same adrenal. Myelolipomas show specific characteristics at noncontrast CT with hypoattenuation of 130–23 HU containing macroscopic fat (47). At MRI, macroscopic fat appears hyperintense on T1-weighted images, whereas the marrow elements are T1 hypointense but of variable intensity on T2 signal (43). Less than 40 cases of bilateral adrenal myelolipomas have been reported so far (48). Surgical removal should be reserved for secreting myelolipomas and/or those larger lesions (>6–7 cm) that may cause pain or be prone to rupture of hemorrhage (48, 49).

Non-tumoral causes of bilateral adrenal enlargement include infections such as tuberculosis, histoplasmosis and blastomycosis. The adrenal glands are among the most common sites involved in disseminated histoplasma infections in immunocompetent individuals and bilateral adrenal enlargement has been reported (50). Long-term infection may lead to adrenal glands destruction and adrenal insufficiency. Infiltrative diseases such as amyloidosis are part of the differential diagnosis of bilateral adrenal lesions that may be found incidentally.

Adrenal hemorrhage may be found bilaterally and may result in acute primary adrenal insufficiency (51). Predisposing factors include trauma, anticoagulation therapy, antiphospholipid syndrome, sepsis such as meningococemia (Waterhouse–Friderichsen syndrome) and stress as surgery (51, 52). Adrenal hemorrhage is recognized in noncontrast CT showing hyperdense adrenal enlargement. Follow-up in these cases is essential to eliminate underlying adrenal tumoral lesions.

### Hormonal work-up for bilateral AIs

The initial work-up for bilateral AI is similar to unilateral AI and is based on two main clinical questions; 1) do these lesions secrete excess hormones? 2) Are they malignant

masses? The assessment should include a detailed questionnaire and physical examination of the patients to assess the signs of adrenal hormones oversecretion. The investigation should be able to identify even mild adrenal hormone excess (1, 10, 12, 14, 53). In contrast to unilateral AI, adrenal insufficiency and CAHs should be excluded specifically for patients with bilateral AI. Cortisol excess should be excluded in all patients with a 1 mg dexamethasone suppression test (1 mg DST). DST requires taking 1 mg oral dexamethasone at 23 h or 24 h then measuring cortisol level the next morning at 8 h–9 h; normal levels should be <50 nmol/L. Evaluation of catecholamines excess is performed either by a 24-h urinary collection of metanephrines and fractionated catecholamines or by measuring free plasma levels of free metanephrines and normetanephrines after 30 minutes of rest in supine posture (54). When arterial hypertension or hypokalemia are present, plasma aldosterone and renin after 15 minutes of sitting position should be performed to detect primary aldosteronism. Additional specific samplings should be done according to clinical suspicion including estrogens in the presence of gynecomastia and DHEAS, total testosterone, SHBG in the presence of hirsutism/virilization or suspicion of adrenocortical carcinoma.

Two additional investigations should be performed specifically in bilateral AI. First, adrenal insufficiency should be ruled out because destruction of more than 90% of the cortex of both glands may lead to adrenal insufficiency. Second, late-onset forms of CAH (specially 21-hydroxylase deficiency) may be diagnosed late in adulthood. For this fasting blood samples for cortisol, 17-hydroxyprogesterone and ACTH are obtained early morning and depending on the results may be followed by stimulation with 250 µg of ACTH 1–24 where levels of cortisol and 17-hydroxyprogesterone are measured at 30 and 60 min later. Adrenal insufficiency is present when cortisol increase is incomplete (< 430–550 nmol/L depending the method of measurement) and basal ACTH levels are high. Samples of plasma aldosterone and renin in sitting position are then indicated to evaluate the requirement for mineralocorticoids replacement. Increased levels of basal and post 250 µg ACTH stimulation test of 17-hydroxyprogesterone (17-hydroxyprogesterone >43 nmol/L) (55) could reveal a partial congenital deficiency in 21-hydroxylase. However, screening for CAH with 17-hydroxyprogesterone may lack specificity and CYP21A2 mutation analyses will be the most reliable test for CAH diagnosis confirmation. A mild enzymatic deficiency with modest rise in 17-hydroxyprogesterone

is also frequently found in adenomas and BMAH (31). In these cases, we should expect that ACTH levels could discriminate between CAH (increased ACTH), whereas ACTH levels are within or below the normal limit values usually in BMAH. In patients with BMAH, following a 250 µg cosyntropin test, an overproduction of plasma cortisol and 17-hydroxyprogesterone levels reflect the mass of hyperplastic adrenal glands with relative deficiency of 21 hydroxylase expression (31) (Fig. 3). It should be kept in mind that the nature of the bilateral adrenal lesions may be different in the two sides with a secreting adrenal lesion on one side and a non-secreting on the other side (Fig. 4).

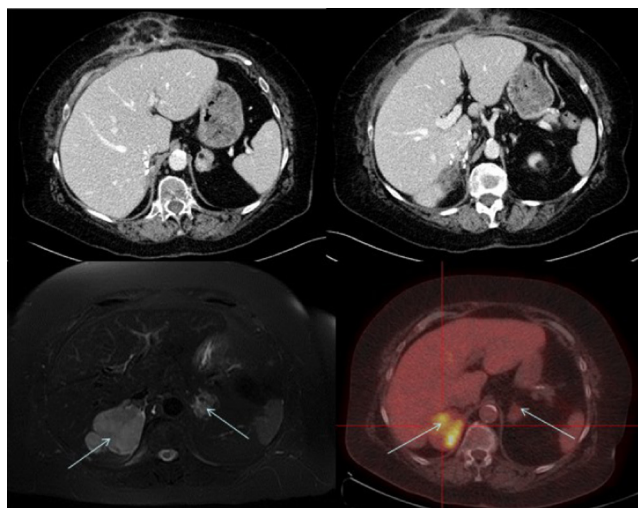
### Modest secretion of cortisol is more frequent in bilateral AIs than in unilateral AIs

A cortisol-secreting adenoma with overt Cushing symptoms rarely presents as an AI (0.8%) (11) while adenomas with modest cortisol secretion (previously termed subclinical Cushing syndrome) are found in up to 25% of AI (13, 56). Modest cortisol secretion that is not high enough to result in classical clinical stigmata

of Cushing syndrome was recently termed (possible) autonomous (for non-ACTH-dependent) cortisol-secretion (14). Its biochemical definition varied among authors and to date, there is still no consensus on its diagnostic criteria (14, 57) except for a serum cortisol post dexamethasone between 51 and 140 nmol/L for possible autonomous cortisol secretion and autonomous cortisol secretion for higher values. Nevertheless, patients secreting mild cortisol excess might carry an increased risk of osteoporotic, metabolic and cardiovascular complications compared to control patients matched for age, gender and BMI (2, 58, 59). In 2014, Di Damalzi *et al.* studied a retrospective cohort of patients with AIs and found that survival rates for all-cause mortality were lower in patients with abnormal suppression to 1 mg DST (>50 nmol/L) compared to patients with non-secreting adrenal masses (60). Factors associated with mortality were age and mean concentration of cortisol post DST (60). Similarly, in 2014, Debono *et al.* assessed survival in a retrospective cohort of 206 patients with AIs. There was a significant decrease in survival rate (deaths were mainly due to circulatory or respiratory/infectious causes) with increasing post-dexamethasone serum cortisol level (61).

Morelli *et al.* compared prospectively 175 unilateral AI to 38 bilateral AI; the prevalence of mild cortisol excess, hypertension, diabetes type 2 and dyslipidemia were comparable between the two groups, whereas fractures were more frequent in patients with bilateral AI (62).

In 2011, Vassiliadi *et al.* reported in a retrospective cohort of adrenal incidentalomas that mild cortisol excess was more frequent in bilateral AI vs unilateral AI with a prevalence of 41.5% vs 12.2% (63). An other study in 2011 by Androulakis *et al.* showed that patients with bilateral AI have more pronounced cortisol and aldosterone secretion and glucose metabolism alterations than patients with unilateral AI (64). These data were confirmed in a prospective study of 224 unilateral AI and 74 bilateral AI, where mild cortisol excess was present in 35.1% of patients with bilateral AI, but only in 17.9% of patients with unilateral AI (65). However, hypertension, diabetes type 2 and dyslipidemia were comparable in both groups (65). More recently, in a surgical series including 112 unilateral AI and 23 bilateral AI, mild cortisol excess was present in 21.7% bilateral AI vs 6.2% of unilateral AI (66). Vassiliadi *et al.* demonstrated an exaggerated response of cortisol and ACTH in patients with bilateral AI during the combined test of DST followed by CRH stimulation compared to unilateral AI and to a control group suggesting that the regulation of hypothalamic–pituitary axis was disturbed in patients with bilateral AI;



**Figure 4**

Bilateral adrenal lesions in a 78-year-old woman with Cushing's syndrome and hyperandrogenism. She was initially referred for bilateral adrenocortical carcinomas. Revised CT scan showed a right 5.9×7.7 cm lesion suggesting an adrenocortical carcinoma (36 HU) with SUVmax of 9.5 at FDG-PET and a 2.7×2.1 cm left adrenal mass compatible with an adenoma with low HU and lower SUVmax (SUVmax 3.8).

nevertheless, the diagnosis of BMAH was not excluded in this group (67).

### BMAH and *ARMC5* gene mutations

Inactivating germline mutations of Armadillo repeat containing 5 (*ARMC5*) gene were identified in 55% of the first series of 33 apparently sporadic cases of BMAH with Cushing's syndrome (68). The prevalence of these mutations is closer to 25% based on larger recent studies (34, 69, 70). The germline mutation is responsible for the diffuse hyperplasia and additional somatic mutations are necessary for the formation of different macronodules (68, 70). The possible association between *ARMC5* mutations and the expression of aberrant receptors has been described (68, 70, 71, 72) as well as the association between these mutations and the presence of other tumors such as meningiomas suggesting the possibility of a new multiple neoplasia syndrome (73). Although *ARMC5* mutations are the most common genetic alterations described in BMAH, no clear *ARMC5* genotype–phenotype correlations were identified (72). Very recently, Emms *et al.* investigated whether *ARMC5* mutations play a role in the development of incidentally discovered bilateral adrenal nodules (74). Among the 39 patients included in their study, only one patient carried a likely pathogenic *ARMC5* mutation (74).

Other genetic alterations could be associated with BMAH such as in the *menin* (*MEN1*), fumarate hydratase (*FH*) and adenomatosis polyposis coli (*APC*) genes (33, 75, 76, 77).

In all cases, these gene mutations have an autosomal dominant mode of transmission; thus, clinicians should be aware that patients may develop BMAH in the context of hereditary syndromes. Evaluation of BMAH patients should include a detailed family history, and a reference for specialized genetic counseling. Genetic testing should be offered and then be available to first-degree relatives of individuals who carry a germline mutation. Several individuals from BMAH families described previously were affected by various degrees of cortisol excess mainly obesity, hypertension and diabetes and had unsuspected BMAH before systematic clinical and genetic screening (69, 71). In these cases, surgical and/or specific drugs targeting the aberrant receptors within the adrenal BMAH tissues led to complete or partial reversibility of metabolic morbidities with significantly improved health and reduced need for long-term numerous medications (71).

### Management of bilateral AI

Unilateral adrenalectomy is recommended for unilateral AI with suspicious malignant lesions on imaging, or for certain lesions larger than 4–6 cm, as well as for tumors with clear overt hormonal secretion (cortisol, aldosterone or catecholamines) (1, 10, 12, 53). However, the management is quite different in BMAH because the size of the tumors is not a criterion for surgery. As there is no clear consensus on the criteria defining abnormal cortisol secretion, the indication for adrenalectomy remains controversial (14); however, recent data on decreased survival of patients with abnormal cortisol suppression to dexamethasone tends to influence our management of patients with mild cortisol secretion. Bilateral adrenalectomy may be considered if urinary cortisol levels are higher than 3–4 times the upper limit of normal (ULN) with both adrenals having relatively symmetrical size (28). Many groups reported the benefits of unilateral adrenalectomy in small series of patients with BMAH and modest cortisol secretion (<2–3 times ULN): their combined data show a remission rate of hypercortisolism reaching 97% with a recurrence rate of 23% (78, 79, 80). The choice of which adrenal to remove remains uncertain: some choose to remove the adrenal with the largest size or the one with the highest uptake of iodo-cholesterol (yet limited availability depending on centers), whereas others rely on the results of adrenal venous sampling (selectivity criteria using free metanephrines remain poorly defined). Post-operative follow-up is essential to detect adrenal insufficiency that was present in 40% of cases in a French series (80). In 14 patients with bilateral AI and mild cortisol secretion, resection of the largest adenoma reduced cortisol excess in a significant way and improved the metabolic complications (81). To avoid hormonal replacement, concomitant total adrenalectomy and contralateral partial adrenalectomy was performed in a patient with BMAH using 3D adrenal gland printing and volumetric measurement before partial adrenalectomy to improve the determination of the remnant gland volume (82). Very recently, the experts from the European Society suggested that in selected patients, a unilateral adrenalectomy of the dominant lesion may be considered based on age of the patients, degree of cortisol excess, general condition and comorbidities and very importantly patient preference (14).

For AI with bilateral secretion of aldosterone confirmed by adrenal venous sampling, medical treatment with mineralocorticoids receptors antagonists remains the treatment of choice.

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Bilateral adrenalectomy is suggested for bilateral pheochromocytomas; however, the risk of adrenal insufficiency and the side effects of glucocorticoids replacement have led certain groups to perform partial tumor resection sparing the adrenal cortex particularly in the setting of genetic syndromes such as VHL and MEN2A where the risk of malignant tumors is very low (83). Infection-causing adrenal enlargement should be treated appropriately.

## Conclusion

Overall, physicians face many uncertainties for the management of bilateral adrenal incidentalomas: (1) studies emitting guidelines for the work-up and management of bilateral AI remain scarce, (2) absence of consensus for the definition of mild cortisol excess Cushing's syndrome, (3) data on natural history of bilateral AI and studies evaluating cost/benefit of diagnostic and therapeutic strategies are lacking.

Nonetheless, bilateral AI represents a frequent pathology that requires conduction of thorough diagnostic and therapeutic approaches adapted to each case, taking into consideration many factors such as risk of malignancy and level of secretion. The distribution of etiologies is quite different from unilateral AI with a predominance of metastases, BMAH with mild cortisol excess, bilateral pheochromocytomas and CAH. Patients with bilateral disease in the context of BMAH, pheochromocytomas or CAH should be offered genetic counseling. Better knowledge of BMAH genetics will improve its early molecular diagnosis and abolish the biochemical and radiological investigations required for diagnosis and allow earlier therapy of affected individuals. Long-term prospective studies are needed to determine the evolution of bilateral AI and the risk of recurrence of hypercortisolism after unilateral adrenalectomy in cases with BMAH.

## Note added in proof

A recent study revealed an incidence of 5% of mild glucocorticoid resistance (heterozygous NR3C1 mutations) in patients with adrenal incidentalomas, particularly if bilateral characterized by elevated UFC, incomplete suppression of cortisol and ACTH after overnight 1-mg dexamethasone test. This was associated with hypertension and/or biological hypercortisolism without clinical Cushing's signs (84)

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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