REVIEW

Diagnosis and management of primary bilateral macronodular adrenal hyperplasia

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Abstract

Primary bilateral macronodular adrenal hyperplasia (PBMAH) is a highly heterogeneous entity. The incidental identification of an increasing number of cases has shifted its clinical expression from the rarely encountered severe forms, regarding both cortisol excess and adrenal enlargement, to mild forms of asymptomatic or oligosymptomatic cases with less impressive imaging phenotypes. Activation of cAMP/PKA pathway, either due to alterations of the different downstream signaling pathways or through aberrantly expressed G-protein-coupled receptors, relates to both cortisol secretion and adrenal growth. Germline *ARMC5* mutations are a frequent genetic defect. The diagnostic approach consists of both imaging and hormonal characterization. Imaging characterization should be done separately for each lesion. Endocrine evaluation in cases with clinically overt Cushing's syndrome (CS) is similar to that applied for all forms of CS. In incidentally detected PBMAH, hormonal evaluation includes testing for primary aldosteronism, pheochromocytoma and evaluation for autonomous cortisol secretion, using the 1 mg overnight dexamethasone suppression test. Midnight cortisol or 24-h urinary free cortisol may aid in establishing the degree of cortisol excess. In patients with hypercortisolism, ACTH levels should be measured in order to establish ACTH independency. At variance with other forms of CS, PBMAH may be characterized by a distinct pattern of inefficient steroidogenesis. The appropriate management of PBMAH remains controversial. Bilateral adrenalectomy results in lifetime steroid dependency and is better reserved only for patients with severe CS. Unilateral adrenalectomy might be considered in selected patients. In cases where the regulation of cortisol secretion is mediated by aberrant receptors there is some potential for medical therapy.

Key Words

- adrenal cortex
- primary bilateral macronodular adrenal hyperplasia
- Cushing's syndrome
- autonomous cortisol secretion
- aberrant receptors
- ARMC5

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Introduction

Macronodular adrenal hyperplasia (MAH) refers to adrenal enlargement by large (>1 cm) nodules (Fig. 1A and B), as opposed to micronodular adrenal hyperplasia (Fig. 1C), which is characterized by multiple sub-centimeter nodules. Rarely, diffuse adrenal hyperplasia without macronodules may be seen (Fig. 1D). MAH is a heterogeneous entity presenting in a variety of clinical settings. ACTH is the principal regulator of adrenal growth and thus MAH may be the result of hyperplasia of the adrenal cortex driven by ACTH (ACTH-dependent MAH), either due to chronic ACTH secretion by tumors, such as in Cushing's disease (CD) or ectopic ACTH secretion (Sohaib *et al.* 1999, Imaki *et al.* 2004) or due to excessive ACTH secretion that compensates for enzymatic defects of cortisol synthesis as in patients with congenital adrenal hyperplasia (CAH). Kirschner *et al.* (1964) described an

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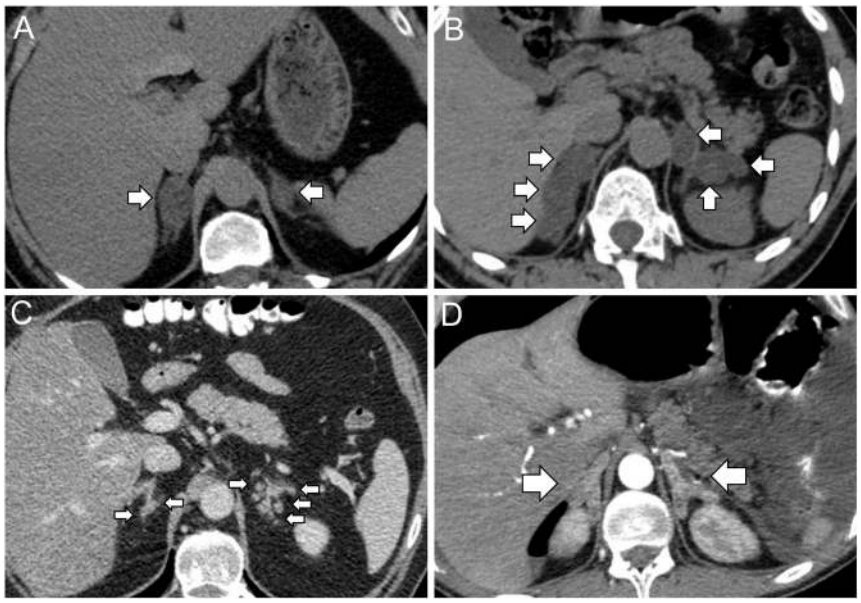

Figure 1
Forms of bilateral adrenal hyperplasia. (A) Discrete bilateral adrenal nodules. (B) Multiple bilateral adrenal macronodules. (C) Multiple bilateral adrenal micronodules in a patient with Carney complex. (D) Diffuse adrenal hyperplasia without macronodules.

unusual form of Cushing's syndrome (CS), characterized by the constellation of long-standing hypercortisolism, markedly enlarged multinodular adrenal glands and lack of cortisol suppression to high doses of dexamethasone. In the era where the measurement of ACTH was not widely available, failure of corticoid suppression on large doses of dexamethasone was the biochemical marker of ACTH independency. Swain *et al.* (1998) retrospectively reviewed the clinical, hormonal and pathologic characteristics of similar subsequently reported cases and established this entity as a discrete form of ACTH-independent CS. The term nodular cortical adrenal hyperplasia (Kirschner *et al.* 1964) was initially used and, impressively, many terms were subsequently designated; ACTH-independent massive bilateral adrenal disease (Lieberman *et al.* 1994), massive macronodular hyperplasia (Strohm *et al.* 1994), giant MAH (Cugini *et al.* 1989), MAH (Faucz *et al.* 2014) and ACTH-independent macronodular adrenal hyperplasia (AIMAH) (Malchoff *et al.* 1989), which was recently replaced by the term primary bilateral macronodular adrenal hyperplasia (PBMAH) (Lacroix 2013) since it was shown that in some cases paracrine ACTH production contributed to cortisol secretion (Louiset *et al.* 2013).

Once considered a rare disease, PBMAH is now encountered with increasing frequency mainly due to the incidental detection of clinically mild or asymptomatic cases during abdominal imaging performed for unrelated reasons. Thus, currently, PBMAH is characterized by a high clinical heterogeneity, both with regard to the severity of cortisol excess and the morphologic appearance of the adrenals. In fact, the identification of genetically predisposed subjects who present with unilateral macronodules (Alencar *et al.* 2014) broadens the spectrum even further, making the diagnosis and management a challenge for physicians.

Clinical presentation, prevalence and diagnostic uncertainties

The majority of PBMAH cases have a sporadic presentation with a female preponderance but also familial cases are encountered (Findlay *et al.* 1993, Minami *et al.* 1996, Miyamura *et al.* 2002, Nies *et al.* 2002, Lee *et al.* 2005, Vezzosi *et al.* 2007) with an equal female-to-male ratio.

PBMAH detected during evaluation of clinical hypercortisolism, represents <2% of causes of CS (Stratakis 2008). However, only a minority of PBMAH cases present with clinically overt CS. Typically, hypercortisolism follows an insidious course and both tumor growth and cortisol excess progress gradually hampering the diagnosis in most cases by several years or decades. Many patients have a mild clinical picture remaining undiagnosed until abdominal imaging for an unrelated reason reveals bilateral adrenal enlargement. The estimated prevalence of adrenal incidentalomas is about 5%; 8–17% of them are bilateral (Vassiliadi & Tsagarakis 2011). The most common imaging appearance of bilateral incidentalomas is that of two well-defined adenomas, one on each adrenal (Fig. 1A), whereas the presence of multiple macronodules (Fig. 1B) is less often encountered. About one-third of patients with bilateral adrenal incidentalomas exhibit biochemical

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evidence of cortisol excess, depending on the applied criteria (Vassiliadi *et al.* 2011*b*). So far, it remains open whether all these cases represent different presentations of PBMAH, or whether the definition should be restricted to cases with multiple adrenal nodules and evidence of autonomous cortisol secretion. Since a comprehensive definition of PBMAH is currently lacking it is not possible to estimate its actual prevalence and clear diagnostic criteria are warranted in order to better characterize this entity and develop tailored treatment options.

Pathology

PBMAH is characterized macroscopically by the presence of macronodules that is, nodules larger than 1 cm. This size criterion is important for the distinction of macro- from micronodular hyperplasia. Micronodular hyperplasia is usually associated with the Carney complex and is referred as primary pigmented nodular adrenocortical disease (PPNAD) due to the presence of nodular pigment (Stratakis 2008). Micro-adenomatous hyperplasia without pigment and with hyperplasia of the surrounding zona fasciculata has also been described. In PBMAH, adrenal nodules are more than 1 cm and can reach 5 cm and more (Lacroix 2009, Malayeri *et al.* 2013). Multiple macronodules can be seen in each adrenal gland and adrenal diameter may reach 10–12 cm. In the most characteristic cases the adrenals are strikingly large, weighing more than 10–100 times the normal weight (Swain *et al.* 1998, De Venanzi *et al.* 2014). Initially, the presence of atrophy of the inter-nodular adrenal cortex was suggested as a criterion for identification of PBMAH, as opposed to the presence of both nodular and inter-nodular hyperplasia in ACTH-dependent adrenal hyperplasia. However, cases of PBMAH with inter-nodular cortex hyperplasia were subsequently described, and it is now established that two different histologic subtypes can be distinguished: PBMAH with atrophic inter-nodular cortex (type 1) and PBMAH with both nodular and inter-nodular tissue hyperplasia (type 2) (Stratakis 2008, Hsiao *et al.* 2009, De Venanzi *et al.* 2014). The nodules usually consist of two types of cells: large clear cells, also called spongiocytes, and smaller compact cells. In contrast to ACTH-dependent adrenal hyperplasia and cortisol-producing adrenocortical adenoma, where the two types of cells have positive immunoreactivity for both 3-beta-HSD and 17-hydroxylase, in PBMAH 3-beta-HSD is expressed almost exclusively in clear cells, while 17-hydroxylase is expressed in compact cells (Sasano *et al.* 1994, Wada *et al.* 1996). This differential enzyme expression is considered a characteristic trait of PBMAH and possibly relates to the distinct pattern of steroidogenesis that is observed in many patients with this disorder. In clear cells progesterone, produced by 3βHSD, may not be efficiently converted to 17-OH-progesterone leading to inefficient cortisol production, whereas selective 17-hydroxylase expression in compact cells may restrict the flux of cholesterol to Δ5-steroids explaining the reported increased DHEA secretion in some cases (Kirschner *et al.* 1964).

Pathophysiology

Although recent research has unraveled many aspects of PBMAH (Lefebvre *et al.* 2015), the pathophysiology of this disorder remains largely unclear, due to the perplexity of the mechanisms involved in the processes of adrenal growth as well as hormonal hypersecretion and, also, to the intrinsic heterogeneity of this disorder. Different pathogenetic processes may lead to similar phenotypes of adrenal enlargement with formation of nodules and various degrees of cortisol hypersecretion.

Hormonal hypersecretion in particular is linked to activation of the cAMP/PKA pathway (de Joussineau *et al.* 2012, Bonnet-Serrano & Bertherat 2018). Theoretically alterations at each step of the pathway may be involved, such as activating mutations of *MC2R* (Swords *et al.* 2004) and *GNAS* (Fragoso *et al.* 2003), or decreased activity of phosphodiesterases (PDE) (Vezzosi *et al.* 2012) resulting in reduced hydrolysis of cAMP and alterations of the expression and activity of PKA subunits (Bourdeau *et al.* 2006) (Hsiao *et al.* 2009, Lacroix 2009, Lacroix *et al.* 2010, Libe *et al.* 2010).

Additionally, in a significant proportion (77–87%) of patients with PBMAH, activation of the cAMP/PKA pathway may result through stimulation of aberrantly expressed G-protein-coupled receptors (GPCRs) by ligands other than ACTH (Lacroix *et al.* 2010, Hofland *et al.* 2013). Many ectopically expressed receptors have been identified, such as those for glucose-dependent insulinotropic peptide (GIP), catecholamine, V2 or V3 vasopressin receptor, serotonin (5-HT7 receptor) and angiotensin II (AT1) receptors. Receptors that are normally present in the adrenals, albeit at low levels (eutopic), such as vasopressin (V1-vasopressin receptor), luteinizing hormone/human/chorionic gonadotropin (LH/hCG-R), serotonin (5-HT4 receptor) and leptin (Hsiao *et al.* 2009, Lacroix *et al.* 2010, Libe *et al.* 2010, Hofland *et al.* 2013) may be overexpressed. A transcriptome study

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identified increased mRNA of additional GPCRs; motilin, gamma-amino-butyric acid (GABBR1) and a-2 adrenergic (ADRA2A) receptors (Assie *et al.* 2010). Responses to up to four stimuli has been reported in 50% of the patients indicating that multiple aberrant receptors may co-exist in each patient (Hofland *et al.* 2013, El Ghorayeb *et al.* 2015, St-Jean *et al.* 2018). The molecular mechanisms leading to ectopic GPCRs expression in adrenal tissue are not known. A recent study (Lecoq *et al.* 2017) documented GIPR expression through transcriptional activation of a single allele of the *GIPR* gene and in some cases somatic duplications and chromosomal rearrangements of the *GIPR* gene were detected.

Another intriguing contributing mechanism involves the local production of ACTH, by the steroidogenic cells themselves (Lefebvre *et al.* 2013, Louiset *et al.* 2013). Of note, aberrant hormone receptors have been shown to also regulate the paracrine secretion of ACTH creating an autocrine/paracrine loop that promotes adrenal growth and steroid secretion (Louiset *et al.* 2013, Cavalcante *et al.* 2018). Paracrine regulatory loops involving ligands such as serotonin or vasopressin have also been implicated in the pathophysiology of steroid hypersecretion (Lefebvre *et al.* 2013, 2015).

With regard to adrenal growth and tumor formation, it is noteworthy that activation of different elements of the cAMP/PKA pathway results in different forms of adrenal hyperplasia (Bourdeau & Stratakis 2002, Almeida *et al.* 2012). Constitutive activation of the MC2R has a minor, if any, role in the development of PBMAH. In the only two reported cases it was associated with adrenal hyperplasia in one (Hiroi *et al.* 1998, Swords *et al.* 2002, 2004), whereas two published studies failed to identify germline or somatic *MC2R* gene mutations in adrenal hyperplasia, adenoma or carcinoma (Latronico *et al.* 1995, Light *et al.* 1995, Fragoso *et al.* 2003). GNAS1 activation may result in adrenal nodule formation, not necessarily associated with cortisol excess, as seen in patients with McCune–Albright syndrome (MAS), but its role in subjects without MAS features is controversial. Only one study identified somatic activating mutations of *GNAS1* in three of five patients with CS due to PBMAH (Fragoso *et al.* 2003). Germline phosphodiesterase (*PDE11A* and *PDE8B*) defects have been initially associated with micronodular hyperplasia. Later, *PDE11A* variants, some of them with decreased enzymatic activity *in vitro*, were identified in 24–28% of patients with MAH (Libe *et al.* 2008, Vezzosi *et al.* 2012). Genetic abnormalities in the PKA subunits, especially the protein kinase A regulatory-subunit type 1A (PRKAR1A), result mainly in micronodular adrenocortical disease (Kirschner *et al.* 2000). Somatic mutations of the catalytic subunit (*PRKACA*) have been associated with unilateral cortisol-producing adrenal adenomas, whereas germline duplication of *PRKACA* were found in bilateral micronodular and macronodular adrenal disease (Beuschlein *et al.* 2014).

Other pathways, such as the wnt/b-catenin signaling (Bourdeau *et al.* 2004, Almeida *et al.* 2012, de Joussineau *et al.* 2012, Mazzuco *et al.* 2012, Lerario *et al.* 2014) as well as overexpression of genes such as WISP2, GSK3B, and CTNNB1 (Bourdeau *et al.* 2004, Horvath *et al.* 2006), have also been implicated in promoting adrenal growth in PBMAH. Interestingly, integrated transcriptomic and genomic analysis of nodules of different size from the same patient showed that smaller nodules harbor mainly metabolic derangements, whereas aberrant expression of oncogenic pathways characterize larger lesions, supporting the hypothesis of a progression to a more tumor-like profile with increasing nodule size (Almeida *et al.* 2011). Nevertheless, PBMAH is a benign condition with no reports of malignant transformation or metastasis.

We sought to investigate whether alterations in the glucocorticoid feedback sensitivity of the hypothalamus–pituitary–adrenal (HPA) axis might contribute to the development of bilateral lesions (Vassiliadi *et al.* 2015). To this end, we used the combined dexamethasone-CRH test, and observed responses in an unexpectedly high proportion (41%) of patients with bilateral adrenal incidentalomas, compared with only 2.6% of patients with unilateral adrenal lesions, regardless of the presence of cortisol excess. The only noted difference was that responders had larger adrenal lesions compared to non-responders. Although an explanation of this observation is largely speculative it provides some ground that HPA dysregulation, in the direction of HPA axis hyperactivity, may be potentially involved in adrenocortical hyperplasia. A potentially relevant recent study suggests a role for mutations of the *NR3C1* gene, encoding for the glucocorticoid receptor (GR), in adrenocortical hyperplasia (Vitellius *et al.* 2018). Heterozygous loss-of-function *NR3C1* mutations were identified in 5% of patients with bilateral adrenal incidentalomas associated with hypertension and/or cortisol excess without clinical CS. Based on these data, GR partial loss-of-function mutations represent a potential cause of bilateral adrenal hyperplasia, which, however, is clearly distinct from PBMAH in pathophysiology, since it depends, at least to some extent, on compensatory chronic pituitary ACTH overstimulation. These patients exhibit special features, such as increased UFC, unsuppressed ACTH

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levels and elevated post-dexamethasone cortisol levels without clinical stigmata of CS, consistent with a mild glucocorticoid resistance syndrome.

Genetics

As discussed, PBMAH may be associated with genetic alterations of the ACTH receptor *MC2R* (extremely rare), *PRKACA* and *PDE11A*. Rarely, PBMAH may be part of hereditary familial tumor syndromes including multiple endocrine neoplasia type 1 (*MEN1*), familial adenomatous polyposis (*APC*) and hereditary leiomyomatosis and renal cell cancer syndrome (fumarate hydrogenase, *FH*). Despite the fact that the majority of PBMAH cases have a sporadic presentation, it has recently been shown that a fair number of patients carry germline mutations of the *ARMC5* gene (Assie *et al.* 2013). Interestingly, tumorigenesis follows the 'two-hit' model since different nodules from the same patient carry the germline mutation but different second somatic *ARMC5* alterations. *ARMC5* mutations reduce the steroid secretory capacity of each cell, consistent with the early clinical observations that steroidogenesis is impaired in PBMAH, with many patients displaying lower than anticipated cortisol levels but increased secretion of steroid precursors. Despite ineffective steroidogenesis, cortisol secretion increases in proportion to the enlarging adrenal mass and this explains the usually indolent and slowly progressive course leading to late development of CS when the adrenals are massively enlarged. In the original study by Assie *et al.* (Assie *et al.* 2013), *ARMC5* mutations were present in 55% of their cohort. Subsequent studies confirmed that *ARMC5* mutations are common in patients with PBMAH (Faucz *et al.* 2014). They account for the vast majority of familial cases (13 out of the 16 reported families) (Zhu *et al.* 2013, Alencar *et al.* 2014, Gagliardi *et al.* 2014, Elbelt *et al.* 2015, Suzuki *et al.* 2015, Bourdeau *et al.* 2016, Yu *et al.* 2018), whereas in apparently sporadic cases (Assie *et al.* 2013, Alencar *et al.* 2014, Faucz *et al.* 2014, Espiard *et al.* 2015, Emms *et al.* 2016, Albiger *et al.* 2017, Yu *et al.* 2018) the frequency varies, depending on the characteristics of the studied cohort. Thus, the prevalence of *ARMC5* mutations is about 40% (28–55%) in patients with overt CS, but much less, about 11%, in patients with subclinical CS (Table 1). Morphologic criteria also vary between studies, which may impact on the reported prevalence; *ARMC5* mutated patients usually have larger adrenals and multiple macronodules (Albiger *et al.* 2017). In an unselected cohort of 39 patients with incidentally detected bilateral adrenal nodules, representative of the typical cases that present in the Endocrine Clinic, most of the patients had bilaterally single discrete adrenal nodules and only seven had multiple macronodules, including the one with a pathogenic *ARMC5* mutation (Emms *et al.* 2016).

Although the underlying mechanism governing the effects of ARMC5 inactivation on the process of tumorigenesis is not fully understood, there is evidence that it acts as a tumor-suppressor increasing apoptosis (Assie *et al.* 2013) and that its function relates to the wnt pathway (Alencar *et al.* 2014). The relationship between aberrant GPCRs and *ARMC5* mutation needs further exploration; cortisol responses to upright posture and serotonin agonists have been reported but, so far, no *ARMC5* mutations were found in cases of GIP-dependent PBMAH providing evidence that the presence of certain GPCRs may relate to specific genetic causes (Drougat *et al.* 2015). Germline *ARMC5* mutations have an emerging role in other neoplasias, such as intracranial meningiomas, suggesting that it may constitute a new inherited tumor syndrome (Elbelt *et al.* 2015).

Mutation of the endothelin receptor type A (*EDNRA*) gene has also been reported in two members of a family with PBMAH (Zhu *et al.* 2013) and one sporadic case, but a causative role needs to be proven by functional assays.

Table 1 Frequency of patients with ARMC5 mutations among apparently sporadic cases of PBMAH.

	ARMC5 mutated patients with overt CS % (n/total)	**ARMC5 mutated patients with 'subclinical' CS %** (n/total)	**ARMC5 mutated patients without cortisol hypersecretion**
Assie *et al.* 2013	58% (15/26)	50% (3/6)	–
Alencar *et al.* 2014	24% (5/21; 4 with overt and 1 with 'subclinical' CS)		–
Faucz *et al.* 2014	33% (7/21)	0	–
Espiard *et al.* 2015	41% (17/41)	16% (7/43)	0/8
Emms *et al.* 2016	–	5% (1/20)	0/19
Albiger *et al.* 2017	28% (9/32)	5% (1/19)	0/18
Yu *et al.* 2018	44% (4/9)	7% (1/14)	–
Overall	40% (52/129)	11% (13/115)	

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Diagnostic evaluation of PBMAH

The diagnostic approach depends on the clinical context. The clinical presentation of PBMAH is characterized by great heterogeneity ranging from patients with florid CS and unequivocal evidence of ACTH-independent hypercortisolism to completely asymptomatic subjects with normal hormonal testing identified as a result of abdominal imaging performed for unrelated to adrenal pathology reasons. Nowadays, an emerging clinical scenario involves MAH identified during investigation of genetically predisposed individuals. Therefore, the diagnostic evaluation of PBMAH requires (a) careful assessment of the imaging characteristics of the lesions, particularly in those cases that are incidentally discovered and (b) a thorough endocrine evaluation in order to delineate the functional activity of the disorder in conjunction with coexisting comorbidities.

Imaging characterization

The initially described cases of PBMAH had a quite striking imaging phenotype characterized by massively enlarged adrenals with multiple macronodules distorting the normal adrenal configuration. With the increasing use of imaging modalities, however, less impressive cases of bilateral adrenal enlargement are recognized. Bilateral adrenal enlargement may be seen in several forms (Fig. 1); either as multiple large macronodules on both adrenals or more commonly as one discrete macro-nodule on each adrenal. Bilateral adrenal lesions may be discovered incidentally on cross-sectional imaging or may be detected on targeted imaging when the endocrine workup suggests the presence of a functional adrenal mass.

Table 2 Causes of bilateral adrenal lesions.

Tumors of adrenal origin
• Adenomas/hyperplasia
• Pheochromocytomas (Fig. 2D)
• Adrenocortical carcinomas (rare)
• ACTH-dependent hyperplasia
◦ Cushing's disease (Fig. 2C) or ectopic ACTH secretion
◦ Congenital adrenal hyperplasia
◦ GR resistance syndrome
Non-adrenal tumors
• Metastases (Fig. 2B)
• Lymphoma
• Myelolipomas
Infections (tuberculosis, histoplasmosis blastomycosis)
Infiltrative lesions (amyloidosis)
Adrenal hemorrhage
Two different entities (Fig. 2A)

Regardless of the source of detection, detailed characterization is a crucial part of the diagnostic approach of bilateral adrenal lesions aiming mainly to exclude malignancy and also to aid in the diagnosis and management. The differential diagnosis of bilateral adrenal lesions is shown in Table 2.

The imaging modality of choice for the adrenals, and the most widely used, is the CT scan, which can provide information about the shape, size and density of the lesion on non-contrast images. Previously, size has been considered an important factor, mainly because of an increasing risk of malignancy with increasing tumor size. Lesions measuring more than 4 cm (an arbitrary cut-off) have been considered to harbor a high risk for malignancy. Recent evidence suggests, however, that the imaging characteristics are more important (Dinnes *et al.* 2016). Most benign lesions are rich in fat (lipid-rich) and, on non-contrast CT studies display low attenuation values, typically less than 10 Hounsfield Units (HU) (Dinnes *et al.* 2016). About 30%, however, of benign adenomas are lipid poor displaying higher attenuation values. In these cases, additional information may be obtained after administration of intravenous contrast and calculation of the absolute and relative contrast washout (Fassnacht *et al.* 2016). Benign lesions demonstrate rapid enhancement after contrast injection followed by rapid washout at delayed-phase images. Non-adenomatous lesions display less rapid washout or low contrast enhancement (Malayeri *et al.* 2013) with the exception of some pheochromocytomas, which however have higher attenuation values (Canu *et al.* 2019), and benign pseudocysts (Marty *et al.* 2018). In special situations other imaging modalities may be used. MRI scan is preferred in children and young adults to reduce the radiation burden, whereas FDG-PET/CT scan may be used when there is a substantial possibility of malignancy (i.e. patients with known cancer) (Fassnacht *et al.* 2016). On MRI, a decrease of signal intensity at the axial out of-phase images as compared to the in-phase images indicates high fat content and a benign lesion, an information that is similar to that of unenhanced CT. On FDG-PET/CT increased uptake may indicate malignancy, although functioning masses, including pheochromocytomas, may also demonstrate increased FDG uptake reducing the specificity of this modality to detect malignancy (Fassnacht *et al.* 2016). It should be noted that although the radiological criteria for CT and MRI are widely applied, they are not supported by high-quality data as shown in a recent meta-analysis (Dinnes *et al.* 2016). The most supporting evidence was for the non-contrast CT tumor density cut-off of ≤10 HU to exclude malignancy.

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Although there are currently no large series looking specifically into the imaging characteristics of PBMAH, it is evident from the reported cases that the abovementioned general recommendations may not always apply. In many cases, large macronodules up to 5 cm or more are encountered; in fact, size as a predictor of malignancy is not relevant in PBMAH since it is an invariably benign entity. Attenuation values above 10 HU (Bourdeau *et al.* 2016) and increased FDG uptake (Alencar *et al.* 2011) have been reported. On MRI imaging the adrenals are hypointense compared with the liver on T1-weighted images and often hyperintense relative to liver on T2-weighted images (Doppman *et al.* 2000, Lacroix 2009).

As emphasized in the recent recommendations of the European Endocrine Society (ESE) and European Network for the Study of Adrenal Tumors (ENS@T) (Fassnacht *et al.* 2016), during the investigation of bilateral adrenal masses each adrenal lesion should be assessed separately. This is important because in some occasions pathologically different lesions may co-exist either on the same adrenal or on each adrenal (Fig. 2A). In addition, imaging evaluation should always be complemented by a detailed endocrine workup. This is of particular relevance for pheochromocytomas since they may behave as adenomas in washout studies or for cases of bilateral metastases (Fig. 2B), hemorrhage or infiltrative diseases which may be suspected because of the presence of adrenal insufficiency.

Endocrine evaluation

It is important to establish that hypercortisolism results from adrenocortical hyperfunction, which is both independent from pituitary ACTH stimulation and bilateral.

In cases with clinically overt CS the initial endocrine evaluation is similar to that applied for the diagnosis of all forms of CS according to published guidelines (Nieman *et al.* 2008). In case of incidentally detected PBMAH, the recent ESE and ENS@T guidelines (Fassnacht *et al.* 2016) propose a comprehensive hormonal evaluation, including testing for primary aldosteronism in patients with hypertension and pheochromocytoma in all patients, as well as evaluation for autonomous cortisol secretion (ACS), which is the most common hormonal alteration. The term 'autonomous' is employed in the context of pituitary ACTH independency, but it should be taken into consideration that in many cases cortisol secretion is regulated by aberrant GPCRs and autocrine/paracrine loops. ACS follows a continuum and is best assessed using the 1-mg overnight dexamethasone suppression test. Post-dexamethasone cortisol values of ≤50 nmol/L (1.8 µg/dL) exclude ACS, values of >140 nmol/L (5 µg/dL) confirm ACS and values between 51 and 140 nmol/L (1.9–5.0 µg/dL) indicate possible ACS. Additional tests including midnight cortisol or 24-h urinary free cortisol may aid in establishing the degree of cortisol excess.

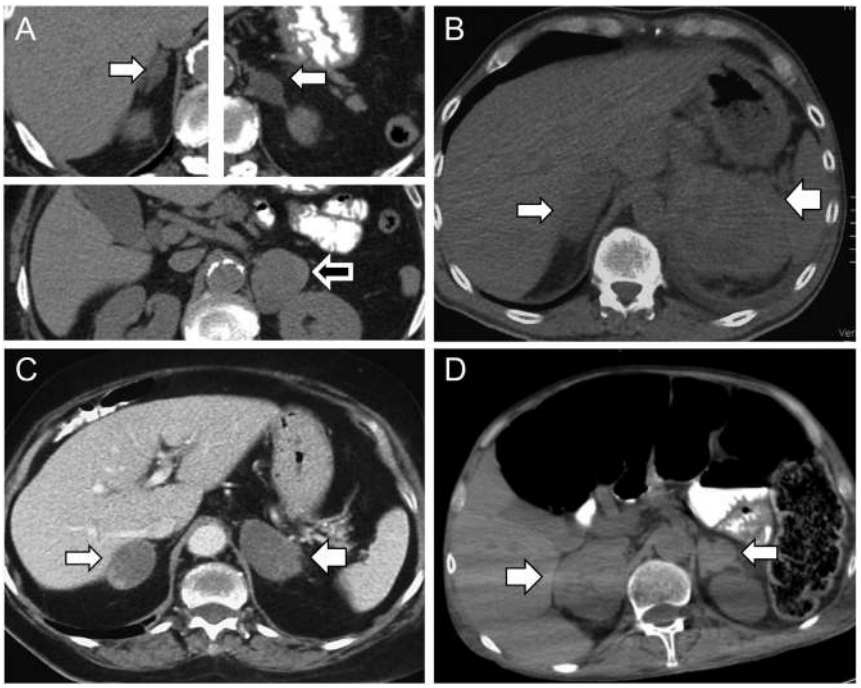

Figure 2
Causes of bilateral adrenal enlargement other than PBMAH. (A) Coexistence of bilateral adrenal adenomas (white arrows) with a left adrenal pheochromocytoma (black-filled arrow). (B) Bilateral adrenal metastases. (C) Bilateral adrenal masses in a patient with ACTH-dependent CS. (D) Bilateral ACTH-secreting pheochromocytomas.

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In case of biochemical hypercortisolism, with or without clinical CS, measurement of ACTH levels is important, not only to support the diagnosis of ACS, by demonstrating low or supressed levels, but also to exclude pituitary ACTH-dependency. Persisting ACTH stimulation may lead to adrenal cortex hyperplasia that is usually nodular (Fig. 2C) rather than diffuse (Smals *et al.* 1984) and in a few cases evolvement into varying degrees of adrenal autonomy may occur (Hermus *et al.* 1988). Although extremely rare, ACTH-dependent CS with bilateral adrenal masses may also be encountered in pheochromocytomas with ectopic ACTH secretion (Fig. 2D). Occasionally, the demonstration of ACTH independency may not be straightforward. ACTH levels may not be fully suppressed in PBMAH, especially in patients with mild cortisol hypersecretion. Additional reasons include ectopic ACTH production by the adrenal glands (Louiset *et al.* 2013) or in patients with GR loss-of-function mutations (Vitellius *et al.* 2018). The use of dexamethasone-CRH test may lead to the erroneous diagnosis of ACTH-dependent CS, since a number of patients may have positive responses (Vassiliadi *et al.* 2015).

From the early description (Kirschner *et al.* 1964) it was noted that PBMAH may be characterized by a distinctive pattern of steroidogenesis; markedly elevated steroid precursors as well as DHEA and other 3β-hydroxy-Δ^5 metabolites, and less impressive excretion of cortisol metabolites, indicating ineffective cortisol synthesis, a pattern that apart from normal excretion of tetra-hydro-deoxycortisol (THS) resembles that of adrenocortical carcinomas. This observation has been confirmed by subsequent studies that showed that although the main secretory product in PBMAH is cortisol, steroidogenesis may be ineffective and total daily cortisol secretion, as reflected by 24-h urinary free cortisol levels (UFC), may not be particularly high or may be even normal (Hsiao *et al.* 2009). Thus, the diagnosis relies mostly on demonstrating lack of cortisol suppression post dexamethasone and elevated night salivary or serum cortisol.

Given the distinct pattern of steroid excretion in PBMAH, caution should be taken in order to differentiate it from adrenocortical carcinoma and CAH. Bilateral adrenocortical carcinomas are extremely rare and in most cases the imaging phenotype (i.e. low HU, lack of significant growth in a short period of time) will aid in the differential diagnosis. Also, a slightly different pattern of steroid excretion exists and a useful future tool will be the analysis of a comprehensive urinary steroid profile measured by GC-MS or LC-MS (Arlt *et al.* 2011). Differentiation from CAH may be needed in some cases since increased 17-OH-progesterone levels, the hallmark of CAH, may be detected also in patients with PBMAH (Antonini *et al.* 2006). In such instances low or even supressed levels of ACTH and evidence of autonomous cortisol secretion differentiate PBMAH from CAH.

Investigation for the presence of aberrant GPCRs may also be part of the endocrine evaluation, either in the context of a research protocol or in order to identify patients with responses to specific receptors that would permit targeted treatment. The applied diagnostic protocols are fairly exhaustive. Documentation involves administration to patients of various stimuli in order to document release of serum cortisol (Lacroix *et al.* 2001). Many individuals have multiple responses to different hormonal signals (Hofland *et al.* 2013). Most patients respond to AVP and upright posture (related not only to AVPR but also to catecholamine and angiotensin II receptors) as well as metoclopramide (agonist of 5-HT4R) (Hofland *et al.* 2013). In case of positive responses administration of antagonists to the respective receptors blunts the stimulatory effect upon re-testing (Lacroix *et al.* 1997, 2010, Karapanou *et al.* 2013). Notably, there are only scarce data on performing these tests in healthy individuals (Reznik *et al.* 2004) as compared to PBMAH patients, thus the definition of what represents an aberrant response remains arbitrary. Another confounding factor may be the induction of cortisol elevation through ACTH secretion, either due to possible effects of the applied stimuli on the pituitary, due to stress of a given individual during the procedure or, especially for patients in whom ACTH levels are not fully suppressed, as a result of spontaneously fluctuating ACTH levels. For this reason, Lacroix *et al.* proposed to better conduct the tests under dexamethasone suppression (Lacroix *et al.* 2010). In a previous study of 33 patients with bilateral adrenal enlargement we noted that a significant number of tests would have been misclassified as positive or partial responses if they had not been repeated after dexamethasone suppression (Vassiliadi *et al.* 2011*a*). In this study we also observed a greater prevalence of responses in patients with bilateral macronodular hyperplasia (80%) compared to those with discrete bilateral adenomas (21.4%). It should be noted that not only PBMAH but also unilateral adrenocortical adenomas and carcinomas, may overexpress receptors responsive to these signals (Lacroix *et al.* 2010).

In addition to hormonal workup, screening for the presence of relevant cortisol excess comorbidities, such as diabetes, hypertension, osteoporosis is recommended, not only in order to provide appropriate treatment, but also

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because the presence of comorbidities weighs in favor of more aggressive management, such as surgery (Fassnacht *et al.* 2016).

Evaluation of genetically predisposed individuals

There are currently no criteria on whom to screen for a pathogenic mutation. After the discovery that a significant percentage of apparently sporadic cases are due to ARMC5 mutations, it became evident that family history is not a reliable indicator. Clinical, biochemical or imaging criteria may be more relevant; patients with cortisol excess and large multinodular adrenal glands may be more likely to harbor an ARMC5 mutation, but this needs to be proven. Genetic screening of family members of ARMC5-mutated patients resulted in recognition of asymptomatic or pre-symptomatic cases (Drougat *et al.* 2015). Considering that the onset of PBMAH is often delayed and that a high proportion of PBMAH patients exhibit subtle or no symptoms, genetic screening of the relatives of index cases is indicated to identify those at risk for the development of PBMAH. Further evaluation of mutated subjects involves biochemical testing for hypercortisolism and adrenal imaging using CT scan. In the largest family that has been published so far, a few old members had normal appearing adrenals on CT scan and normal cortisol after dexamethasone suppression despite carrying a germline ARMC5 mutation, suggesting that, PBMAH may present with incomplete or delayed penetrance. Thus, in case of negative results, it is prudent to re-evaluate the subject. Many questions need to be answered such as the appropriate tests, the frequency and extent of evaluation, the indication for surgical management, as well as the duration of follow-up.

Management of PBMAH

Surgery

Bilateral adrenalectomy

Bilateral adrenalectomy is generally considered the treatment of choice for patients with overt CS due to PBMAH. This choice, when made, needs to be based on good clinical grounds supporting that the benefits outweigh the adverse consequences (Guerin *et al.* 2016). There are several concerns regarding bilateral adrenalectomy; it necessitates lifelong adrenocortical hormone replacement and places the patient at risk for life-threatening adrenal crisis. Moreover, it practically converts mild endogenous hypercortisolism to mild exogenous hypercortisolism, due to the fact that currently many of these patients are over-replaced. For these reasons, it is more justified for patients with overt Cushing' s syndrome and is not advised for patients with mild or subclinical hypercortisolism (Fassnacht *et al.* 2016, Guerin *et al.* 2016).

Unilateral adrenalectomy

Unilateral adrenalectomy has recently been advocated as a therapeutic approach with lower complications compared to bilateral adrenalectomy. Although the data are limited, deriving exclusively from small retrospective studies (Lamas *et al.* 2002, Iacobone *et al.* 2008, Xu *et al.* 2013, Albiger *et al.* 2015, Debillon *et al.* 2015, Osswald *et al.* 2019), it appears that it offers clinical and biochemical benefits in the majority of cases with overt CS (Table 3). Initial remission is reported in more than 90% of cases, although the definition of remission varies greatly among the published studies. Clinical improvement and amelioration of cortisol-related comorbidities, such as obesity, hypertension or diabetes, are more consistently reported. With regard to hormonal alterations associated with hypercortisolism, UFC levels normalize in most patients while other biochemical abnormalities, such as raised midnight cortisol levels or suppression of cortisol after dexamethasone may persist in some patients, albeit at lower levels. It is noteworthy that adrenal insufficiency, despite the presence of residual hyperplastic adrenal, occurs in about one-third of patients, which is usually transient. The post-operative assessment of adrenal function in these patients may be tricky. The post-operative assessment of adrenal function in these patients may be tricky. The cosyntropin (Synacthen) test provides an indirect assessment of HPA axis relying on adrenal cortical atrophy due to chronic ACTH deficiency and there is a risk of falsely reassuring responses due to the remaining contralateral adenomatous cortical tissue. Therefore, it is better to rely on baseline cortisol levels and clinical evaluation. We also exploited the effectiveness of this approach in patients with bilateral adrenal masses and autonomous cortisol secretion without clinical evidence of overt CS (Perogamvros *et al.* 2015), a population where bilateral adrenalectomy is discouraged (Fassnacht *et al.* 2016). In contrast to the group of patients who were not operated, biochemical improvement and even complete normalization was observed in all operated patients.

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Table 3 Outcome of unilateral adrenalectomy in patients with overt CS due to PBMAH.

	No. of patients with overt Cushing's syndrome	Months follow-up	Choice of which adrenal to excise	Concordant prevalent uptake on scintigraphy	Initial remission	Adrenal Insufficiency postoperatively	Recurrence	Completion contralateral adrenalectomy
Lamas *et al.* 2002	4	30–137 (range)	Largest	No details	4	2	0	0
Iacobone *et al.* 2008	7	27–68 (range)	Largest	6/7	6	2	0	1
Xu *et al.* 2013	13	69 (median)	Largest	No details	12	2	0	1
Albiger *et al.* 2015	8	12–180 (range)	Largest	7/8	8	2	5	4
Debillon *et al.* 2015	15	39–105 (range)	Largest	8/8	15	6	2	1
Osswald *et al.* 2019	25[a]	50 (median)	Size and additional criteria[b]	No details	21	11	3 (out of 20)[a]	3
Overall	72			21/23	66/72	25/72	10/67	10/72

[a]Long-term follow-up was available for 20 patients; [b]additional criteria included cortisol gradients during adrenal vein sampling and iodine-131 or [^{123}I] iodometomidate scintigraphy.

Lasting clinical improvement in hypertension, hyperglycemia and osteoporosis occurred in patients who were operated, whereas comorbidities persisted in the conservatively managed group.

The decision on which gland to remove is not simple. Size was a main criterion in all studies and in most cases the largest adrenal was excised (Table 3), based on observations that the size of the adrenal lesion correlates with the degree of cortisol excess. A few studies applied additional criteria, such as the side of prevalent uptake in adrenal scintigraphy, which was almost invariably on the side of the largest adrenal mass, as expected, since uptake usually correlates with the volume of the gland (Guerin *et al.* 2016). Adrenal venous sampling has also been proposed as a reliable method to detect lateralization of cortisol excess as analogous to its use in aldosteronism but its utility is as yet undetermined due to the very limited number of investigated subjects (Young *et al.* 2008, Ueland *et al.* 2018, Acharya *et al.* 2019), most with subclinical hypercortisolism. It is a cumbersome invasive and demanding method, therefore not widely available, with a less than optimal success rate and requires measurement of epinephrine or preferably metanephrine (Dekkers *et al.* 2013) to document successful catheterization. According to the sparse available data (Young *et al.* 2008, Acharya *et al.* 2019) lateralization often coincides with the largest adrenal. Intuitively it may not be superior to deciding upon the size of the mass since in most cases of PBMAH cortisol is secreted from both adrenals, albeit asymmetrically, whereas it may be of better use in the occasional patient with a cortisol-secreting adenoma on one side and a contralateral non-functioning lesion.

Certainly, a major concern of this approach is the long-term sustainability of remission and whether some patients will eventually require contralateral adrenalectomy due to recurrence of hypercortisolism. From the published data the rate of recurrence and the necessity of completion adrenalectomy is fairly low, about 10–15%. It may occur, however, even 15 years following unilateral adrenalectomy and thus this rate may increase with longer follow-up. Nevertheless, owing to the usually indolent and slowly progressing hypercortisolism many patients will remain controlled for years, even decades, without the risk of adrenal crisis. In fact, in a recently published study (Osswald *et al.* 2019), none of the patients with BMAH submitted to unilateral adrenalectomy experienced an adrenal crisis in contrast to 38% of bilaterally adrenalectomized patients who experienced one crisis per year on average. However, three deaths (two attributed to infection and one sudden death)

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were recorded in PBMAH patients who had undergone unilateral adrenalectomy compared to none in patients with bilateral adrenalectomy. Of note, all deaths occurred in patients who were not biochemically controlled, emphasizing the necessity of close hormonal follow-up, besides clinical assessment, as well as the need to promptly proceed to further management in inadequately controlled subjects.

Medical options

The implication of aberrant receptors in the pathophysiology of PBMAH led to considerations for use of targeted treatment in patients with confirmed responses to specific receptors, such as octreotide, propranolol, long-acting GnRH agonist or AT-1 receptor antagonists for PBMAH associated with GIP receptors, b-adrenergic receptors, LH/hCG receptors or AT-1 receptors, respectively (Albiger *et al.* 2015). Somatostatin analog administration to inhibit the postprandial release of GIP effectively abolishes the postprandial cortisol surge and has been shown to lead to clinical and biochemical improvement, but this effect is transient due to desensitization of somatostatin receptors in GIP-secreting duodenal K cells. In contrast cases of LH/hCG-dependent and catecholamine-dependent PBMAH with long-term control of cortisol excess with long-acting GnRH agonist and beta-blocker, respectively, have been reported (Bourdeau *et al.* 2016, Albiger *et al.* 2017). Biochemical improvement, however, may not always result in clinical response (Albiger *et al.* 2015) and intolerance, especially to the usually high required doses of beta-blockers, may limit the usefulness of this approach (Bourdeau *et al.* 2016). Despite biochemical control tumor regression may not occur, supposedly due to accumulation over time of additional genetic defects that induce proliferation (Lacroix *et al.* 2010).

Steroid enzyme inhibitors are efficient and may be used with the same indications as with other forms of CS (Nieman *et al.* 2015). A compelling approach is to use steroidogenesis inhibitors in a manner that aims to restore normal cortisol rhythm, that is to lower evening and night cortisol levels without affecting morning levels, by administering timed evening doses of a short-acting compound, such as metyrapone (Debono *et al.* 2017). In a proof-of-concept study, this approach resulted in restoration of a normal circadian cortisol pattern and reduced the cardiovascular risk factor IL-6. Although an appealing concept, certainly more studies including larger patient numbers and more robust outcomes are required.

Conclusions

PBMAH is no longer a rare entity. With the universal increase in use of imaging and the introduction of whole-exome sequencing, it currently encompasses a wide spectrum of clinical phenotypes, inclusive of patients with manifest CS and massive macronodular hyperplasia, milder cases with less striking adrenals on imaging, as well as asymptomatic carriers of mutations in predisposing genes. From the limited existing data, it seems that there are differences among these phenotypes; the prevalence of ARMC5 mutations as well as the prevalence of aberrant receptors is lower in patients with bilateral solitary adenomas compared to those with multiple macronodules. The diagnostic investigation of PBMAH patients includes a thorough and systematic assessment of the imaging phenotype as well as endocrine investigation. The management of patients with PBMAH and concomitant autonomous cortisol secretion depends on various parameters that include the severity of biochemical abnormalities, the presence of comorbidities and the age of the patient. Bilateral adrenalectomy is only reserved for patients with severe forms of cortisol excess. In mild forms unilateral adrenalectomy may be considered. Although medical treatment is a possibility for patients with aberrant receptors, the number of patients that benefit from this intervention is rather limited. Medical therapy with anti-adrenal medications in a manner that aims to restore normal cortisol rhythm is a compelling and promising alternative. Undoubtedly, better characterization and, probably, subtyping of PBMAH will facilitate research and enable individualized approaches.

Declaration of interest

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