Differential Phenotype of Primary Bilateral Macronodular Adrenal Hyperplasia and Other Bilateral Adrenal Lesions With Associated Subclinical Hypercortisolism. Study of 98 Patients.

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Research Article

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Abstract

Purpose: To evaluate the prevalence of primary bilateral macronodular adrenal hyperplasia (PBMAH) in patients with adrenal incidentalomas (AIs) with subclinical hypercortisolism. Also to analyse the differential phenotype of patients with PBMAH compared to other bilateral adrenal lesions which do not meet PBMAH definition.

Methods: Retrospective study of patients with AIs diagnosed in our centre between 2013 and 2019 (n=730). Patients with bilateral disease and associated subclinical hypercortisolism (possible ACS or ACS) were included (n=98). Possible ACS and ACS were defined as a cortisol post-1mg-dexamethasone suppression test (DST)>1.8µg/dl but ≤5.0µg/dl and >5.0µg/dl. without specific clinical signs of Cushing´s syndrome, respectively. PBMAH diagnosis was established in patients with subclinical hypercortisolism, hyperplasia and bilateral adrenal nodules >1cm.

Results: PBMAH was confirmed in 31.6% of bilateral AIs with subclinical hypercortisolism. Patients with PBMAH presented a higher prevalence of ACS than non-PBMHA (OR 4.1, 95%CI 1.38-12.09, *P*=0.010), but differences disappeared after adjusting by tumour size and total adenomatous mass (adjusted OR 2.3, 95%CI=0.65-8.27 and 2.3, 95%CI 0.47-11.21, respectively). However, no significant differences in the cardiometabolic profile of both groups were observed. Tumour size and total adenomatous mass were significantly higher in PBMAH (30.2±12.16 vs 24.3±8.47, *P*=0.010 and 53.9±20.8 vs 43.3±14.62, P=0.023).

Conclusion: PBMAH is common in patients with incidentally detected bilateral adrenals lesions with associated subclinical hypercortisolism. The higher prevalence of ACS in PBMAH compared to non-PBMAH is associated with a higher tumour size and total adenomatous mass in PBMHA, but no differences in the cardiometabolic profile were observed between both groups.

Introduction

Primary bilateral macronodular adrenal hyperplasia (PBMAH) is a rare cause of Cushing's syndrome and is frequently diagnosed as bilateral adrenal incidentalomas (AIs) with modest autonomous cortisol secretion (MACE) [1]. It is a highly heterogeneous entity, both regarding the severity of cortisol excess and the morphologic appearance of the adrenals. Moreover, no consensus in its definition has been reached. Its reported prevalence is usually low [2][3][4][5][6] and it represents less than 2.0% of the cases of endogenous Cushing´s syndrome [7].

It is well known that 3–5% of the general population may harbour AIs [8], 15% of them bilateral. The latter may have associated possible autonomous cortisol secretion (ACS) or ACS in up to 40% [9][10]. Therefore, the actual prevalence of PBMHA is expected to be higher than that reported from series of patients with Cushing´s syndrome. Further, few data exist about the clinical, hormonal, and radiological features of this entity which may differ from those presented by other adrenal lesions associated with MACE that do not meet PBMHA criteria.

The aim of our study was to evaluate the prevalence of PBMAH in a large series of 730 patients with AIs and analyse the clinical, hormonal, and radiological phenotype of these patients. We then compared them with the features of patients with bilateral adrenal hyperplasia and bilateral adrenal nodules with possible ACS or ACS that do not meet the criteria for PBMHA definition (non-PBMHA).

Methods

Patient cohorts

Patients were selected from the ADRENAL INCIDENTALOMA database. Patients with AIs were identified through an electronic search in the Biochemical database of our hospital. All 1mg-dexamethasone suppression tests (DST) performed between 2013 and 2019 were identified. Only those patients who met the inclusion criteria to enter the ADRENAL INCIDENTALOMA database were included. The inclusion and exclusion criteria were previously published (5). These were patients between 18 and 90 years old, with incidentally discovered unilateral and/or bilateral AIs, of at least 10 mm in largest diameter. Exclusion criteria were: i) known diagnosis of hereditary syndromes associated with adrenal tumours; ii) chronic treatment with glucocorticoids or drugs that affect dexamethasone metabolism; iii) current treatment with oral hormonal contraceptives (treatment should be suspended for at least 6 weeks before performing the functionality study) and iv) AIs identified during the extension study of an extra-adrenal primary cancer. Only patients with MACE (possible ACS or ACS) and bilateral AIs with or without hyperplasia were included in this study, so patients with primary aldosteronism, pheochromocytoma and overt Cushing´s syndrome were excluded. Neither patients with missing information in the hormonal or radiological study were included (Fig. 1). The study was approved by the local ethics committee of our hospital (Approval date: 23th September 2019).

Clinical definitions

AI was defined as the presence of an asymptomatic adrenal lesion greater than 1 cm detected in imaging tests not performed in the context of suspected adrenal disease (such as the extension study of a primary extra-adrenal cancer, or other abdominal diseases) [11]. The definitions of hypertension, type 2 diabetes, obesity and dyslipidaemia were the same as a previous research shows [12]. Cardiovascular disease was defined as ischemic heart disease or heart failure, and cerebrovascular disease as transient ischemic attack or acute stroke. Moreover, the presence of active smoking was analysed.

For the MACE definition, the most sensitive criterion was used to optimize the identification of patients with AI with increased cardiometabolic risk, considering that there was possible ACS when the cortisol post-DST was > 1.8μg/dL and equal or lower than 5.0μg/dL in the absence of specific data of hypercortisolism [11], and ACS was confirmed when cortisol post-DST was > 5.0μg/dL [8]. The diagnosis of PBMHA was based on the presence of possible ACS or ACS due to bilateral adrenal hyperplasia associated with the presence of one or more AIs greater than 1 cm in each adrenal gland [1][13]. Those patients with possible ACS or ACS and bilateral AIs without hyperplasia or bilateral AIs < 1cm were classified as non-PBMHA.

Biochemical and hormonal study

All patients underwent a 1mg-DST (n = 98). Measurement of adrenocorticotropic hormone (ACTH) (n = 85), dehydroepiandrosterone sulphate (DHEA-S) (n = 62), late-night salivary cortisol (n = 76) and 24-urinary free cortisol (UFC) (n = 73) was performed based on physician judgment. The DST was repeated at the follow-up visit in 75 patients. Moreover, in 48 patients an intermediate DST between first and last visit was performed. Other hormones were also determined at the discretion of the treating physician. A biochemical study including fasting plasma glucose, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides, was performed in all patients. Besides, HbA1c was measured in 43 patients.

Study of aberrant receptors

Aberrant receptors study was performed on five patients. The protocol of our centre was performed on an outpatient basis over 4 consecutive or non-consecutive days. On the first day, 250 μg of cosyntropin was administered intravenously to serve as a reference for the cortical response capacity. This day, a wandering test was also performed, taking a baseline sample and repeating the extraction after 2 walking hours. The second day, a mixed standard food test was conducted with a meal of 450 Kcal with 46% of carbohydrates, 32% of lipids and 22% of proteins. The third day, an intravenous administration of 100μg of GnRH and an intravenous administration of 200μg of TRH were performed. The fourth day, the patient received an intravenous dose of 1 mg of glucagon, then 4 μg of desmopressin and, finally, an oral dose of 10 mg of metoclopramide. In all tests, baseline, and serial determinations of cortisol, aldosterone and DHEA-S were performed. A change of less than 25% of cortisol level was defined as no response, a 25–49% change as partial response, and a 50% or greater as a positive response to the test.

Laboratory assays

The following assays were employed: serum and urine cortisol were measured by chemiluminescence assays in Architect i2000 systems Abbott Diagnostics with an intra-assay coefficient of variation (CV) < 10%; the normal range for serum cortisol was 3,7–19,4 μg/dl and for urine cortisol was 140 μg/24h. ACTH was measured by chemiluminescence in Immulite 2000 Siemens system with an intra-assay CV of < 10%, and in Liaison XL Diasorin from 2019 with an intra-assay CV of < 10%. The normal range for ACTH was 9–46 pg/ml in Immulite systems and 4.7–48.8 pg/ml in Liaison XL systems. DHEA-S was measured by chemiluminescence assay in Immulite 2000 Siemens system with an intra-assay CV of < 15%. Salivary cortisol was measured in Cobas 6000 Roche by electrochemiluminescence with an intra-assay CV of < 10% and normal range lower than 5.74 nmol/L.

Radiological study

Abdominal computed tomography (CT) or MRI were performed in all patients at diagnosis (CT and MRI in 53 patients, only CT in 38 and only MRI in 7 patients). The size of the largest adenoma was included in the analyses. Moreover, we calculated the total adenomatous mass as the sum of the largest diameters of both adrenal incidentalomas [12]. Lipidic content was analysed in 85 patients, and the presence of necrosis, haemorrhage or other atypical radiological features were described in all AIs. During follow-up,

radiological studies were repeated in 89 patients (CT and MRI in 8 patients, only CT in 52 and only MRI in 27 patients).

In 15 patients, norcholesterol scintigraphy (potassium iodide was administered before the radiopharmaceutical administration) was performed, evaluating grade and laterality of the uptake.

Statistical analysis

All statistical analyses were performed with STATA.15. Shapiro-Wilk test was used to check the normality assumption and Levene's test to evaluate variance homogeneity. Categorical variables are expressed as percentages and absolute values. Quantitative variables are expressed as mean ± standard deviation or median and interquartile range (IQR) depending on the normal distribution of the variable. Odds ratios (with 95% confidence intervals) and mean differences were calculated as association measures using logistic regression model, and β coefficient using linear regression model. For variables following the normal distribution, we used Student's t test to compare differences between two groups. The chi-square test was performed for the comparison of categorical variables between independent groups. In all cases, a two-tailed P value < 0.05 was considered statistically significant.

Results

Differential phenotype of patients with PBMHA and non-PBMHA

Ninety-eight patients were enrolled in the study, 31 patients with PBMHA and 67 with no-PBMHA. Patients with PBMHA presented a higher prevalence of ACS compared to non-PBMHA (OR 4.1, 95%CI 1.38 to 12.09, $P = 0.010$). This finding could be explained by the higher tumour size and total adenomatous mass in patients with PBMHA than non-PBMHA, as differences in the prevalence of ACS disappeared after adjusted by tumour size (adjusted OR 2.3, 95%CI = 0.65–8.27) or by total adenomatous mass (OR 2.3, 95%CI 0.47 to 11.21) (Table 1 and Fig. 2). Moreover, a positive correlation was found between total adenomatous mass (r = 0.45, $P < 0.001$), although not with tumour size (r = 0.19, $P = 0.084$). Nevertheless, no significant differences were found in the cardiometabolic profile of both groups. The only observed difference in the hormonal profile was the presence of lower DHEAS levels in patients with PBMHA (Table 1).

Table 1

Baseline characteristics of patients with PBMHA and non-PBMHA

	PBMHA (n=31)	Non-PBMHA (n=67)	P value
% females	56.7	55.2	0.895
Age (years)	65.0 ±10.5	66.1±9.70	0.621
Active smoking (%)	39.3	47.0	0.493
BMI (kg/m2)	28.2 ±6.04	28.2 ±5.17	0.981
Systolic blood pressure (mmHg)	137.4±16.39	140.4±17.28	0.478
Diastolic blood pressure (mmHg)	77.4±9.39	79.8±8.17	0.257
Any comorbidity (%)	86.7	91.0	0.512
Hypertension (%)	71.0	65.7	0.603
Type 2 diabetes (%)	45.2	25.4	0.050
Dyslipidaemia (%)	54.8	55.2	0.972
Obesity (%)	25.9	35.9	0.461
Cerebrovascular disease (%)	0	1.5	0.494
Cardiovascular disease (%)	24.1	16.4	0.374
Possible ACS (%)	67.7	89.5	0.008*
Confirmed ACS (%)	32.3	10.5	0.008*
Fast plasma glucose (mg/dl) (n=97)	111.2±39.01	106.8 ±27.03	0.515
HbA1c (%) (n=43)	7.1±2.12	6.1 ±0.84	0.030*
LDL-c (mg/dl) (n=74)	106.8 ±39.93	122.9 ±39.13	0.110
HDL-c (mg/dl) (n=74)	50.5 ±15.47	53.5 ±15.79	0.463
Triglycerides (mg/dl) (n=92)	114.8 ±57.0	104.5±41.49	0.331
1mg DST (µg/dl) (n=98)	4.7 ±2.98	3.5 ±3.25	0.073
Repeated 1mgDST (µg/dl) (n=48)	6.6±3.62	5.2±6.00	0.315
UFC (µg/24h) (n=73)	50.5 ±39.17	60.8 ±74.62	0.446
UFCx2 (µg/24h) (n=50)	42.4±24.29	45.5±45.56	0.758
ACTH (pg/ml) (n=85)	23.6 ±48.57	14.0±9.70	0.150
DHEAS (µg/dl) (n=62)	337.1 ±202.9	494.6 ±377.31	0.039*

LNSC (µg/dl) (n=76)	5.2±3.15	5.0±4.75	0.850
Tumour rich in lipidic content (%) (n=87)	82.1	82.5	0.972
Tumour size (mm)	30.2 ±12.16	24.3±8.47	0.010*
Total adenomatous mass (mm)	53.9±20.8	43.3±14.62	0.023*
Calcification, haemorrhage or other atypical features (%)	25.9	20.7	0.590

Abbreviations: BMI= body mass index; DST= dexamethasone suppression test; LNSC= late-night salivary cortisol; UFC= urinary free cortisol.

*Makes reference to statistically significant results

Norcholesterol scintigraphy was performed in 9 patients with BMHA and 6 patients with non-PBMHA. In all patients, bilateral uptake was observed, with the exception of one patient with non-PBMHA with no uptake (Fig. 2).

Follow-up study

Two patients with PBMHA underwent unilateral adrenalectomy of the one with the largest adenoma, improving their cardiometabolic comorbidities and cortisol secretion. Two patients with non-PBMHA died (one due to an infection and the other with no identified cause). After a median follow-up of 33.7 (range 3.7 to 194.8) months, 7 of 58 patients (12.1%) with possible ACS developed ACS. 10 patients developed dyslipidaemia, 5 type 2 diabetes, 5 cardiovascular disease, 4 obesity, and 2 high blood pressure. No new cases of cerebrovascular events were reported. No differences in the risk of developing comorbidities or tumour growth were observed between PBMHA and non-PBMHA (Table 2).

Table 2
Follow-up differences between PBMHA and non-PBMHA

	PBMHA (n = 31)	Non-PBMHA (n = 67)	HR, 95% CI, p value
New comorbidities (%)	84.2 (n = 16)	90.7 (n = 39)	HR 0.8 [0.45–1.47], P = 0.493
New hypertension (%)	0%	11% (n = 2)	NC
New type 2 diabetes (%)	6.3 (n = 1)	9.5 (n = 4)	HR 0.4 [0.04–3.61], P = 0.370
New Dyslipidaemia (%)	15.4(n = 2)	29.6 (n = 8)	HR 0.5 [0.10–2.17], P = 0.289
New Obesity (%)	5.3 (n = 1)	9.1 (n = 3)	HR 0.7 [0.08–7.10], P = 0.787
New Cardiovascular disease (%)	5.0 (n = 1)	8.5 (n = 4)	HR 0.5 [0.06–4.88], P = 0.565
ACS development (%)	18.8 (n = 3)	9.5% (n = 4)	HR1.5 [0.35–7.01], p = 0.564
ΔFPG (mg/dl) (n = 92)	-1.3 ± 33.39	1.8 ± 23.10	P = 0.597
ΔHbA1c (%) (n = 25)	-0.5 ± 1.04	0.3 ± 1.03	P = 0.087
ΔLDL (mg/dl) (n = 48)	-9.8 ± 29.85	-12.7 ± 40.00	P = 0.809
ΔHDL (mg/dl) (n = 49)	1.9 ± 10.77	2.6 ± 9.39	P = 0.816
ΔTriglycerides(mg/dl) (n = 81)	4.9 ± 47.11	7.7 ± 55.08	0.821
ΔDST (µg/dl) (n = 74)	0.6 ± 2.47	-0.0 ± 1.64	P = 0.197
ΔUFC (µg/24h) (n = 30)	7.3 ± 41.21	-28.2 ± 33.36	P = 0.014*
ΔACTH (pg/ml) (n = 50)	-2.6 ± 16.00	-3.5 ± 11.61	P = 0.804
Δ LNSC (µg/dl) (n = 43)	2.7 ± 12.39	1.0 ± 8.84	P = 0.611
% ΔTumour size > 5mm (n = 51)	12.5% (n = 2)	14.3 (n = 5)	HR 0.7 [0.12–3.57], P = 0.614
ΔTumour size (mm) (n = 51)	0.4 ± 4.75	0.7 ± 3.98	P = 0.855
ΔTotal adenomatous mass (mm) (n = 51)	0.6 ± 6.66	0.6 ± 7.26	P = 0.997

Abbreviations: Δ = mean increased during the follow-up period (mean value in last visit – mean value in initial visit); BMI = body mass index; DST = dexamethasone suppression test; FPG = fasting plasma glucose; NA = not applicable; UFC = urinary free cortisol.

Results of the study of aberrant receptors in PBMHA

Aberrant receptors study was performed in 5 patients with PBMHA. It was negative in 2 patients, positive in the metoclopramide test in 2 patients (cortisol increase of 63% in one and of 40–50% in the other patient), and positive for metoclopramide and mixed food test in the other one (cortisol increase of 48% and 62%, respectively). The patient with positive mixed food test was treated with 120 μg/month of Lanreotide with no response, and one of the patients with positive metoclopramide test received amitriptyline with no response either. Two patients (one of the patients with negative study and one with positive response in metoclopramide test) underwent unilateral adrenalectomy.

Discussion

The prevalence of PBMHA in patients with AIs and with bilateral AIs and subtle hypercortisolism in our series was of 4.2% and 31.6%, respectively. The prevalence of PBMHA has not been determined in popular studies despite the fact that 15% of AIs are bilateral [6] and up to 40% of bilateral lesions are associated with ACS [9]. Song *et al.* reported a cohort of 1049 patients with AIs [14] and showed that only 1 patient (0.1%) had PBMHA. Lomte *et al.* [5] retrospectively analysed a cohort of 70 patients with bilateral adrenal masses and they found that only 3 patients (4.3%) harboured PBMHA. The prevalence of PBMHA in our cohort is higher than in those two other studies. This may be explained by the fact that in the cohort of Song *et al.* [14] the diagnosis of PBMHA was established by histology (the number of biopsied masses was low, only 12) and not on the basis of the secretory profile and radiological features. The differences with Lomte *et al.*´s study [5] can be attributed to the higher prevalence of familial pheochromocytoma (40%) and tuberculosis (27.1%) which is more prevalent in India than in our country.

Patients with PBMHA presented a prevalence four times greater of ACS than non-PBMHA, but these differences were related to a higher tumour size and total adenomatous mass of patients with PBMHA. The ACS prevalence in AIs is widely variable in the previous reported studies [12][15][16]. In two observational studies performed in Italian population, the prevalence of ACS varied from 9,2% in a multicentre cohort with more than a thousand patients with AIs [15] to 29% in a small group of 41 patients with AIs and typical adrenal adenoma image [16]. However, no previous study compared the prevalence of ACS in PBMHA vs. other bilateral AIs without PBMHA definition criteria. Therefore, we believe that larger prospective and multicentre studies should be carried out to confirm our findings.

Regarding tumour size and ACS risk, there is some discrepancy in previous studies about the prevalence of ACS and the size of AIs. In accordance with our findings, Vassiliadi *et al.* [9] found a significantly higher size and levels of cortisol after DST in bilateral AIs when compared with unilateral lesions. Besides, the ACS was diagnosed in more patients with bilateral than in unilateral AIs (41.5% vs 12.2%, respectively), even when various criteria were used to define the ACS. In another small retrospective study with 33 bilateral AIs (5 of them PBMAH), those subjects with positive responses to the aberrant receptor study had bigger adenomas, higher cortisol levels after DST, higher night cortisol levels and a tendency to lower levels of ACTH [17]. According to these results, it seems that the significant higher size of the

bilateral lesions could justify the more frequency of ACS in this group. Perhaps, the larger tumour size in bilateral than in unilateral AIs could be related to a longer duration of the disease in bilateral tumours, which may also explain the higher risk of ACS. On the other hand, Morelli *et al* [18] performed a prospective study with 175 patients with unilateral AIs and 38 with bilateral AIs (30 of them corresponding to PBMAH), and although the maximum diameter of the adrenal lesions was significantly higher in bilateral than unilateral forms, the magnitude of hypercortisolism was similar in both unilateral and bilateral AIs.

Despite the higher prevalence of ACS in patients with PBMHA than in non-PBMHA, no differences in the cardiometabolic risk were observed between them. To our knowledge, no previous study has analysed this issue. Previous AIs incidentalomas series focused in the differential phenotype of unilateral and bilateral AIs have described similar results [19][18][20]. Actually, the lack of association of bilateral AIs with ACS-related comorbidities was observed in some studies reporting an association between the prevalence of ACS and bilaterality of AIs [19][18]. This finding could be related to the presence of different sensitivity to hypercortisolism, in patients with bilateral AIs [21]. In this sense, Majnik *et al* [21] found that the prevalence of T2DM in patients with bilateral AIs (40.9%) was significantly higher compared with unilateral adrenal tumours (23.2%). This could be related with the higher prevalence of N363S variant in bilateral AIs suggesting a role in the pathogenesis in bilateral AIs. Even though, the studies that focused on the role of single-nucleotide polymorphisms (SNP) of the glucocorticoid (GC) receptor gene analysis in the risk of ACS in AIs found controversial results [21][22]. Some authors showed an association between GC receptor SNP and ACS risk [23] [24], other authors [22][21][25] found that the presence of SNP of GC receptor did not influence the development of Cushing's disease, or adrenal dependent Cushing´s syndrome. So, scanty data are available in patients with AIs to confirm the hypothesis that single polymorphic variant could influence cortisol secretion and risk of comorbidities, and even less about the differences in GC receptor SNP prevalence in bilateral and unilateral AIs.

Aberrant receptors study was positive in 60% of patients with PBMHA, being metoclopramide test the most frequently altered. Previous studies also described that aberrant receptors are highly prevalent in PBMHA [26][27][28]. Hsiao *et al*. [26] showed that the most frequent response to aberrant receptor expression tests in 14 patients with PBMHA was vasopressin (45.5%); Mircescu *et al*. [27], described AVP administration and upright posture test (in 3 of 6 patients with PBMHA) as the most affected one; Libé *et al.* [28] showed in a prospective study of 32 patients with PBMAH, that the most frequently observed responses were to upright posture (67%) and metoclopramide (56%) tests. Therefore, most studies, including ours, supported that vasopressin and serotonin receptors are probably the more prevalent functional receptors in PBMAH, which is in accordance with previous reports [29][30].

The presence of abnormal receptors can lead to innovative pharmacological therapies as alternatives to adrenalectomy, including suppression of the ligands or the use of specific receptor antagonists [27]. However, it should be noted that in none of the 2 patients of our study the medical treatment was effective. Libé *et al.* [28] found an inhibition of cortisol secretion by octreotide in the three Cushing's syndrome patients who positively responded to the mixed meal, in all the glucagon responsive patients,

and in 12 of 13 (92%) patients with ACS. In accordance with this, previous studies demonstrated a correction of hypercortisolism with chronic subcutaneous octreotide administration in patients with food-dependent Cushing's syndrome [31][32], and endogenous GIP levels inhibition is thought to be the possible underlying mechanism [17]. Moreover, long-term control of hypercortisolism has also been obtained by blockade of ectopic -adrenergic receptor with propranolol [27][33] and by inhibition of LH secretion with leuprolide acetate [27][34]. In contrast, Albiger *et al.* [35] reported, on the follow-up of 16 patients with PBMAH and Cushing's syndrome, one case with food-dependent CS treated with octreotide LAR and two patients with a positive postural test treated with propranolol, with a limited clinical response despite marked improvement in biochemical values. Thus, surgery is the current recommended therapy for PBMAH [36]. However, adrenal steroidogenesis inhibitors remain a valid option for nonsurgical candidates.

One of the major strengths of our study is that it includes a large number of subjects who were consecutively evaluated in our centre between 2013 and 2019, and the long-term follow-up. Moreover, this is the first study focusing on the differential phenotype of PBMHA compared to other bilateral AIs with associated MACE. The limitations are mainly related to the retrospective nature of the study, and the possible bias induced by individual decisions for adrenalectomy or medical treatment of comorbidities. Moreover, information in the last visit was not available in all patients, so a follow-up bias should be considered.

Conclusions

PBMHA is relatively common in patients with incidentally detected bilateral adrenals lesions with associated subtle hypercortisolism. The higher prevalence of ACS in PBMHA compared to non-PBMHA is related with the higher tumour size and total adenomatous mass in patients with PBMHA, but no differences in the cardiometabolic profile was observed between both groups.

Declarations

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Conflict of Interest:

The authors have no conflict of interest.

Ethical approval:

All procedures performed in the participants of the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Figures

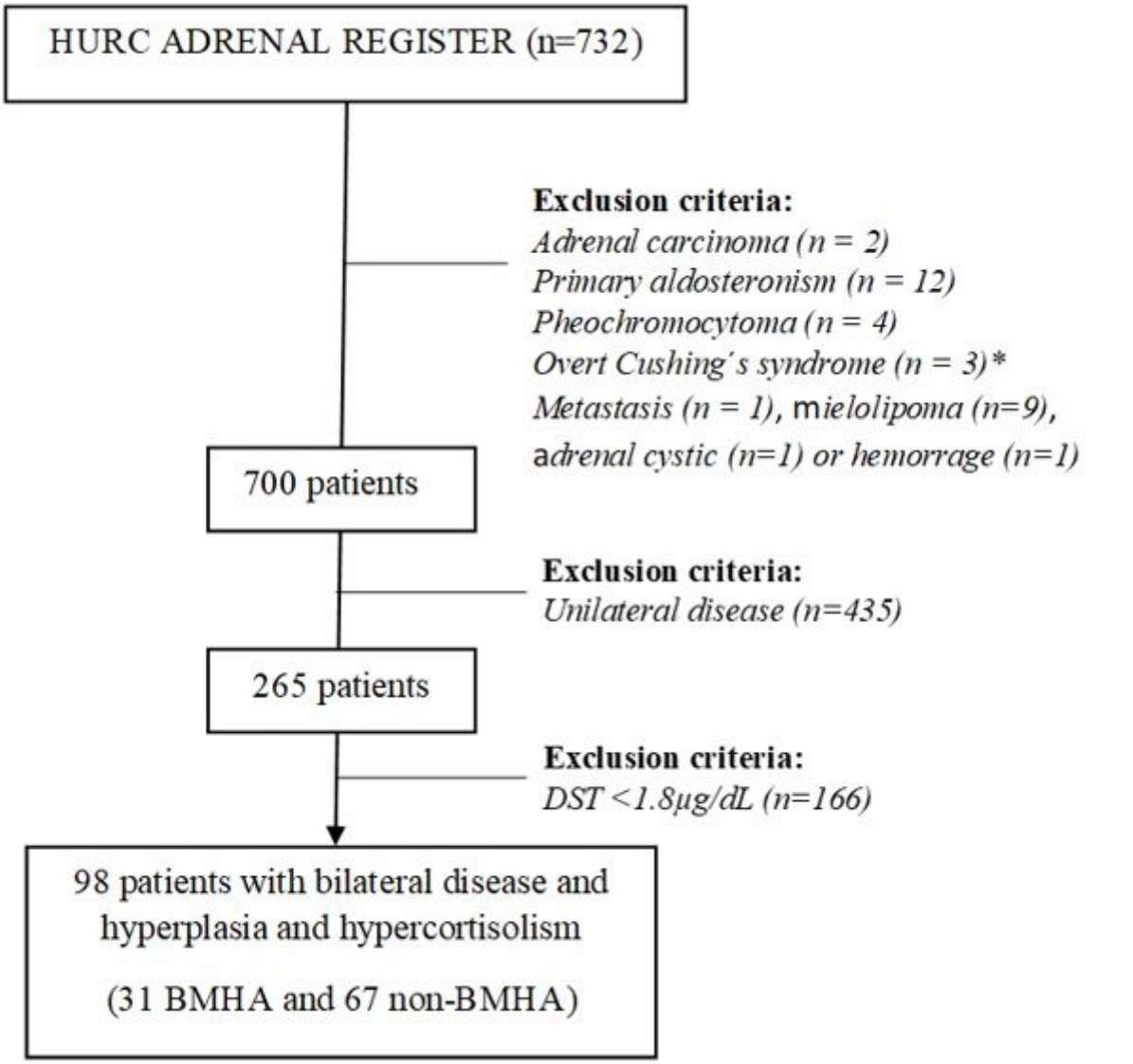

Figure 1

Study population and inclusion study population Abbreviations: AIs, adrenal incidentalomas; PBMHA= primary bilateral macronodular adrenal hyperplasia, DST=dexamethasone suppression test *Only 1 of the 3 patients with overt Cushing syndrome had PBMHA

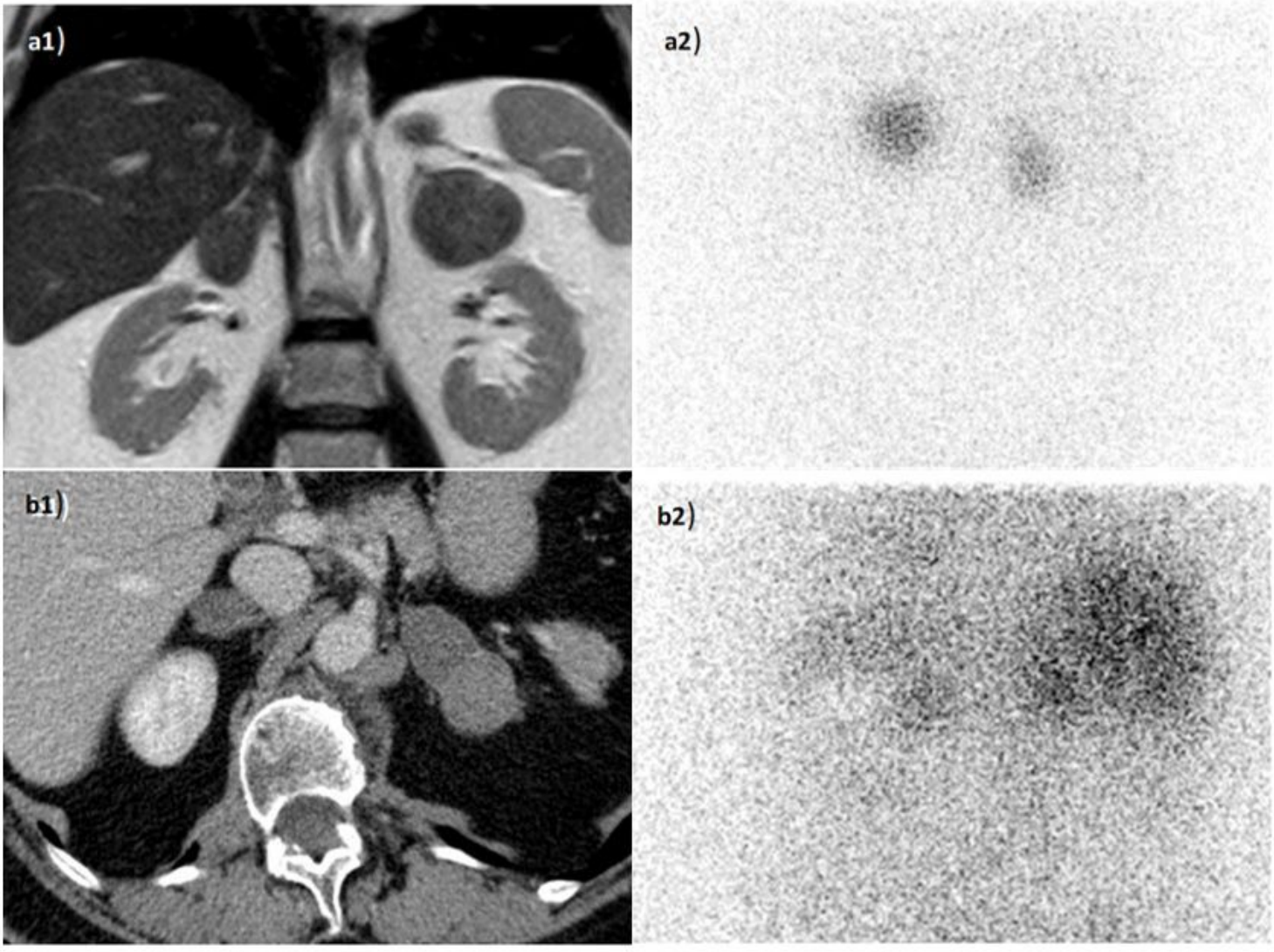

Figure 2

Radiological features of the patients PBMHA Figure a1 and a2 make reference to a woman patient of 56 y-o with PBMHA. a1) Coronal section of suprarenal MRI in a patient with primary bilateral macronodular adrenal hyperplasia (PBMHA) with two large adrenal nodules (of 24 and 34 mm) and in a2) norcholesterol scintigraphy with bilateral uptake, and of high intensity in the larger adenoma. Figure 2a and 2b correspond to a 59 y-o woman with PBMHA. B2) Axial section of MRI (two enlarged adrenal glands, greater in the left side) and b2) bilateral uptake in norcholesterol scintigraphy (higher in left side).