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Adrenal Vein Cortisol to Metanephrine Ratio for Localizing ACTH-Independent Cortisol-Producing Adenoma: A Case Report

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Abbreviations: ACTH, adrenocorticotropic hormone; AV, adrenal vein; AVS, adrenal vein sampling; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; PV, peripheral vein; SCS, subclinical Cushing syndrome.

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Abstract

Context: Finding the source of adrenocorticotropic hormone (ACTH)-independent cortisol-producing adenoma in the patients with subclinical Cushing syndrome (SCS) and bilateral adrenal nodules is sometimes challenging. Computed tomography (CT) and positron emission tomography are helpful, but adrenal venous sampling (AVS) is the gold standard approach. However, interpretation of AVS is important to improve the accuracy of decision-making for surgery. We report a case and review of the literature to assess the benefit of using adrenal vein cortisol to metanephrine ratio to determine the source of cortisol production in SCS and bilateral nodules.

Evidence Acquisition: Three authors searched PubMed for data on patients with SCS who had AVS procedure and measurements of cortisol and catecholamines.

Case Description: A 51-year-old woman with SCS and hypertension crisis presented to our clinic. Paraclinical investigations revealed that she had an ACTH-independent cortisol-producing adenoma and her CT scan showed bilateral adrenal nodules. After AVS, cortisol (high to low) lateralization ratio could not determine the source of cortisol production but the cortisol to metanephrine ratio localized the source to the left side, which included the larger nodule according to CT measurements. Left adrenalectomy led to clinical and paraclinical improvement.

Conclusion: There is a possibility of co-secretion of other steroids accompanied with cortisol in the setting of ACTH-independent SCS. Moreover, cortisol measurement alone

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and interpretation of AVS results based on cortisol values may not help lateralizing the source of cortisol production with bilateral adrenal nodules. Therefore, we suggest applying cortisol to metanephrine ratio with the same gradient (gradient > 2.3, highest to lowest concentration) when the source of cortisol production cannot be determined by cortisol lateralization ratio.

Key Words: subclinical Cushing, adrenal venous sampling, cortisol to metanephrine ratio

The increased use of imaging modalities has led to greater detection of incidental adrenal nodules. Adrenal incidentalomas are common, approximately 0.2% in the young and up to 7% in people over the age of 70 [1]. Physicians must differentiate between a nonfunctional versus hormonally active nodule and between benign versus malignant nodules, on the basis of imaging and biochemical workup. The majority of adrenal incidentalomas are benign and nonfunctional; however, subclinical hypercortisolism is present in approximately 5% to 30% of adrenal incidentalomas. Subclinical Cushing syndrome (SCS) is defined by the presence of biochemical autonomous cortisol production without overt symptoms or signs of hypercortisolism [2, 3] and other terms for this condition is mild autonomous cortisol excess/secretion (MACE/MACS), or autonomous cortisol secretion (ACS) [4]. Patients with SCS are at increased risk of comorbidities, such as diabetes, osteoporosis, vertebral fractures, hypertension, dyslipidemia, and obesity [5, 6]. Furthermore, surgical intervention with an adrenalectomy improves cardiovascular risk and comorbidities, such as hypertension, diabetes, dyslipidemia, and obesity [7-10].

It is sometimes difficult to ascertain the source of cortisol production in SCS. Although one would tend to think that the dominant nodule is the one making the excess cortisol, this is often not the case, and the assumption can result in surgical removal of the wrong adrenal. To localize the source of the excess cortisol production, both imaging methods and selective adrenal vein sampling (AVS) have been used. Adrenal scintigraphy using iodine-168-labeled 19-iodocholesterol [11-13] and fluorine-18-labeled fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET)/computed tomography (CT) scanning [14] are applied to localize the source of cortisol production. Selective venous sampling is another method, which is used for primary hyperaldosteronism [15], adrenocorticotropic hormone (ACTH)-independent Cushing syndrome [16, 17], SCS [18], and hyperandrogenism [19]. Although scintigraphy and AVS are reported as acceptable methods to localize the cortisol-producing adenoma [20], these methods often give discordant findings [21]. Furthermore, surgical approach based on the nodule size is used [16], but the accuracy of AVS for surgical decision-making can be very important [17, 21].

When AVS is used for evaluation of SCS patients, the measurements should be performed after an overnight fast and with low-dose (1-2 mg) or high-dose (8 mg) dexamethasone the day before the procedure to suppress ACTH and minimize the effect of stress on cortisol level. In addition, the correct catheter position is important, which is based on the adrenal vein (AV) to peripheral vein (PV) metanephrine ratio. An AV:PV metanephrine ratio greater than 12 indicates correct adrenal vein position and successful catheterization [17, 21]. There are 2 usual approaches to lateralize a cortisol-secreting adenoma. The AV:PV cortisol gradient is one method, with a ratio less than 3.3 not clinically significant, between 4.1 and 6.4 associated with adrenal hyperplasia, and greater than 6.5 consistent with cortisol-producing adenoma [17, 18]. The second approach involves a higher to lower cortisol gradient between the 2 adrenal veins. It has been reported that a gradient greater than 2.3 proves lateralization and less than 2 is associated with bilateral cortisol production [17, 21]. However, this is a very narrow window of cortisol ratios on which to base a surgical decision of which adrenal to remove, and it also does not account for a gradient between 2 and 2.3. We present a case to justify the role of cortisol to metanephrine ratio as an alternative approach in the situation where the current criteria cannot lateralize a cortisol-producing adenoma.

Methods

We (3 authors) searched PubMed using the keywords *subclinical Cushing syndrome*, *mild autonomous cortisol production*, *adrenal venous sampling* for literature that included patients with bilateral adrenal nodules and SCS who underwent AVS. We selected cases with information regarding cortisol and catecholamines (metanephrine, normetanephrine, epinephrine/adrenaline, and norepinephrine/noradrenaline) levels of peripheral and adrenal veins. We used the side-to-side adrenal vein cortisol concentration and cortisol to catecholamines ratio ([cortisol/catecholamines in dominant adrenal vein]/[cortisol/

catecholamines in nondominant adrenal vein]) to determine the lateralization of cortisol secretion. We measured the cortisol to catecholamines lateralization ratio in comparison with cortisol, cortisol/aldosterone, and cortisol/dehydroepiandrosterone sulfate (DHEAS) lateralization ratio. Patients were deemed to have an acceptable response to unilateral adrenalectomy if they developed adrenal insufficiency after unilateral adrenalectomy, serum cortisol less than 2 mcg/dL after dexamethasone suppression test, or improved clinically (hypertension, obesity, and diabetes).

Case Report

A 51-year-old Caucasian woman presented to the outpatient endocrinology clinic for evaluation of bilateral adrenal masses incidentally diagnosed on CT scan of her abdomen during workup for uncontrolled vaginal bleeding. Review of system was positive for intermittent flushing and hypertensive crisis. On examination, the patient's weight was 268 pounds and body mass index was 37.5 kg/m^2. The patient did not have classic features of Cushing syndrome, such as purple abdominal striae or plethora. Fasting glucose was 100 mg/dL and her glycated hemoglobin (HbA1c) was 5.5%. An abdominal CT scan from February 2019 revealed 2.3 cm right and 3.5 cm left side adrenal nodules (Hounsfield units < 10). On review of a previous CT scan of abdomen from 2017, bilateral adrenal lesions measuring <1 cm were noted. ACTH-independent mild autonomous cortisol secretion was confirmed with 1 mg overnight dexamethasone suppression test, which failed to suppress cortisol (2.9 mcg/dL), along with suppressed baseline ACTH and DHEAS. Plasma fractionated metanephrines, plasma renin activity, and plasma aldosterone concentration were normal (Table 1). Because there were bilateral nodules, AVS was pursued to differentiate between a bilateral versus unilateral source of cortisol excess prior to planning surgical intervention (Table 2). Due to concerns of cortisol excess confounding interpretation of AVS results, metanephrine levels were used to ascertain proper catheterization. Dekkers et al [22] has suggested that the AV:PV metanephrine ratio should be >12 if there is adequate catheterization. As shown in Table 2, the AV:PV ratio was 60 on the right and 24.5 on the left for this patient. Cortisol was detected from both sides, 24 µg/dL from the right, and 37.4 µg/dL from the left, demonstrating that there was not a predominant cortisol-producing nodule that was suppressing the contralateral side (cortisol gradient < 2). However, the cortisol to metanephrine ratio was 7.6 on the left, and 2.0 on the right. The left to right cortisol to metanephrine ratio of 3.8 was suggestive of dominant left side cortisol production. Hence, a decision to pursue unilateral left adrenalectomy was taken and the patient underwent a successful left adrenalectomy in September 2019. An ACTH stimulation test 1 week following surgery showed cortisol levels of 14.7, 21, and 19.1 mcg/dL at baseline, 30 minutes, and 60 minutes, respectively. After surgery, she was started on a physiologic dose of hydrocortisone. Four weeks post-adrenalectomy, blood pressure was controlled and her lisinopril was stopped. She lost approximately 6 pounds within 3 months after surgery and continued to remain normotensive without any antihypertensive. Hydrocortisone was gradually tapered off over 5 months post-adrenalectomy, as early discontinuation resulted in symptoms of nausea, abdominal

Table 1. Biochemical Studies Confirming Autonomous Cortisol Secretion From Adrenal Gland Before Surgery and Improvement After Surgery[1, 2, 18, 21]

Diagnostic Workups (Reference Interval)	Results	
	Before Surgery	After Surgery
1-mg overnight dexamethasone suppression test	2.9 (293), 3.3 (311)	< 2 (329), 1.1 (370)
Cortisol (<1.8 mcg/dL) [21]	6 and 7 months before surgery	6 and 12 months after surgery
(Serum dexamethasone level 140 – 295 ng/dL)		
4-mg dexamethasone suppression test for AVS, cortisol (mcg/dL)	2.9	
24-hour urine free cortisol (< 90 mcg per day) [18]	35	
Plasma ACTH level (9 – 52 pg/mL) [18]	6, < 5	17.5, 17.8
Plasma DHEAS level (35-430 mcg/dL)	32, 32	26, 23
Late-night salivary cortisol (< 0.145 mcg/dL) [1] or (< 0.17 mcg/dL) [2]	0.069, 0.070	0.098
Aldosterone level (normal 3-16 ng/dL)	< 1	
Plasma renin activity (0.25 – 5.82 ng/mL/h)	0.19	
Free normetanephrine/metanephrine (< 0.9/0.5 nmol/L)	0.38/<0.20	

Abbreviations: ACTH, adrenocorticotropic hormone; AVS, adrenal venous sampling; DHEAS, dehydroepiandrosterone sulfate; NA, not applicable.

Table 2. Results of Adrenal Venous Sampling After 4-mg Overnight Dexamethasone Suppression

Venous blood source	Metanephrine nmol/L	Normetanephrine nmol/L	Cortisol nmol/L	Aldosterone nmol/L	Cortisol lateralization ratio	Cortisol/ metanephrine ratio	Cortisol/ metanephrine lateralization ratio
Right AV 2.3 cm nodule	12	8.2	662	1.50	1.558	55.2	3.8
Left AV 3.5 cm nodule	4.9	3.7	1031	<0.028		210.4	
PV (femoral vein)	<0.2	< 0.2	80	0.194	NA	NA	NA

Abbreviations: AV, adrenal veins; AVS, adrenal venous sampling; NA, not applicable; PV, peripheral veins.
AV:PV metanephrine ratio > 12 indicates correct adrenal vein position and successful catheterization [22].
AV:PV cortisol gradient distinguishes cortisol-producing conditions. The gradient ≤3.3 suggests nonsecretory adenoma, between 4.1 and 6.4 is associated with adrenal hyperplasia, and >6.5 is consistent with adrenal adenoma [17, 18].
A side-to-side (high-side to low-side) adrenal vein cortisol gradient (cortisol lateralization ratio) >2.3 suggests unilateral cortisol overproduction, while a gradient ≤2.0 is considered as bilateral overproduction [17, 21]. However, the lateralization is toward the left adrenal nodule, based on the nodule size and cortisol/metanephrine ratio gradient.

pain, and diarrhea. After weaning off the hydrocortisone, an overnight 1 mg dexamethasone suppression test was normal (Table 1). A follow up CT scan of her abdomen in December 2019 showed a mild increase in size of the right adrenal nodule, from 2.3 cm in maximum dimension to 3 cm in maximum dimension, but the size remained stable at 3 cm in September 2020.

Discussion

This patient had SCS with bilateral adrenal nodules along with hypertension and obesity. She improved clinically and biochemically with unilateral adrenalectomy. SCS management poses a challenge, especially in the setting of bilateral adrenal mass. It is important to solve the puzzle of which adrenal gland should be removed and avoid permanent adrenal insufficiency secondary to bilateral adrenalectomy or surgical removal of the wrong adrenal.

The first step in the workup is confirmation of autonomous cortisol production. This can be challenging because patients with SCS do not demonstrate the clear and continuous high cortisol production typical of Cushing syndrome. For example, the absence of a diurnal rhythm of cortisol production is consistent with autonomous cortisol production from Cushing syndrome [23], specifically Cushing disease [24] and can be assessed by measuring midnight salivary cortisol, midnight serum cortisol, or urine free cortisol [2]. However, the evaluation of altered circadian rhythm of cortisol in the setting of autonomous production is not sensitive for detection of SCS [2, 25, 26]. The late-night salivary cortisol is more sensitive for detecting Cushing syndrome [27]. The measurement of urine free cortisol does not appear to be a sensitive screening test for SCS [2], since the increased cortisol production in SCS does not usually exceed the binding capacity of plasma for cortisol leading to urine free cortisol that is typically normal [2, 7].

The atrophy of contralateral adrenal gland in the setting of unilateral cortisol-producing adenoma is a relatively well-known event due to the decrease in ACTH production [28]. Applying techniques such as multidetector CT [28], cholesterol scintigraphy [13, 21, 29, 30], or PET-CT using ^{18}F-FDG [14, 31], may help lateralizing the cortisol-producing adenoma in a patient with bilateral adrenal mass. However, contralateral atrophy does not necessarily happen in patients with SCS. In addition, suppression of ACTH may lead to reduction in size of a contralateral cortisol-producing adenoma and hence create the appearance of a unilateral tumor on CT imaging, but with bilateral overproduction of cortisol. Ueland et al reported 9 patients with unilateral nodule on CT scan who had had bilateral cortisol production after AVS study [21].

Generally, AVS provides useful information to lateralize the source of cortisol production. However, we may face some limitations, which requires better understanding of AVS pitfalls, to avoid unnecessary adrenalectomy. Acharya et al reported 8 cases with ACTH-independent Cushing syndrome with bilateral adrenal masses and successful catheterization showed a cortisol lateralization ratio ≤ 2 in 7 cases, suggesting bilateral cortisol overproduction. However, 3 of 8 patients underwent unilateral adrenalectomy based on size of adrenal lesion and remission was seen in 1 case [16].

These data suggest that AVS is the best method for lateralizing the source of cortisol-producing adenoma but the current lateralizing criteria might not detect unilateral autonomous cortisol production in certain situations. Hypothetically, the proximity of the

catheter to the adrenal gland and co-secretion of other hormones, such as aldosterone and DHEAS, can affect cortisol concentration [17, 32]. The usual method to correct the dilution changes is using the ratio of cortisol to aldosterone, DHEAS, or catecholamines [33]. However, co-secretion of aldosterone and cortisol from different adrenals [34, 35] or same adrenal gland [32] can affect the result of the cortisol to aldosterone ratio. In addition, the incidence of adenoma with co-secretion of cortisol and aldosterone may be higher than earlier thought [36, 37]. Furthermore, AVS results showed that cortisol secretion from adrenal vein of patients without autonomous cortisol secretion has variation. Even measurement of the adrenal androgens, androstenedione and DHEA, may help in correcting the side-to-side gradient [38], but co-secretion of androgens in the SCS patient [32] will potentially interfere with this correction. The benefits of using catecholamine for correction is more important (Table 3), as co-secretion of aldosterone and other steroids [32] precludes applying the cortisol to aldosterone or cortisol to DHEAS ratio for interpreting the AVS outcomes. In addition, the shorter half-life of aldosterone (20 minutes) versus that of cortisol (60-70 minutes) is a limitation [33]. However, half-life for the fractionated metanephrines (60-105 minutes for free metanephrine, and 95 minutes for normetanephrine) [39] is longer than aldosterone and comparable to cortisol (60-70 minutes) [33]. Furthermore, with metanephrine and normetanephrine, especially metanephrine, plasma levels are less responsive to sympathoadrenal stimulation [40]. Other catecholamines, such as adrenaline and noradrenaline, have shorter half-lives (just a few minutes) [39, 41] and are not good options for overcoming the dilution changes of cortisol concentration. It is important to mention that pheochromocytoma alters the cortisol concentration [42] and co-secretion of catecholamines with cortisol may happen in the setting of an ACTH- or corticotropin-releasing hormone–producing pheochromocytoma [43], which is a rare condition that can easily be identified during biochemical workup for adrenal incidentaloma detectable by measuring fractionated catecholamines and ACTH. Therefore, side-to-side cortisol to metanephrine ratio comparison is useful for lateralization, because of the possible changes in concentration of cortisol during the AVS. We must also consider that applying dexamethasone before intervention can diminish the effect of stress during intervention [33, 44] on cortisol secretion by suppressing ACTH.

Based on our case experience and literature review (Table 3), we propose an algorithm taking into consideration cortisol to metanephrine ratio for selecting candidates for unilateral adrenalectomy (Fig. 1). Patients with unilateral adenoma and contralateral adrenal atrophy in the setting of clinical and paraclinical findings suggestive for SCS should receive unilateral adrenalectomy after considering the benefits and risks of surgical intervention. If a patient has bilateral adenoma, then AVS is the best method to confirm the source of cortisol production and avoiding unnecessary surgery. An AV:PV metanephrine ratio > 12 suggests successful catheterzation. An AV:PV cortisol gradient > 6.5 is consistent with cortisol-producing adenoma and a high to low cortisol gradient > 2.3 is compatible with unilateral cortisol-producing adenoma [17, 21, 33]. If the AV:PV cortisol gradient is < 6.5 or high to low cortisol gradient is < 2.3, we suggest measuring high to low cortisol/metanephrine ratio gradient. High to low cortisol/metanephrine ratio gradient > 2.3 suggests unilateral cortisol-producing adenoma. The proximity of the catheter to adrenal gland is a possible reason for the dilution differences and cortisol to metanephrine ratio may help to correct the dilution differences. Cosrtisol to aldosterone ratio [33] or cortisol to androrgen [38] ratio may also help lateralizing the source of cortisol production but because of the co-secretion of other hormones [32], which can affect the concentration of cortisol, aldosterone, and other plama steroids, making the interpretation of lateralization more difficult. However, the co-secretion of metanephrine and cortisol form an adrenal adenoma is rare [45-48] and associated pheochromocytoma can be ruled out with serum and 24-hour urine measurements. In addition, the current algorithm (Fig. 1) is based on limited experience with a few patients and needs validation in a bigger study.

Conclusion

AVS sampling is the best method to lateralize the source of cortisol production in SCS patients with suspected bilateral nodules or sources of cortisol. In certain situations, if the cortisol lateralization ratio does not help in lateralization of cortisol hypersecretion, then the cortisol to metanephrine ratio would be another option to find the major source of cortisol production and provide an option for unilateral adrenalectomy.

Table 3. AVS Results of the Patients With Cortisol-Producing Adenoma and Comparison of Cortisol/Catecholamine Lateralization Ratio With Other Ratio From the Literature

Reference	Patient	Cortisol lateralization ratio	Cortisol/catecholamine lateralization ratio	Cortisol/aldosterone lateralization ratio	Cortisol/DHEAS lateralization ratio	Outcomes
Papakokkinou et al. [33]	1. Case 1	2.5 R to L ratio	3.6 Cortisol/noradrenaline, 4.2 Cortisol/adrenaline	2.6	1.5	Adrenal insufficiency after right unilateral adrenalectomy, adrenal adenoma, CT Bilateral adrenal incidentaloma (R 32 × 18, L 14 × 8 mm)
	2. Case 7	1.65 L to R ratio	12.5 Cortisol/noradrenaline, 330 Cortisol/adrenaline	7.1	1.6	Adrenal insufficiency after left unilateral adrenalectomy, adrenal adenoma, CT Bilateral adenomas (R 22 × 15, L 64 × 50 mm)
	3. Case 8	1.53 R to L ratio	2.6 Cortisol/noradrenaline, 2.1 Cortisol/adrenaline	1.1	1	Bilateral adrenalectomy, PBMAH with bilateral nodules, CT Bilaterally enlarged adrenal glands (R 50 × 47, L 41 × 32 mm)
	4. Case 9	1.99 R to L ratio	2.6 Cortisol/noradrenaline, 2.6 Cortisol/adrenaline	0.82	1.5	Bilateral adrenalectomy, PPNAD, with normal CT
	5. Case 10	1.28 L to R ratio	1.44 Cortisol/noradrenaline, 2.7 Cortisol/adrenaline	0.97	1.28	Bilateral adrenalectomy, PPNAD, with normal CT
Lee et al. [34]	6. Case 1	4.62 L to R ratio	5.18 Cortisol/epinephrine	4	NA	Right side adrenalectomy for PA and left side adrenalectomy for SCS, adrenal insufficiency after second left side adrenalectomy
Maghrabi et al. [18]	7. Case 1	0.86 L to R ratio 1.16 R to L ratio	2.1 L to R Cortisol/epinephrine 0.5 R to L Cortisol/epinephrine	NA	NA	Left adrenalectomy, AIMAH (left adrenal mass 3.1 × 2.5 cm, right adrenal nodule 1.2 × 1.9 cm) improvement of blood pressure, but no satisfactory effects on blood sugar and lipid profile

Listed in reverse order of the year of publication [18, 33, 34].

The cortisol/catecholamine ratio is sometimes a better method to detect the source of cortisol production (Number 1, 2, and 7). The cortisol/aldosterone ratio and cortisol/DHEAS ratio are less sensitive than cortisol/catecholamine ratio in lateralizing the source of cortisol production.

Abbreviations: AIMAH, adrenocorticotropin independent macronodular adrenocortical hyperplasia; ACTH, adrenocorticotropic hormone; AVS, adrenal venous sampling; DHEAS, dehydroepiandrosterone sulfate; L, left; NA, not available; PBMAH, primary bilateral macronodular adrenal hyperplasia; PPNAD, primary pigmented nodular adrenocortical disease; R, right.

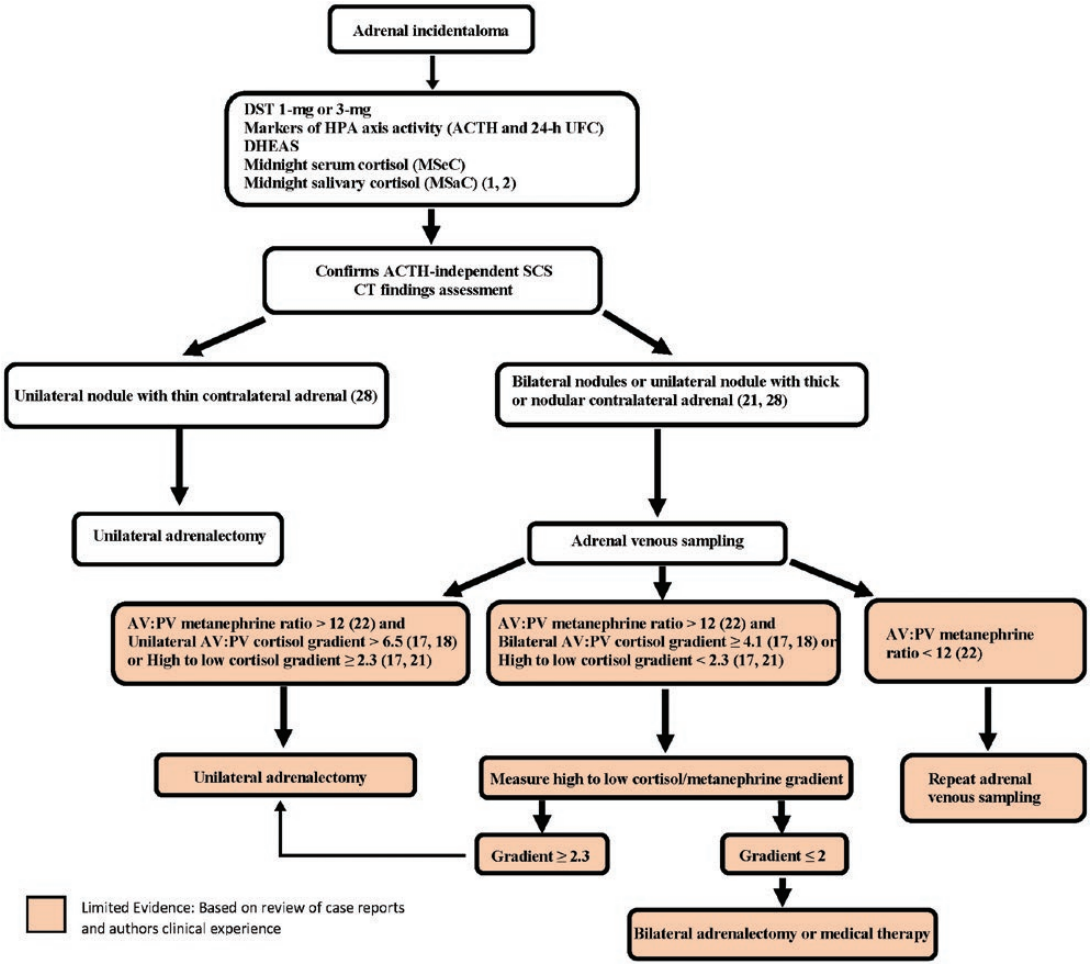

Figure 1. Proposed algorithm for diagnosis and confirmation of the source of cortisol-producing adenoma in subclinical Cushing syndrome (SCS) patients with adrenal incidentaloma (ACTH-independent cortisol secretion) [17, 18, 21, 22, 28]. First, it is important to confirm ACTH-independent SCS [1, 2]. Second, the source of excess cortisol production should be investigated by CT or AVS, when CT is not definitive [21, 28]. AVS results need interpretation, including confirmation of correct catheterization [22] and the presence of unilateral cortisol production based on the current evidence [17, 18, 21]. If using the current criteria for laterlaizing the source of cortisol production was not successful, then the cortisol/metanephrine ratio can be used to avoid unnecessary bilateral adrenalectomy, which is associated with increased mortality [16]. **Abbreviations**: ACTH, adrenocorticotropic hormone; AV, adrenal vein; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; HPA, hypothalamic-pituitary-adrenal; PV, peripheral vein; SCS, subclinical Cushing syndrome; UFC, urine free cortisol.

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Additional Information

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