Bojan Marković[1], Jovana Babić[1], Sanja Klet[1], Tamara Janić[1], Ivana Đurković[1], Mirjana Stojković[1,2], Biljana Nedeljković Beleslin[1,2], Jasmina Ćirić[1,2], Miloš Žarković[1,2]

# SEMPLOVANJE IZ ADRENALNIH VENA KOD BILATERALNIH ADRENALNIH TUMORA SA AUTONOMNOM HIPERKORTIZOLEMIJOM

**Sažetak**: Bilateralni adrenalni tumori predstavljaju retku patologiju, ali se sve češće otkrivaju zahvaljujući širokoj primeni dijagnostičkih vizuelizacionih procedura kao što su ultrazvuk, kompjuterizovana tomografija i magnetna rezonanca. Promene mogu da budu maligne ili benigne, ali i da imaju sposobnost autonomne proizvodnje hormona. Ranije je tuberkuloza bila jedan od vodećih uzročnika bilateralnih promena zbog nižeg socio-ekonomskog statusa i lošije higijene.

Kod pacijentkinje je dijagnoza hipertenzije postavljena u njenoj 38. godini, inicijalno je razmišljano u pravcu sekundarnih endokrinoloških uzročnika hipertenzije, tj. primarnog aldosteronizma. Kompjuterizovanom tomografijom su opisane obostrano uvećane nadbubrežne žlezde, sa više nodularnih promena apsolutnog i relativnog wash-out indeksa karakterističnog za adenom, od kojih je najveća veličine: desno 17x23 mm i levo 21x23 mm. Najniže vrednosti kalijuma su bile do 3.3 mmol/L. Navodi da joj se javljaju spontane modrice na rukama i nogama, kao i da se goji u stomačnom delu. Učinjeno je testiranje kojim je zaključeno da kod pacijentkinje postoji ACTH-nezavisni hiperkorticizam. Zbog precizne lokalizacije hiperprodukcije kortizola učinjeno je **semplovanje adrenalnih vena.**

## *Uvod*:

Bilateralni adrenalni tumori predstavljaju retku patologiju, a prethodne studije su pokazale da su promene uglavnom bile porekla metastaza udaljenih karcinoma. Međutim, razvojem dijagnostičkih procedura, poput ultrazvuka (UZ), kompjuterizo-

[1] Bojan Marković, Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Univerzitetski klinički centar Srbije, Odeljenje za bolesti štitaste žlezde

[2] Medicinski fakultet Univerziteta u Beogradu, Srbija

vane tomografije (CT) i magnetne rezonance (MR), povećana je stopa otkrivanja bilateralnih promena. U jednoj retrogradnoj studiji, od ukupno 18 pacijenata sa obostranim tumorima nadbubrežnih žlezda, 6 pacijenata je imalo feohromocitom, 4 pacijenta primarni limfom, 4 pacijenta nefunkcionalni kortikalni adenom, 2 pacijenta metastaze primarnih tumora i 1 *Cushing*-ov sindrom. U drugu etiologiju se ubrajaju tuberkuloza, infiltrativne i infektivne bolesti, kao mogući uzročnici ovog kliničkog entiteta.

U odnosu na unilateralne promene, učestalost bilateralnih tumora je ređa pojava, dok u etiopatogenezi genetski faktor igra značajnu ulogu u njihovom formiranju. Predstavljamo Vam pacijentkinju sa bilateralnim adrenalnim promenama i *Cushing*-ovim sindromom sa kliničkim pitanjem da li je reč o unilateralnoj ili bilateralnoj kortizolskoj produkciji.

## ***Prikaz slučaja***:

Pacijentkinja 48 godina, hospitalizovana na Klinici za endokrinologiju, dijabetes i bolesti metabolizma u cilju funkcionalnog ispitivanja nadbubrežnih žlezda. Zbog ranije postavljene dijagnoze hipertenzije u 38. godini i registrovane hipokalijemije do 3,3 mmol/L, razmišljano je u pravcu sekundarnih endokrinoloških uzročnika hipertenzije. U martu 2024. g. najpre ultrazvučno, a zatim i CT-om abdomena, opisane su obostrano uvećane nadbubrežne žlezde, sa više nodularnih promena apsolutnog i relativnog wash-out indeksa karakterističnog za adenom, od kojih je najveća veličina desno 17x23 mm i levo 21x23 mm. Primetila je da joj se javljaju spontane modrice na rukama i nogama, kao i da se goji u stomačnom delu.

Tokom hospitalizacije je učinjeno testiranje kojim je zaključeno da kod pacijentkinje postoji ACTH nezavisni hiperkorticizam (ACTH 0.4 pmol/L; DEX screening: 354 i 349 nmol/L) *dif. dg* poreklom iz jednog od opisanih adenoma nadbubrega ili AIMAH. Vrednosti ostalih hormona su bile uredne, dok je u jednom uzorku bio povišen dopamin (ALDO 154.6... 96.6 ng/L; PRA 22.90... 16.20ng/ml/h). Budući da je dokazana autonomna produkcija kortizola, indikovano je operativno lečenje, ali u cilju lokalizacione dijagnostike kortizolske hipersekrecije najpre je učinjeno adrenalno vensko semplovanje (Tabela 1 i 2). U fizikalnom nalazu bez osobitosti, osim prisustva 3 hematoma na donjim ekstremitetima uz centripetalnu gojaznost. Nema druge kliničke znake *Cushing*-ovog sindroma.

U ličnoj anamnezi navodi da leči astmu od 2012. godine, koja je stabilna sa terapijom, ali u periodu od godinu dana nije uzimala kortikosteroidnu terapiju. Porodična anamneza je pozitivna za hipertenziju. Bivši pušač.

**Tabela 1. Rezultati laboratorijskih analiza**

| Parametar | Rezultat | Parametar | Rezultat |
|---|---|---|---|
| WBC | 7.8 | PLT | 373 |
| RBC | 4.51 | CRP | 2.5 |
| HGB | 136 | Glc | 5.0 |
| HCT | 0.415 | **HbA1c** | **5.6** |
| MCV | 92.0 | Urea | 2.8...5.0 |
| RDW | 14.7 | Cr | 61...62 |
| GFR | > 60 | Mokraćna kiselina | 366 |
| Bilirubin | 5.4 | Bilirubin-D | 1.8 |
| Protein | 70 | Albumin | 43 |
| **Na** | **138...142...141** | **Na-ureza** | **169.3mmol/24h** |
| **K** | **3.1...4.1...4.2...4.4** | **K-ureza** | **63mmol/24h** |
| Cl | 97...102 | Ca | 2.39 |
| PO4 | 1.08 | Mg | 0.76 |
| **HCO3** | **23** | **Osm. seruma** | **288mOsmol/kg** |
| AST | 21 | ALT | 20 |
| ALP | 55 | g-GT | 8 |
| Holesterol | 5.72 | HDL | 1.76 |
| LDL | 3.49 | Trigliceridi | 1.04 |
| Proteinurija | 72mg/24h | Albuminurija | 5.4mg/24h |
| Vitamin D | 40 | PTH | 44 |
| TSH | 1.370 | fT4 | 17.4 |
| At-TPO | 6.00 | At-TG | 12.00 |
| FSH | 4.4 | LH | 2.8 |
| E2 | 1280 | Testosteron | 0.61 |

| | | | |
|---|---|---|---|
| DHEA-S | 0.2 | βhCG | < 2.3 |
| **ACTH** | **0.4pmol/L** | **Profil kortizol** | **413...304...339nmol/L** |
| **DEX screening** | **354...349nmol/L** | AFP | 2.9 |
| CEA | 2.4...< 1.73 | CA 125 | 18...14 |
| CA 19-9 | 6 | Cyfra 21-1 | 0.7 |
| HE4 | 55.1 | ROMA indeks (pre) | 9.17 |
| ROMA indeks (meno) | 12.04 | NSE | 7.4 |
| Urin | b.o. | **Osmolalitet urina** | **819mOsmol/kg** |
| ADR | 8.5...13.2 | NOR | 511.7...246.7 |
| DOP | 3748.7...1170.4 | CgA | 99.2 ng/mL |
| 17-OH Pg | 1.8 | Androstenedion | 0.3 ng/mL |
| Aldo/PRA | 0,6 | | |

**Tabela 2. Vrednosti kortizola dobijenih u semplovanju adrenalnih vena**

| Lokalizacija uzorkovanja | Vrednosti kortizola (nmol/L) |
|---|---|
| Periferija | 587 |
| Ispod *V. Cava* | 566 |
| Iznad *V. Cava* | 515 |
| *V. suprarenalis sinistra* | 2583 |
| *V. suprarenalis dextra* | 477 |
| *CAV/Cperipheral* sin | 4.56 |
| *CAV/Cperipheral* dex | 0.84 |
| CRL | 5.42 |

## *Diskusija*:

*Cushing*-ov sindrom (*CS*) podrazumeva autonomnu endogenu hipersekreciju kortizola, koja može da bude ACHT zavisnog i nezavisnog oblika. U kliničkoj praksi postoje stresori poput fizičkih, mentalnih i metaboličkih poremećaja koji dovode organizam u stanje hiperkortizolemije, tj. *pseudo-Cushing*-ov sindrom, te je neophodno da se utvrdi uzrok povišenih vrednosti kortizola. Najčešći dijagnostički testovi koji se koriste su: određivanje dnevnog ritma kortizola i slobodnog kortizola u 24h urinu, prekonoćni supresioni test sa 1mg deksametazona. U slučaju da su dobijeni rezultati nekonkluzivni, evaluacija *CS* treba da se dopuni analizom salivarnog kortizola, uz dodatne supresione ili stimulacione testove.

ACTH nezavisni oblik predstavlja endogenu hiperkortizolemiju iz primarnih lezija nadbubrežnih žlezda (adenom, karcinom, makronodularna-*MAH* ili mikronodularna adrenalna hiperplazija). Pored hipersekrecije kortizola, ove promene mogu pojačano da luče i androgene, što nas najpre navodi da razmišljamo u pravcu karcinoma, ali to nije bio slučaj kod naše pacijenkinje. Postoji redak oblik *CS*, poznatiji *McCune-Albright* sindrom, kojeg karakteriše prerani pubertet nastao kao posledica adrenalne hiperfunkcije.

Pored gorenavedenog, etiologija bilateralnih promena nadbubrežnih žlezda može ukazati na: 1) metastaze iz dojke, pluća, debelog creva, jednjaka, itd; 2) krvarenje; 3) kongenitalnu hiperplaziju; 4) feohromocitom; 5) infiltracione bolesti. Zato je važno utvrditi etiologiju promena u nadbubrežnim žlezdama, kao i da li imaju autonomnu aktivnost, u slučaju hipersekrecije da li postoji jednostrana ili obostrana funkcionalnost.

Kao kod naše pacijentkinje, u literaturi kod bilateralnih nadbubrežnih promena i *CS* nezavisnim od *ACTH*, uzroci hiperkotizolemije mogu da budu *MAH*, bilateralni adenomi ili pojedinačni adenom sa kontralateralnim nefunkcionalnim adenomom. U cilju utvrđivanja lokalizacije hipersekrecije, neophodno je da se uradi semplovanje adrenalnih vena ili scintigrafija 131I-NP-59.

Adrenalno vensko semplovanje (*AVS*) je invazivna dijagnostička procedura kojom se plasira mali kateter venskim putem do nadbubrežnih žlezda. Najčešće mesto punkcije je *v. femoralis,* u slučaju da je taj put onemogućen pristupa se kroz regiju vrata *v. jugularis*. Prvo, da bi se AVS rezultati tumačili neophodno je isključiti nepravilno uzorkovanje dobijenih vrednosti kortizola. Budući da se uzorci kortizola, osim adrenalnih vena (*CAV*), dobijaju iz *v. cave inferior* (*Cperipheral*), računa se indeks selektivnosti (*SI=CAV/Cperipheral*), u kojem vrednosti CAV treba da budu veći nekoliko puta od kortizola u *v. cave inferior*. Preporučeni indeks (*SI*) treba da bude >2.

Inicijalno, kod naše pacijentkinje registrovana je hipokalijemija, uz podatak o ranoj dijagnozi hipertenzije, što je prethodno kliničare prvo navelo da razmišljaju u pravcu aldosteronizma, koji je isključen dobijanjem vrednosti *ALDO/PRA*, a fenomen hipokalijemije u *Cushing*-ovom sindromu je objašnjen delovanjem kortizola

na mineralokortikoidne receptore. U nekim slučajevima sa bilateralnim promenama nadbubrežnih žlezda može da postoji koegzistirajuća produkcija kortizola i aldosterona iz jednog adenoma ili iz različitih adrenalnih tumora, ali i jednostrana produkcija aldosterona sa bilateralnom autonomnom produkcijom kortizola. Uzimajući u obzir navedeno, *AVS* zauzima značajno mesto u dijagnostici.

Autori *Young et al.* u radu *The clinical conundrum of corticotropin-independent autonomous cortisol secretion in patients with bilateral adrenal masses*, preporučuju da merenje adrenalina takođe daje podatak o uspešnosti izvedene procedure, te tako koncentracija adrenalina u adrenalnoj veni treba da bude za 100pg/ml viša od uzorka u *v. cavi inferior* (*AV–IVC* >100 pg/ml), da bi se procedura smatrala uspešnom.

U ovom slučaju autonomna sekrecije kortizola se procenjuje indeksom lateralizacije, odnosno meri se nivo kortizola u adrenalnim venama i na perifernim venama (*CAV/Cperipheral*). Ako je odnos kortizola među nadbubrežnim žlezdama ≥ 2,3, to nam ukazuje na jednostrano pojačano lučenje kortizola, a odnos ≤ 2 ukazuje na bilateralnu hipersekreciju kortizola.

## *Zaključak*:

U ovom prikazu slučaja se najverovatnije radi o **bilateralnoj makronodularnoj hiperplaziji**, koja se u literaturi opisuje kao više čvorova većih od 1cm, uz uvećanje mase nadbubrežnih žlezda. S obzirom na dobijene rezultate semplovanja adrenalnih vena, postoji autonomna kortizolska sekrecija. Međutim, ne može se decidirano tvrditi da se radi o unilateralnoj ili bilateralnoj produkciji kortizola jer rezultati ukazuju da je kortizol iz desne nadbubrežne žlezde ili suprimovan ili neadekvatan usled tehničkih nedostataka **(*CAV2/ Cperipheral2*=0.84).**

Budući da se kod pacijentkinje radi o bilateralnim promenama nadbubrežnih žlezda i da je leva žlezda veća, veličine 21x23 mm, u ovom trenutku savetovana je levostrana adrenelektomija.

## *Literatura*

1. Young Jr, W. F., du Plessis, H., Thompson, G. B., Grant, C. S., Farley, D. R., Richards, M. L., Erickson, D., Vella, A., Stanson, A. W., Carney, J. A., Abboud, C. F., & Carpenter, P. C. (2008). The clinical conundrum of corticotropin-independent autonomous cortisol secretion in patients with bilateral adrenal masses. *World Journal of Surgery, 32*(5), 856–62.
2. Laurent, I., Astère, M., Zheng, F., Chen, X., Yang, J., Cheng, Q., & Li, Q. (2019). Adrenal venous sampling with or without adrenocorticotropic hormone stimulation: a meta-analysis. *The Journal of Clinical Endocrinology Metabolism, 104*(4), 1060–1068.

3. Newell-Price J, Bertagna X, Grossman AB & Nieman LK 2006. Cushing's syndrome. Lancet 367: 1605–1617.
4. Young WF Jr, du Plessis H, Thompson GB, Grant CS, Farley DR, Richards ML, Erickson D, Vella A, Stanson AW & Carney JA et al. 2008. The clinical conundrum of corticotropin-independent autonomous cortisol secretion in patients with bilateral adrenal masses. World Journal of Surgery 32: 856–862. 10.1007/s00268-007-9332-8
5. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr & Montori VM 2008. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. Journal of Clinical Endocrinology and Metabolism 93: 3266–3281.
6. Daunt N 2005. Adrenal vein sampling: how to make it quick, easy, and successful. Radiographics, 25: S143–S158.
7. Zhou J, Ye D, Wu M, Zheng F, Wu F, Wang Z, Li H. Bilateral adrenal tumor: causes and clinical features in eighteen cases. Int Urol Nephrol. 2009; 41(3): 547–51.
8. Mundada, O.P., Aron, M., Sivaramakrishna, B. et al. Bilateral adrenal metastases from a primary hepatocellular carcinoma. Int Urol Nephrol 35, 303–305 (2003).

Bojan Marković[1], Jovana Babić[1], Sanja Klet[1], Tamara Janić[1], Ivana Đurković[1], Mirjana Stojković[1,2], Biljana Nedeljković Beleslin[1,2], Jasmina Ćirić[1,2], Miloš Žarković[1,2]

# ADRENAL VEIN SAMPLING IN BILATERAL ADRENAL TUMORS WITH AUTONOMOUS HYPERCORTISOLISM

**Abstract:** Bilateral adrenal tumors are a rare pathology, increasingly detected due to the widespread use of diagnostic imaging procedures such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). These changes can be either malignant or benign, with the potential for autonomous hormone production. Historically, tuberculosis was a leading cause of bilateral adrenal changes due to lower socio-economic status and poor hygiene. In this case, the patient was diagnosed with hypertension at 38 years old, and initial considerations included secondary endocrine causes of hypertension, specifically primary aldosteronism. CT imaging revealed bilaterally enlarged adrenal glands with multiple nodular changes showing absolute and relative washout indices characteristic of adenomas, with the largest measuring 17 x 23 mm on the right and 21 x 23 mm on the left. The patient had a history of hypokalemia, with the lowest recorded potassium level being 3.3 mmol/L. She reported spontaneous bruising on her arms and legs and weight gain in the abdominal area. Testing indicated the presence of ACTH-independent hypercortisolism. To precisely localize cortisol hypersecretion, adrenal vein sampling (AVS) was performed.

## *Introduction*:

Bilateral adrenal tumors are a rare pathology, and previous studies have shown that such changes are primarily due to metastases from distant carcinomas. However, with advancements in diagnostic procedures such as ultrasound (US), computed

[1] Bojan Marković, Clinic for Endocrinology, Diabetes, and Metabolic Diseases, University Clinical Center of Serbia, Department of Thyroid Diseases.

[2] Faculty of Medicine, University of Belgrade, Serbia.

tomography (CT), and magnetic resonance imaging (MRI), the detection rate of bilateral changes has increased. In one retrospective study of 18 patients with bilateral adrenal tumors, 6 had pheochromocytoma, 4 had primary lymphoma, 4 had non-functional cortical adenoma, 2 had metastases from primary tumors, and 1 had Cushing's syndrome. Other potential etiologies include tuberculosis, infiltrative diseases, and infectious conditions as possible causes of this clinical entity. Compared to unilateral changes, the occurrence of bilateral tumors is less common, with genetic factors playing a significant role in their development. We present a case of a patient with bilateral adrenal changes and Cushing's syndrome, with the clinical question of whether cortisol production is unilateral or bilateral.

## *Case Presentation:*

A 48-year-old female patient was hospitalized at the Clinic for Endocrinology, Diabetes, and Metabolic Diseases for the functional evaluation of the adrenal glands. Due to a previously diagnosed hypertension at the age of 38 and recorded hypokalemia down to 3.3 mmol/L, secondary endocrine causes of hypertension were considered. In March 2024, ultrasound and subsequent CT imaging of the abdomen revealed bilaterally enlarged adrenal glands with multiple nodular changes, showing absolute and relative washout indices characteristic of adenoma, with the largest measuring 17 x 23 mm on the right and 21 x 23 mm on the left. The patient noticed spontaneous bruising on her arms and legs and weight gain in the abdominal area.

During hospitalization, testing indicated the presence of ACTH-independent hypercortisolism (ACTH 0.4 pmol/L; DEX screening: 354 and 349 nmol/L), with a differential diagnosis of hypercortisolism originating from one of the described adrenal adenomas or AIMAH. Other hormone levels were within normal limits, except for an elevated dopamine level in one sample (ALDO 154.6...96.6 ng/L; PRA 22.90...16.20 ng/ml/h). Given the confirmed autonomous cortisol production, surgical treatment was indicated, but to localize cortisol hypersecretion, adrenal vein sampling (AVS) was first performed (Tables 1 and 2). The physical examination was unremarkable except for the presence of three hematomas on the lower extremities and centripetal obesity. There were no other clinical signs of Cushing's syndrome.

The patient's medical history includes stable asthma under treatment since 2012, with no corticosteroid therapy taken in the past year. The family history is positive for hypertension. She is a former smoker.

**Tabel 1. Results:**

| Parameter | Result | Parameter | Result |
|---|---|---|---|
| WBC | 7.8 | PLT | 373 |
| RBC | 4.51 | CRP | 2.5 |
| HGB | 136 | Glc | 5.0 |
| HCT | 0.415 | **HbA1c** | **5.6** |
| MCV | 92.0 | Urea | 2.8...5.0 |
| RDW | 14.7 | Cr | 61...62 |
| GFR | > 60 | Urea Acid | 366 |
| Bilirubin | 5.4 | Bilirubin-D | 1.8 |
| Proteins | 70 | Albumin | 43 |
| **Na** | **138...142...141** | **Na urine** | **169.3mmol/24h** |
| **K** | **3.1...4.1...4.2...4.4** | **K urine** | **63mmol/24h** |
| Cl | 97...102 | Ca | 2.39 |
| PO4 | 1.08 | Mg | 0.76 |
| **HCO3** | **23** | **Osm. serum** | **288mOsmol/kg** |
| AST | 21 | ALT | 20 |
| ALP | 55 | g-GT | 8 |
| Cholesterol | 5.72 | HDL | 1.76 |
| LDL | 3.49 | Tgl | 1.04 |
| Proteinuria | 72mg/24h | Albuminuria | 5.4mg/24h |
| Vitamin D | 40 | PTH | 44 |
| TSH | 1.370 | fT4 | 17.4 |
| At-TPO | 6.00 | At-TG | 12.00 |
| FSH | 4.4 | LH | 2.8 |
| E2 | 1280 | Testosterone | 0.61 |

| | | | |
|---|---|---|---|
| DHEA-S | 0.2 | βhCG | < 2.3 |
| **ACTH** | **0.4pmol/L** | **Circadian rhythm of cortisol** | **413...304...339nmol/L** |
| **DEX screening** | **354...349nmol/L** | AFP | 2.9 |
| CEA | < 1.73 | CA 125 | 14 |
| CA 19-9 | 6 | Cyfra 21-1 | 0.7 |
| HE4 | 55.1 | ROMA index | 9.17 |
| ROMA index (meno) | 12.04 | NSE | 7.4 |
| Urine | ok | **Osmol. urine** | **819mOsmol/kg** |
| ADR | 8.5...13.2 | NOR | 511.7...246.7 |
| DOP | 3748.7...1170.4 | CgA | 99.2 ng/mL |
| 17-OH Pg | 1.8 | Androstenedione | 0.3 ng/mL |
| Aldo/PRA | 0,6 | | |

**Tabel 2. Cortisol value obtained in adrenal vein sampling**

| Localisation of sampling | Cortisol values (nmol/L) |
|---|---|
| *Peripheral* | 587 |
| Under *V. Cava* | 566 |
| Above *V. Cava* | 515 |
| *V. suprarenalis sinistra* | 2583 |
| *V. suprarenalis dextra* | 477 |
| *CAV/Cperipheral* sin | 4.56 |
| *CAV/Cperipheral* dex | 0.84 |
| CRL | 5.42 |

## *Discussion*:

Cushing's Syndrome (CS) involves the autonomous endogenous hypersecretion of cortisol, which can manifest in either ACTH-dependent or independent forms. In clinical practice, stressors such as physical, mental, and metabolic disorders can lead to a state of hypercortisolism, known as pseudo-Cushing's syndrome, making it essential to determine the cause of elevated cortisol levels. The most commonly used diagnostic tests include the measurement of diurnal cortisol rhythm and free cortisol in 24-hour urine, as well as the overnight 1 mg dexamethasone suppression test. If the results are inconclusive, CS evaluation should be supplemented with salivary cortisol analysis and additional suppression or stimulation tests.

The ACTH-independent form represents endogenous hypercortisolism due to primary lesions of the adrenal glands (adenoma, carcinoma, macronodular adrenal hyperplasia [MAH], or micronodular adrenal hyperplasia). In addition to hypersecretion of cortisol, these lesions may also secrete androgens, which may initially suggest a carcinoma, although this was not the case in our patient. A rare form of CS, known as McCune-Albright syndrome, is characterized by precocious puberty resulting from adrenal hyperfunction.

Furthermore, the etiology of bilateral adrenal gland changes can point to: 1) metastases from breast, lung, colon, esophagus, etc.; 2) hemorrhage; 3) congenital hyperplasia; 4) pheochromocytoma; 5) infiltrative diseases. Therefore, it is crucial to determine the etiology of the changes in the adrenal glands, whether they have autonomous activity, and in cases of hypersecretion, whether there is unilateral or bilateral functionality. As in our patient, literature reports suggest that in cases of bilateral adrenal changes and ACTH-independent CS, the causes of hypercortisolism can include MAH, bilateral adenomas, or a single adenoma with a contralateral non-functional adenoma. To determine the localization of hypersecretion, adrenal vein sampling (AVS) or scintigraphy with 131I-NP-59 is necessary.

Adrenal vein sampling (AVS) is an invasive diagnostic procedure in which a small catheter is placed via a venous route to the adrenal glands. The most common puncture site is the femoral vein, but if this route is inaccessible, the jugular vein is used via the neck. First, to correctly interpret AVS results, it is essential to exclude improper sampling of cortisol levels. Since cortisol samples are obtained not only from the adrenal veins (CAV) but also from the inferior vena cava (Cperipheral), a selectivity index (SI=CAV/Cperipheral) is calculated, in which CAV values should be several times higher than cortisol in the inferior vena cava. The recommended selectivity index (SI) should be >2.

Initially, our patient exhibited hypokalemia and an early diagnosis of hypertension, which first led clinicians to consider aldosteronism, which was excluded after obtaining ALDO/PRA values. The phenomenon of hypokalemia in Cushing's

syndrome is explained by cortisol's action on mineralocorticoid receptors. In some cases of bilateral adrenal changes, there may be coexisting cortisol and aldosterone production from one adenoma or from different adrenal tumors, as well as unilateral aldosterone production with bilateral autonomous cortisol production. Considering the above, AVS holds a significant place in diagnosis.

Authors Young et al., in the paper "The clinical conundrum of corticotropin-independent autonomous cortisol secretion in patients with bilateral adrenal masses," recommend that measuring adrenaline levels also provides information on the success of the procedure. The concentration of adrenaline in the adrenal vein should be 100 pg/ml higher than in the inferior vena cava sample (AV–IVC >100 pg/ml) for the procedure to be considered successful. In this case, autonomous cortisol secretion is assessed using the lateralization index, which measures cortisol levels in the adrenal veins and peripheral veins (CAV/Cperipheral). If the cortisol ratio between the adrenal glands is $\geq 2.3$, this indicates unilateral cortisol hypersecretion, while a ratio $\leq 2$ suggests bilateral cortisol hypersecretion.

## ***Conclusion***:

In this case, the most likely diagnosis is bilateral macronodular hyperplasia, which is described in the literature as multiple nodules larger than 1 cm, accompanied by an increase in adrenal gland mass. Given the adrenal vein sampling results, there is evidence of autonomous cortisol secretion. However, it cannot be definitively determined whether the cortisol production is unilateral or bilateral, as the results indicate that cortisol from the right adrenal gland is either suppressed or inadequate due to technical limitations (CAV2/Cperipheral2 = 0.84).

Considering that the patient has bilateral adrenal gland changes and that the left gland is larger, measuring 21 x 23 mm, a left adrenalectomy has been recommended at this time.

## ***Reference/References***:

1. Young Jr, W. F., du Plessis, H., Thompson, G. B., Grant, C. S., Farley, D. R., Richards, M. L., Erickson, D., Vella, A., Stanson, A. W., Carney, J. A., Abboud, C. F., & Carpenter, P. C. (2008). The clinical conundrum of corticotropin-independent autonomous cortisol secretion in patients with bilateral adrenal masses. *World Journal of Surgery, 32*(5), 856–62.
2. Laurent, I., Astère, M., Zheng, F., Chen, X., Yang, J., Cheng, Q., & Li, Q. (2019). Adrenal venous sampling with or without adrenocorticotropic hormone stimulation: a meta-analysis. *The Journal of Clinical Endocrinology Metabolism, 104*(4), 1060–1068.

3. Newell-Price J, Bertagna X, Grossman AB & Nieman LK 2006. Cushing's syndrome. Lancet 367: 1605–1617.
4. Young WF Jr, du Plessis H, Thompson GB, Grant CS, Farley DR, Richards ML, Erickson D, Vella A, Stanson AW & Carney JA et al. 2008. The clinical conundrum of corticotropin-independent autonomous cortisol secretion in patients with bilateral adrenal masses. World Journal of Surgery 32: 856–862. 10.1007/s00268-007-9332-8
5. Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, Young WF Jr & Montori VM 2008. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. Journal of Clinical Endocrinology and Metabolism 93: 3266–3281.
6. Daunt N 2005. Adrenal vein sampling: how to make it quick, easy, and successful. Radiographics, 25: S143–S158.
7. Zhou J, Ye D, Wu M, Zheng F, Wu F, Wang Z, Li H. Bilateral adrenal tumor: causes and clinical features in eighteen cases. Int Urol Nephrol. 2009; 41(3): 547–51.
8. Mundada, O.P., Aron, M., Sivaramakrishna, B. et al. Bilateral adrenal metastases from a primary hepatocellular carcinoma. Int Urol Nephrol 35, 303–305 (2003).