CASE REPORT

Adrenal Cortical Adenoma Resulting from Congenital Adrenal Hyperplasia Managed with Unilateral Laparoscopic Adrenalectomy: a Case Report

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ABSTRACT

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder resulting from mutations in genes encoding enzymes involved in cortisol biosynthesis. Over 90-95% of cases are caused by 21-hydroxylase deficiency, with an incidence of 1:10,000-1:20,000 among Caucasians. This condition leads to cortisol deficiency, causing a loss of negative feedback in the pituitary gland and subsequently increased secretion of adrenocorticotropic hormone (ACTH), which in turn stimulates the production of adrenal androgens and adrenal hyperplasia. We report a 31-year-old female with classic CAH of the simple virilizing subtype and a history of genital reconstruction due to external genital ambiguity. She received glucocorticoid therapy and spironolactone to block androgen receptors. As a result, hirsutism decreased, and MRI evaluation of the adrenal glands revealed a reduction in size compared to pre-treatment (bilateral adrenal gland enlargement). No disturbances due to mineralocorticoid receptor blockade from spironolactone administration were found. In the fourth-year MRI evaluation, the left adrenal gland was larger than normal, while the right was within normal limits. A functional left adrenal gland tumor T1N0M0 was concluded, and a left laparoscopic adrenalectomy was decided upon. The patient consented to the procedure one year later. Laparoscopic adrenalectomy of sinistra was successfully performed with histopathologic examination revealed adrenal cortical adenoma. Monitoring and evaluation of clinic visits, we concluded that unilateral adrenalectomy cannot replace routine medication, but can reduce the dose requirement. Currently, the patient is still under regular control and supervision to evaluate the long-term results of the procedure whether there is a risk of adrenal crisis, whether it can overcome the effects of hyperandrogenism, and whether there is an adrenal rest tumor.

Keywords: *Congenital adrenal hyperplasia, hyperandrogenism, functional adrenal tumor, laparoscopic adrenalectomy, adrenal cortical adenoma*

INTRODUCTION

Congenital adrenal hyperplasia (CAH) comprises a group of seven inherited autosomal recessive disorders, resulting from mutations in genes encoding enzymes involved in the cortisol biosynthesis pathway, including 21-hydroxylase (21OH), 11β-hydroxylase (11βOH), 17α-hydroxylase (17OH), 3β-hydroxysteroid dehydrogenase type 2 (3βHSD2), steroidogenic acute regulatory protein (StAR), P450 cholesterol side-chain cleavage enzyme (SCC), and P450 oxidoreductase (POR).1 Over 90-95% of CAH cases are caused by 21-hydroxylase deficiency, with an incidence of 1:10,000-1:20,000 in the Caucasian population.[1,2]

Deficiency of 21-hydroxylase leads to cortisol deficiency, resulting in the loss of negative feedback in the hypothalamus-pituitary-adrenal axis, thereby increasing adrenocorticotropic hormone (ACTH) secretion, which in turn stimulates adrenal androgen production and causes adrenal hyperplasia.3 CAH patients face two main issues: adrenal insufficiency and androgen excess. Adrenal insufficiency can lead to life-threatening adrenal crises, while androgen excess can cause genital abnormalities in 46 XX neonates, abnormal growth patterns (tall children, short adults), precocious puberty, virilization in females, and infertility in both males and females.[2,3,4]

CAH management involves glucocorticoid therapy aimed at reducing androgen excess and avoiding iatrogenic glucocorticoid excess. The challenge lies in balancing glucocorticoid dosages; insufficient glucocorticoid dosages pose a risk of adrenal crisis, while excessive dosages can result in short stature, obesity, hypertension, metabolic syndrome, osteoporosis, and Cushing's syndrome.[3]

Bilateral adrenalectomy can reduce the risk of virilization in females and potentially allow for a reduction in glucocorticoid dosage; however, the 2018 European Endocrine Society guidelines do not recommend this procedure due to the risk of adrenal crisis and adrenal rest tumors.[5] In this case report, we present a case of CAH with unilateral adrenalectomy, aiming to investigate whether this intervention can reduce glucocorticoid dosage and whether it poses a risk of adrenal crisis.

CASE ILLUSTRATION

A 31-year-old female patient was scheduled for a left laparoscopic adrenalectomy by the urology department. According to the patient's mother, she exhibited no abnormalities at birth and appeared as a typical female infant. However, during second grade, abnormalities in her genitalia began to manifest, including the appearance of an enlarging mass and fusion of the labia, resulting in an increasingly male-like appearance. Karyotype analysis confirmed her as a female (46 XX), and corrective surgery was performed during her third grade. Subsequently, her voice began to deepen, and her body stature was larger than her peers. By middle school, her voice resembled that of an adult male, and during high school, she developed excessive body hair, facial hair requiring routine shaving, and hair loss in the frontal region of the scalp, leading to partial baldness. The patient had never experienced menstruation.

Further examinations were conducted after she completed her college education and began working (around 2018/2019). She was diagnosed with congenital adrenal hyperplasia and was prescribed hydrocortisone (20 mg twice daily) and spironolactone (100 mg twice daily). While the frequency of shaving facial hair decreased after commencing medication, the patient did not experience menstruation. An evaluation of the MRI revealed a reduction in adrenal size compared to the pre-medication MRI, although the left adrenal remained larger than the right. The patient consulted the obstetrics and gynecology department for primary amenorrhea and was prescribed a combination of cyproterone acetate (2 mg) and ethinyl estradiol (0.035 mg). Following two months of medication, the patient experienced menstruation once but discontinued the medication during the COVID-19 pandemic, resulting in the cessation of menstruation. The

2022 MRI evaluation revealed a larger left adrenal gland compared to the right, and the urology department diagnosed the patient with a functional left adrenal tumor T1N0M0. The patient initially declined the laparoscopic adrenalectomy but consented to the procedure in early 2023.

Physical examination showed the patient in generally good health and fully conscious, exhibiting obesity, a BMI of 35.9 kg/m2, and a male-like body stature and voice. Blood pressure was 130/80 mmHg, pulse 90 beats/min, respiratory rate 20 breaths/min, and body temperature 36.6°C. Alopecia was noted in the fronto-occipital region, facial hair was not dense (routinely shaved), and moon face was absent. No thyroid or lymph node enlargement was observed in the neck. Heart and lung examinations were within normal limits, and no pink striae or organomegaly were detected in the abdomen. The extremities examination was within normal limits.

Routine blood tests, liver and renal function tests, blood glucose, and electrolyte levels were within normal limits. Chest X-ray revealed no pulmonary metastases and a normal-sized heart. Lower abdominal ultrasound showed uterine hypoplasia, and contrast-enhanced abdominal MRI indicated a larger left adrenal gland in comparison to the right.

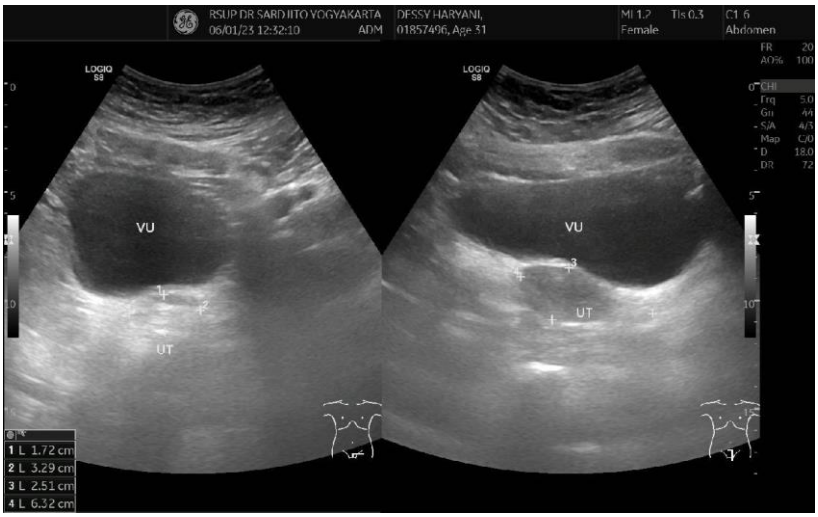


Figure 1. Ultrasound examination of the lower abdomen

Obtained uterine hypoplasia with an anteroposterior x lateral x craniocaudal diameter of 1.72 x 3.29 x 6.32 cm. The normal echo structure did not show a mass.

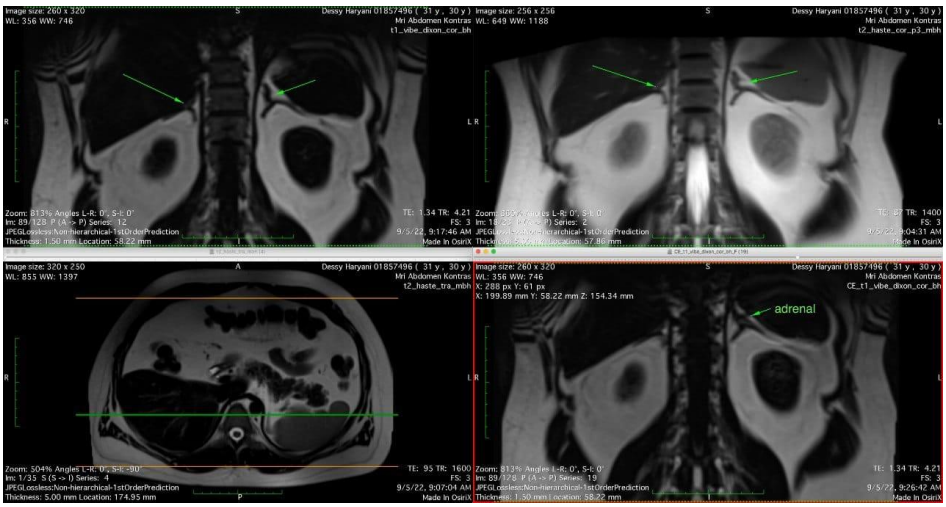


Figure 2. Abdominal MRI examination with contrast

The laterolateral and anteroposterior sizes of the left adrenal were larger than normal, and the size of the right adrenal was within normal limits. Left adrenal: length CC 3.08 (N:4-6 cm), x LL 4.18 (N:2-3 cm), x AP 3.30 (N:3 cm), thickness (limb thickness) 0 .4 (N:<0.6 cm) and normal location, no iso/hypo/hyperintense lesions seen. Right adrenal: length CC 3.3 (N:4-6 cm), x LL 2.62 (N:2-3 cm), x AP 2.2 (N:3 cm), thickness (limb thickness) 0 .9 (N:<0.79 cm) and normal location, no iso/hypo/hyperintense lesions seen.

Monitor evaluation of 17-OHP (17-hydroxyprogesterone) examination results at diagnosis of 13.88 ng/mL (4/12/2018), then successively 138.89 ng/mL (12/6/2019), and 10.14 ng/ mL (6/7/2020) with normal range values for the follicular phase <1.85 ng/mL, and the luteal phase <2.85 ng/mL. A summary of laboratory examination results from August 2018 to November 2022 can be seen in the following table.

Table 1. Summary Of Hormone And Biochemical Test Results

Lab	31/8/18	3/9/18		13/8/18	25/9/18	12/11/18	21/11/18	4/12/18	12/2/19	19/3/19	16/4/19	28/5/19	4/2/19	17/2/20	27/5/20	6/7/20
Testosteron	6,0			6,17		5,85			3,73	4,59	3,76	0,65	0,03	1,12	0,99	
Progesteron	2,3														4,2	1,1
Estradiol	65,73														48,54	44,92
LH	3,1						4,9									
FSH	2,6						4,2									
BUN		8				12		12,7								
Cr		1,07				1,07		0,7								
Prolactin					1,3		19,6									
fT4						2,29										
TSH						2,3										
Na								137					138			
K								4,76					4,4			
Cl								105					103			
GDS										89						
Cortisol														5,2	16,4	
Lab	19/10/20	21/1/21		15/4/21	1/7/21	3/11/21	6/12/21	12/1/21	27/1/22	16/3/22	20/5/22	17/6/22	29/7/22	29/8/22	2/9/22	30/11/22
Testosteron	1,63	1,34		1,51	0,41	2,33		2,48		2,66	2,45	2,41	2,88	1,15		1,10
Progesteron														13,8		
Estradiol		63,06		66,61	32,0											
LH																
FSH																
BUN		9,3							5,72						8	
Cr		1,0							0,96						0,93	
Prolactin																
fT4																
TSH																
Na						137										130
K						4,44										4,2
Cl						106										98
GDS		158														90
Cortisol							5,9									

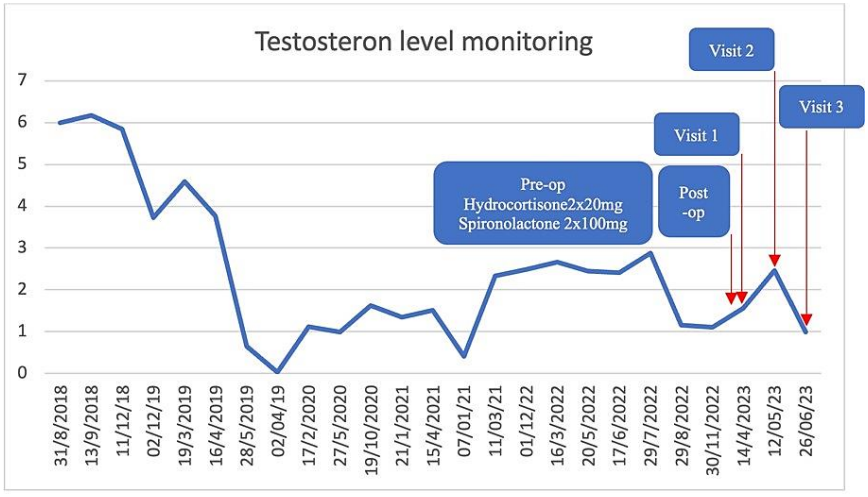
FSH 4-25 IU/L mid cycle peak, LH 10-75 IU/L mid cycle peak, prolactin < 20 ng/mL (425 µg/L), TSH 0,5-5,0 mIU/L, fT4 0,7-1,9 ng/dL, cortisol pagi 3,7-19,4 sore 2,9-17,4 µg/dL, testosterone 0,08-0,60 ng/mL, progesterone 0,2-2,7 ng/mL, estradiol 12,0-4300,0 pg/mL.

A summary of the radiological findings included the following: Lower abdominal ultrasound (6/8/2018) revealed uterine hypoplasia; contrast-enhanced head CT (6/9/2018) showed no signs of micro- or macroadenomas in the pituitary gland; cerebral MRI with contrast (14/11/2018) revealed a normal pituitary gland and sella turcica; contrast-enhanced pelvic MRI (11/12/2018) showed a smaller than normal uterus in an anteflexed and anteverted position, with normal-sized and normal-volume ovaries; abdominal MRI (11/12/2018) revealed bilateral adrenal gland enlargement, predominantly on the left side; contrast-enhanced abdominal MRI (28/1/2022) showed a reduction in adrenal gland size compared to pre-therapy, with the left gland larger than the right; contrast-enhanced abdominal MRI (5/9/2022) indicated an increased laterolateral and anteroposterior size of the left adrenal gland compared to the normal range, with the right adrenal gland size within normal limits.

The patient was diagnosed with a functional left adrenal tumor T1N0M0 resulting from congenital adrenal hyperplasia with hyperandrogenism and was treated with hydrocortisone (20 mg twice daily) and spironolactone (100 mg twice daily). A clinical conference held on February 28, 2023, involving the urology surgery department, internal medicine endocrine division, obstetrics and gynecology endocrine division, and radiology department, decided to perform a left laparoscopic adrenalectomy.

The left laparoscopic adrenalectomy was successfully performed, and histopathological examination revealed an adrenal cortical adenoma. The patient was stable postoperatively, showing improved conditions, with electrolyte and blood glucose levels within normal limits. The patient was discharged with hydrocortisone and spironolactone was discontinued.

At the time of the first clinic visit, two weeks after surgery, she reported that one week postoperatively, had spontaneous menstruation without the need for medication, and laboratory evaluations three weeks postoperatively revealed testosterone levels of 1.56 ng/mL, estradiol levels of 45.7 pg/mL, and progesterone levels of 1.46 ng/mL. At the second clinic visit, one and a half months after surgery, testosterone levels increased sharply compared to before, amounting to 2.46 ng/mL. So we decided to re-administered the routine medication but at a lower dose which were hydrocortisone 2x10mg and spironolactone 2x75mg. At the third clinic visit, one month after the second visit, we found testosterone levels decreased to 0.99ng/mL. We continued the routine medication at lower dosage. So we found that unilateral adrenalectomy in this case was not able to replace the routine medication, but was able to lower the dose requirement.



Post-op to visit 1: hydrocortisone/spironolactone stop; Visit 2and 3: hydrocortisone 2x10mg, spironolactone 2x75mg

Figure 3. Summary of testosterone levels (ng/mL) pre- and post-procedure

DISCUSSION

The clinical presentation of congenital adrenal hyperplasia (CAH) can generally be divided into three categories: classic CAH, non-classic CAH, and cryptic CAH. Classic CAH is further divided into salt-wasting and simple virilizing subtypes. Mutations in the CYP21A2 gene, which encodes the 21-hydroxylase enzyme, cause a blockade in cortisol and aldosterone synthesis. This blockade leads to increased secretion of ACTH, resulting in the accumulation of cortisol precursors, which are then converted to adrenal androgens. The cardinal sign of classic CAH or severe virilizing in female infants is the abnormal development of external genitalia, characterized by virilization.

Complete mutations that inactivate the CYP21A2 gene result in salt-wasting classic CAH, causing severe aldosterone deficiency and even life- threatening adrenal crisis within two weeks post-birth if not detected and managed properly. This condition accounts for 75% of classic CAH cases. In simple virilizing CAH, there is still 1-2% residual activity of CYP21A2, which is sufficient to maintain aldosterone production, thus avoiding crisis. This condition comprises 25% of classic CAH cases. In non-classic CAH, CYP21A2 activity is approximately 50%, preventing adrenal crisis, and only causing a partial glucocorticoid deficiency without external genital abnormalities in female patients. Mild hyperandrogenism with mild or no symptoms is observed. Cryptic CAH is asymptomatic and can only be detected by genetic testing.[1,5] According to this classification, the patient in this case, falls under classic CAH, simple virilizing subtype, as there is external genital ambiguity without adrenal crisis, and karyotype examination confirms the patient as female (46 XX).

Deficiency in the 21-hydroxylase enzyme activity encoded by CYP21A2 results in a decrease in glucocorticoid and mineralocorticoid synthesis, leading to an increase in the precursor 17-OHP. The increased precursor levels are used for diagnostic confirmation. Genotype testing is not performed as a first-line diagnosis due to the complexity of the CYP21A2 locus. A 17-OHP level above 1000 ng/dL (>30 nmol/L = 10 ng/mL) confirms CAH.1,4,5 The patient's 17-OHP level was 13.88 ng/mL (=1388 ng/dL), confirming CAH.

CAH patients face two problems: adrenal insufficiency and androgen excess. Therefore, the aim of therapy is to replace the deficient hormones and manage androgen excess. The current standard therapy for CAH is glucocorticoid therapy, with a target 17-OHP level of < 36 nmol/L (1200 ng/dL). The challenge lies in determining the appropriate glucocorticoid dosage to achieve a balance between cortisol replacement and androgen excess control. Insufficient glucocorticoid dosage can lead to adrenal crisis and symptoms of chronic cortisol deficiency (fatigue, weakness, nausea, loss of appetite, dizziness, hypotension, weight loss), as well as uncontrolled androgen excess effects (hirsutism, acne, menstrual disorders, baldness, infertility, precocious puberty, clitoromegaly).

Excessive glucocorticoid dosage poses risks of developing a cushingoid appearance, weight gain, central obesity, metabolic syndrome, osteoporosis, insomnia, and increased appetite. Additionally, patients are prone to mental health disturbances such as anxiety, depression, alcohol abuse, and even suicide risk.[3,4,5] The patient in this case received routine hydrocortisone and spironolactone therapy. The addition of spironolactone was due to its ability to block androgen receptors.[6] After initiating the routine therapy, the patient reported a decrease in the frequency of shaving facial hair, a reduction in testosterone levels, and a decrease in adrenal gland size on MRI compared to pre-treatment. However, spironolactone also has anti-aldosterone effects by blocking mineralocorticoid receptors in addition to androgen receptor blockade.[6] As a result, patients need to be monitored for adrenal crisis and electrolyte imbalances (hyponatremia, hyperkalemia). In this patient, there was no concern regarding the blockade of mineralocorticoid receptors, as electrolyte levels remained within normal limits.

Testosterone levels tended to decrease compared to pre-treatment levels but still fluctuated. Although the 17-OHP evaluation initially met the target within the first two years of routine therapy, subsequent evaluations could not be performed due to financial constraints, making it unclear whether the 17-OHP target was maintained in the past three years. MRI evaluation of the adrenal glands showed a reduction in size compared to pre-treatment; however, the left adrenal gland was larger than normal. The patient's weight also increased (BMI 39.5 kg/m^2), suspected to be due to excessive glucocorticoid dosage, though no signs of Cushing's syndrome were present. Therefore, the decision was made to perform a left laparoscopic adrenalectomy (unilateral). According to the 2018 European Endocrine Society recommendations, bilateral adrenalectomy is not recommended. While short-term improvements have been demonstrated, long-term problems may arise, such as the risk of adrenal crisis if the patient is non-compliant with glucocorticoid replacement therapy and the inability to fully address hyperandrogenism due to the occurrence of adrenal rest tumors in the testes, ovaries, or retroperitoneal region.[5]

Authors found that unilateral adrenalectomy in this case was not able to replace the routine medication, but was able to lower the dose requirement. The patient continues to attend routine follow-up appointments and remains under observation to evaluate the long-term outcomes of the surgery, including the risk of adrenal crisis, the management of hyperandrogenism effects, and the possibility of adrenal rest tumor occurrence.

CONCLUSION

We found that unilateral laparoscopic adrenalectomy in the case of adrenal cortical adenoma resulting from congenital adrenal hyperplasia was not able to replace the routine medication, but was able to lower the dose requirement. Long-term evaluation is still needed to evaluate the outcomes of the surgery, including the risk of adrenal crisis, the management of hyperandrogenism effects, and the possibility of adrenal rest tumor occurrence.

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