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OPIS PRZYPADKU
CASE REPORT

Therapeutic problems in patients with congenital adrenal hyperplasia from 11-β-hydroxylase deficiency

Problemy terapeutyczne u pacjentek z wrodzonym przerostem nadnerczy z niedoboru 11-β-hydroksylazy

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ABSTRACT

Congenital adrenal hyperplasia (CAH) with 11-β-hydroxylase deficiency accounts for a small percentage of the overall incidence of this disease in the population. The described case of two sisters touches on the therapeutic problems encountered during the treatment of this rare condition. The authors present the problem of selecting appropriate substitutive doses of glucocorticosteroids that will ensure good control of blood pressure and protect against the development of organ complications caused by hypertension and maintain hirsutism at an acceptable level, with as few complications of the applied treatment as possible. The article emphasizes the role of patient–physician cooperation, which is essential to achieve the therapeutic goals.

KEYWORDS

hypertension, hirsutism, congenital adrenal hyperplasia, glucocorticosteroid therapy

STRESZCZENIE

Wrodzony przerost nadnerczy (*congenital adrenal hyperplasia* – CAH) z niedoborem 11-β-hydroksylazy stanowi niewielki procent ogólnej częstości występowania CAH w populacji. Opisywany przypadek dwóch sióstr dotyka problemów terapeutycznych napotykanych w czasie leczenia tego rzadkiego schorzenia. Autorzy przedstawiają trudności związane z doborem odpowiednich dawek substytucyjnych glikokortykosteroidów, które zapewnią dobrą kontrolę ciśnienia tętniczego i zapobiegną rozwojowi powikłań narządowych wywołanych nadciśnieniem tętniczym, a także utrzymają hirsutyzm na akceptowalnym poziomie przy jak najmniejszej liczbie powikłań stosowanego leczenia. W pracy podkreślono rolę współpracy na linii pacjent–lekarz, niezbędnej do osiągnięcia założonych celów terapeutycznych.

SŁOWA KLUCZOWE

nadciśnienie tętnicze, hirsutyzm, wrodzony przerost nadnerczy, glikokortykosteroidoterapia

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INTRODUCTION

Congenital adrenal hyperplasia (CAH) is an enzymopathy inherited in an autosomal recessive manner. The disorder is determined by mutations in the enzymes responsible for adrenal steroidogenesis [1,2]. Reduced cortisol levels, through a feedback pathway, stimulate the hypothalamus and pituitary gland to secrete corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), respectively, resulting in hypertrophy of adrenal cortical tissue [1,2]. Blocking the adrenal glucocorticosteroid (GCS) synthesis pathway results in the accumulation of substrates above the enzymatic block and products of the undisturbed adrenal androgen synthesis pathway. 21-hydroxylase deficiency is responsible for about 90% of cases. In 11-β-hydroxylase deficiency, mineralocorticosteroid precursors of aldosterone (mainly 11-deoxycorticosterone) are also formed, responsible for the onset of hypertension (HTN) [1,2].

CASE REPORTS

41-year-old monozygotic twins with karyotype 46 XX were admitted to the Department for endocrine diagnosis and treatment. The women were diagnosed with salt-wasting CAH caused by 11-β-hydroxylase deficiency in childhood. The diagnosis was made on the basis of analysis of the steroid profile and the high values of 11-deoxycortisol found. This deficiency accompanies 7% of CAH cases and its incidence is estimated at 1:100,000 live births [1]. The conversion of 11-deoxycortisol to cortisol and 11-deoxycorticosterone (DOC) to corticosterone is inhibited. Clinically, no salt loss is observed, which is determined by the mineralocorticosteroid properties of DOC. The accumulation of substrates with mineralocorticosteroid activity results in increased sodium retention and increased potassium excretion, which provokes HTN [1].

Patient 1

The patient was first admitted to the Department in 2019 at the age of 38, diagnosed with CAH, HTN, hypercholesterolemia, and giant obesity with a body mass index (BMI) of 43 kg/m^2.

At birth, the external genitalia was graded IV on the Prader scale. Perineoplasty was performed at age 2, and vaginoplasty at age 12. The onset of sexual maturation occurred at 8 years of age, menarche at 14 years of age, followed by regular menstrual spotting. Later, the onset of hirsutism (currently 24 points on the Ferriman-Gallwey scale) and HTN were noted, and menstrual spotting occurred every few months. On examination, lower limits of potassemia were observed.

A 2018 computed tomography (CT) scan of the abdomen described nodular remodeling of the adrenal glands. The patient was taking hydrocortisone (HC) at a dose of 15 mg per day (10 + 5 + 0 mg) and dexamethasone at a dose of 0.5 mg in the evening. During such substitution treatment there was suppression of ACTH secretion (the morning plasma ACTH concentration was 8.64 pg/ml and 2 hours after HC administration it was 4.48 pg/ml) and low androgen secretion (testosterone 0.14 ng/ml; androstenedione 1.52 ng/ml; free androgen index (FAI) 0.6%), and 17-hydroxyprogesterone (17-OHP) was 2.41 ng/ml. Potassium remained in the lower limits of normal (3.86 mmol/l), and plasma renin activity (PRA) was low (< 0.07 ng/ml/h). Holter monitoring showed fairly good blood pressure (BP) control with the highest BP increases in the morning (e.g. 150/123 mmHg). The aforementioned doses of GCS and previous treatment with the angiotensyn--converting enzyme inhibitor ramipril 10 mg were maintained, and spironolactone 100 mg per day, metoprolol 150 mg in the morning and 100 mg in the evening, and amlodipine 10 mg per day were prescribed.

At the next follow-up, the dose of dexamethasone was reduced to 0.25 mg. The morning plasma ACTH level was 3.69 pg/ml and 2 hours after HC administration it amounted to 1.76 pg/ml, while dehydroepiandrosterone sulfate (DHEAS) 15.50 μg/dl and testosterone 0.18 ng/ml oscillated in the lower limits of normal. Androstenedione at 1.03 ng/ml was in the normal range. An alarming inhibition of gonadotropin secretion (folliculotropin – FSH) 1.99 mIU/ml in the follicular phase was found; lutropin (LH; 0.79 mIU/ml) and estradiol (18 pg/ml in the follicular phase) with normal prolactin (PRL) levels (7.14 ng/ml) were recorded, against which it was decided to reduce the evening dose of dexamethasone again to 0.125 mg. In view of poor blood pressure control (mean arterial pressure – MAP; 153/96 mmHg), the dose of spironolactone was increased to 150 mg per day. Six months later, despite an increase in gonadotropins (in the follicular phase, FSH 3.62 mIU/ml; LH 3.16 mIU/ml) and estradiol (44.0 pg/ml), there was no clinical effect in terms of a return of menstruation and effective control of blood pressure (MAP 160/100 mmHg). In view of the above, the dose of dexamethasone was reduced to 0.125 mg every other day and at the same time the dosage of HC was increased to 20 mg per day and spironolactone to 200 mg per day. The calcium and phosphate metabolism parameters were also assessed. The blood calcium level was 2.23 mmol/l. In the 24-hour urine collection the calcium level was 5.1 mmol/24 h and the phosphate level was 7.6 mmol/24 h.

On admission to the Department in 2021, the patient reported perimenopausal spotting, a weight gain of 5 kg in 6 months and stable hirsutism. She was found to have suppressed ACTH secretion (the morning concentration was 25.37 pg/ml and 2 hours after HC < 1.60 pg/ml) and DHEAS 10.70 μg/dl. The evening dose of dexamethasone was reduced to 0.125 mg every third day and the dose of hydrocortisone was set at 25 mg per day. The patient was diagnosed with vitamin D_3 deficiency with a 25(OH)D_3 level of 22.6 ng/ml. Supplementation with a drug containing 30 000 I.U. of vitamin D_3 per tablet was implemented (2 tablets per week for 2 months, then 1 tablet per week and follow-up of 25(OH)D_3 in 3 months). An oral glucose tolerance test (OGTT) was performed, with high insulin values determined at 120 minutes (776.2 pmol/l); the blood glucose level at 120 minutes was 5.97 mmol/l. The fasting blood glucose level was normal (4.03 mmol/l). 500 mg of metformin was prescribed. The patient undertook dietary treatment and reduced her body weight by 8 kg.

During the next hospitalization, OGTT was performed again. The fasting blood glucose level was 3.96 mmol/l. At 120 minutes, the glucose level was 6.66 mmol/l, while the insulin level was 569.4 pmol/l. Glycated hemoglobin (HbA1c) was 4.9%, HOMA-IR was 1.7. In a 24-hour blood pressure measurement, MAP decreased to 150/95 mmHg, but intermittent blood pressure spikes to 170/130 mmHg were still noted. An additional 1 mg per day of doxazosin was included in the hypotensive treatment. Hormone tests revealed morning ACTH levels of 319.8 pg/ml (2 hours after HC 101.8 pg/ml), testosterone 0.74 ng/ml, 17-OHP 13.29 ng/ml and androstenedione 11.02 ng/ml. In view of this, the evening dose of dexamethasone was increased to 0.125 mg every other day and HC was maintained at 25 mg per day. On an abdominal ultrasound an adrenal tumor was suspected. The diagnosis was deepened with an abdominal CT scan, showing nodular remodeling of both adrenal glands. The right one measured 7 × 2.5 cm, the left 8 × 5.5 cm. A repeat hospitalization in 7 months was recommended.

Patient 2

The patient was first admitted to the Department in 2018 (age 38) with CAH diagnosed in childhood from 11-β-hydroxylase deficiency, refractory HTN (RfHTN), bilateral adrenal tumors visualized on CT, stage 3 chronic kidney disease. On examination, mild microcytic anemia, a nodular goiter, vitamin D_3 deficiency with secondary hyperparathyroidism were found. A suspicion of uterine myoma was raised. The patient's BMI was 30 kg/m^2. Similar to her sister's, at birth the external genitalia was graded IV according to the Prader scale. The patient underwent perineoplasty three times. Since 18 years of age, increasing hirsutism and HTN were observed. She was treated with HC and dexamethasone. During hospitalization, the patient had low values of ACTH (142.3 pg/ml and 80.03 pg/ml 2 hours after HC), 17-OHP 3.33 ng/ml; DHEAS 27.19 μg/dl and testosterone 0.39 ng/ml. The dosage of GCS was then reduced to 25 mg HC in divided doses (1-1-1/2 pills) and dexamethasone to 0.25 mg in the evening dose. Blood pressure, despite the multidrug therapy, remained elevated. On an ultrasound, the flow in the renal arteries was observed to be normal, the methoxycatecholamine concentrations in the daily urine collection were normal. An alarming increase in the renal parameters was observed – an increase in urea to 15.4 mmol/L and creatinine to 194 μmol/L, as well as hyperkalemia (the highest K^+ concentration was 8.28 mmol/L). Hypotensive treatment included doxazosin 6 mg, bisoprolol 10 mg, nitrendipine 60 mg per day and spironolactone 25 mg per day (under strict potassium control). Vitamin D_3 deficiency supplementation at a dose of 4000 I.U. per day was recommended.

During a subsequent stay in the unit in 2018, there was a transient increase in creatinine to 118 μmol/L. In 24-hour blood pressure measurements, high blood pressure values were recorded (especially at night). The dose of spironolactone was increased to 50 mg in the morning (under close control of potassium levels) and doxazosin from 6 to 8 mg per day. An abdominal CT scan showed bilaterally enlarged adrenal glands with nodular remodeling, consistent with adrenal adenomatous hyperplasia. There was increased hirsutism (24 points on the Ferriman-Gallwey scale) and typical androgenetic alopecia. The morning tests showed ACTH levels of 216.7 pg/ml, and 52.29 pg/ml 2 hours after HC (with an observed response to HC), increased androstenedione 41.20 ng/ml and 17-OHP 14.94 ng/ml, with normal DHEAS 69.82 μmol/ml and FAI 6.3% were registered. A persistently low PRA of 0.09 ng/ml/h on lying down (after resting) was found. Blood pressure control was not achieved (daytime mean 188/117 mmHg, nighttime 182/111 mmHg). The evening dose of dexamethasone was increased to 0.5 mg, and a two-component hormonal pill with anti-androgenic progestogen (dienogest + ethinylestradiol) was included (0.03 mg per day + 2 mg per day). Hypotensive treatment was intensified, increasing the dose of spironolactone to 100 mg per day and nitrendipine to 60 mg per day. Attention was drawn to the lower calcium and vitamin D_3 levels, despite supplementation, and intact parathormone (iPTH) 94.7 pg/ml. Vitamin D_3 supplementation at a dose of 4000 I.U. per day was maintained and calcium 500 mg was included.

During hospitalization in 2019, there was a history of significant weight gain (BMI 35.9 kg/m^2) but improvement in the clinical features of hyperandro-

genism. In the determined hormone levels, significant suppression of ACTH secretion (10.73 pg/ml and 3.49 pg/ml 2 hours after HC) with low levels of 17-OHP (2.37 ng/ml) were recorded. It was recommended to change dexamethasone dosing to a regimen of 0.5 mg 1 per day, alternating with ½ pill per day in the evening dose. In 2020 the patient had sustained compensation of the underlying disease (testosterone 0.25 ng/ml, sex hormone binding globulin (SHBG) 286.01 nmol/ml, DHEAS 16.0 µg/dl, FAI 0.31%) confirmed by laboratory tests (ACTH 10.65 pg/ml and 6.91 2 hours after HC) with hypogonadotropic hypogonadism (in the follicular phase FSH 0.28 mIU/ml; LH < 0.12 mIU/ml; estradiol 32,0 pg/ml). Due to persistent blood pressure spikes with lower K^+ levels, the daily dose of spironolactone was increased to 150 mg per day and clonidine 75 mg per day was included. The dose of dexamethasone was maintained in a regimen of 0.5 mg in 1 pill per day alternating with ½ pill per day in the evening dose.

At the next follow-up in 2020, low levels of adrenal androgens (testosterone 0.29 ng/ml, androstenedione 1.66 ng/ml, DHEAS 17.2 µg/dl, 17-OHP 2.39 ng/ml) hypogonadotropic hypogonadism (postmenopausal FSH 1.22 mIU/ml; LH 0.17 mIU/ml; estradiol 66.0 pg/ml), hypokalemia with a K^+ concentration of 3.3 mmol/l were found. On OGTT, the fasting blood glucose level was 4.98 mmol/l and the fasting insulin level was 103.3 pmol/l. At 120 minutes the blood glucose level was 7.37 mmol/l and the insulin level was 1136.6 pmol/l; HOMA-IR was 3.29. Owing to hyperinsulinemia, metformin 750 mg per day was prescribed. Also atorvastatin 10 mg per day was started. In 2021 the Holter blood pressure measurement revealed high MAP values of 182/113 mmHg during the day and 195/116 mmHg at night. Hypotensive treatment was intensified by including 150 mg per day of metoprolol. The patient managed to improve her glycemic results and achieve a HbA1c of 5.2%. Follow-up thyroid fine-needle aspiration (FNA) was performed. The biopsy was graded IV according to the Bethesda scale. The patient was referred for strumectomy.

DISCUSSION AND CONCLUSIONS

The most dangerous complication of CAH from 11-β--hydroxylase deficiency is the development of HTN and its consequences.

In the treatment of low-renin HTN in the course of CAH, the most important thing is the appropriate substitution dose of GCS. Classical pharmacotherapy with hypotensive drugs is ineffective with poorly adjusted doses of GCS. The suppression of excessive ACTH secretion and the inhibition of mineralo-corticosteroid 11-deoxycorticosterone, which increases cardiovascular risk independent of the effect of HTN, should be pursued. Hypokalemia increases the risk of developing HTN-dependent organ complications and can induce the onset of dangerous arrhythmias [3]. Treatment-resistant HTN is a clinical situation when properly administered pharmacotherapy consisting of three or more drugs in optimal, best-tolerated doses and lifestyle modification fail to reduce systolic blood pressure and diastolic blood pressure values to < 140 mmHg and/or < 90 mmHg, respectively, as confirmed by 24-hour BP measurement or home BP measurements [4,5]. Patients require frequent internal medicine follow-up resulting from the high risk of developing HTN-dependent organ complications, including left ventricular hypertrophy, the development of arteriosclerosis with all its complications, and impaired renal function [4,5].

Efforts should be made to establish good cooperation with the patient, as the regular intake of medications in appropriate doses is essential to gain control over the course of the disease.

Further treatment should focus on stopping the development of steroid-dependent diabetes mellitus by controlling body weight (a proper diet and physical activity) and taking metformin. It is very important to prevent and watch patients for the onset of osteoporosis associated with GCS use. Patients should be educated about the importance of vitamin D_3 supplementation. As a consequence of being in the osteoporosis risk group, we should consider referring the patients to a rheumatology clinic in the future. Given the simultaneous membership of groups at risk of developing diabetes and osteoporosis, patients should be suggested to go to a clinical nutritionist. The attending physician must not forget the psychological aspect. Obesity, problems with pregnancy due to hypogonadism and hirsutism are factors that can cause a depressive episode, so they need to be extra vigilant. The patient should be informed about the possibility of laser hair removal, which can have a positive impact on psychological well-being. Low motivation may result in noncompliance with recommendations. In conclusion, effective treatment of a patient with CAH requires commitment from both the patient and the attending physician. Good cooperation, follow-ups and a holistic approach to therapy are essential to achieve good treatment results.

Reference standards:

Testosterone: 0.06–0.82 ng/ml
Androstenedione: 0.30–3.30 ng/ml
17-OHP: 0.1–0.8 ng/ml
SHBG: 19.8–155.2 nmol/l
FAI: < 5%
ACTH (6:00): 5–60 pg/ml

DHEAS: 75–370 µg/dl
25(OH)D_3: > 30 ng/ml
Calcium: 2.1–2.55 mmol/l
Calcium in 24-hour urine collection: 2.5–8 mmol/24 h
Phosphate in 24-hour urine collection: 11–32 mmol/24 h
HbA1c: < 6.5%

Author's contribution

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Manuscript preparation – A. Ptak, K. Podyma
Literature research – A. Ptak, K. Podyma
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REFERENCES

1. Papierska L. Wrodzony przerost nadnerczy. In: M. Otto [ed.]. Diagnostyka i leczenie chorób nadnerczy. Wyd. Lekarskie PZWL. Warszawa 2013, p. 126–132.

2. Starzyk J. Wrodzony przerost nadnerczy. In: W. Kawalec, R. Grenda, M. Kulus [ed.]. Pediatria 2. 2nd ed. Wyd. Lekarskie PZWL. Warszawa 2018, p. 1009–1012.

3. Sun B., Lu L., Gao Y., Yu B., Chen S., Tong A. et al. High prevalence of hy-pertension and target organ damage in patients with 11β-hydroxylase de-ficiency. Clin. Endocrinol. (Oxf.) 2022; 96(5): 657–665, doi: 10.1111/cen.14677.

4. Williams B., Mancia G., Spiering W., Rosei E.A., Azizi M., Burnier M. et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. [Article in Polish]. Kardiol. Pol. 2019; 77(2): 71–159, doi: 10.5603/KP.2019.0018.

5. Januszewicz A., Prejbisz A., Dobrowolski P., Stompór T., Kosiński P., Sułowicz W. Nadciśnienie tętnicze. In: P. Gajewski [ed.]. Interna Szczeklika 2021. Wyd. Medycyna Praktyczna. Kraków 2022, p. 459–484.