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A follow-up history of young man with apparent cortisone reductase deficiency (ACRD) – several years after diagnosis

Historia obserwacji młodego mężczyzny z rozpoznanym niedoborem reduktazy kortyzonu (ACRD) – kilka lat po diagnozie

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Abstract

Introduction. Inactivating mutations in the enzyme hexose-6-phosphate dehydrogenase (H6PDH), the enzyme responsible for NADPH generation playing critical role in 11-hydroxysteroid dehydrogenase type 1 (11b-HSD1) activity, cause apparent cortisone reductase deficiency (ACRD). It leads to increased metabolic clearance rate of cortisol due to a defect in cortisone to cortisol conversion by 11b-HSD1. We want to analyse the process of the disease, efficacy of long-lasting treatment with glucocorticoids throughout childhood and adolescence in only male patient with ACRD. **Case presentation.** A 23 year-old male patient was diagnosed with ACRD at the age of 7 years. The clinical manifestation of ACRD was presented by precocious pubarche. His bone age was assessed as 11.5 years old. Blood tests indicated increased the plasma androgen, with elevated 17-hydroxyprogesterone concentration. A steroid profile analysis of a 24-h urine collection showed extremely reduced THF + allo-THF/THE ratio – 0.021 (normal range: 0.7–1.2). Two months of hydrocortisone therapy was ineffective and dexamethasone was administered in initial dose of 0.375 mg/24 h. Next dosage beetwen 0.125 mg/24h and 0.375 mg/24h has been changed depending on the patient's results of laboratory tests and condition. Control laboratory studies indicated suppression of excess adrenal androgen synthesis, but we never got the THF + allo-THF/THE ratio in normal values. He did not develop any serious side effects, although dexamethasone is the most potent adrenal suppression drug. **Conclusions.** Hydrocortisone treatment is ineffective in ACRD patients because it was rapidly metabolized to cortisone. We have found the balance between the dexamethasone treatment effects of adrenal suppression and the achievement of full height potential considering the condition of our patient.

Key words

dexamethasone, apparent cortisone reductase deficiency, children

Streszczenie

Wstęp. Mutacje inaktywujące w genie kodującym dehydrogenazę heksozo-6-fosforanową, enzym odpowiedzialny za produkcję NADPH niezbędnego do prawidłowej aktywności dehydrogenazy 11β-hydroksysteroidowej typu 1 (11β-HSD1), powodują pozorny niedobór reduktazykortyzonu (ACRD). Charakteryzuje się on zwiększonym klirensem metabolicznym kortyzolu z powodu nieprawidłowej konwersji kortyzonu do kortyzolu przez 11β-HSD1. W pracy przedstawiamy przebieg choroby oraz skuteczność wieloletniego leczenia glikokortykosteroidami zarówno w okresie dziecięcym jak i młodzieńczym u pacjenta z opisanym ACRD. **Prezentacja przypadku.** U naszego pacjenta, obecnie w wieku 23 lat, ACRD został zdiagnozowany w wieku 7 lat. Kliniczna manifestacja była wyrażona przedwczesnym dojrzewaniem. Wiek kostny został określony na 11,5 roku. Badania laboratoryjne wykazały podwyższone stężenie androgenów w surowicy oraz 17-hydroksyprogesteronu. Profil steroidowy z dobowej zbiórki moczu wykazał ekstremalnie obniżony stosunek THF + allo-THF/THE – 0,021 (zakres referencyjny: 0,7–1,2). Po bezskutecznym dwumiesięcznym leczeniu hydrokortyzonem zastosowano deksametazon w dawce początkowej 0,375 mg/24h. Następnie dawkowanie było utrzymywane

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w zależności od wyników laboratoryjnych oraz stanu klinicznego pacjenta w granicach od 0,125 mg/24h do 0,375 mg/24h. Badania kontrolne wykazywały supresję syntezy nadnerczowych androgenów, ale nigdy nie osiągnęliśmy prawidłowych wartości stosunku THF + allo-THF/THE. Nasz pacjent nie rozwinął żadnych poważnych skutków ubocznych w trakcie leczenia, pomimo że deksametazon jest jednym z najsilniejszych leków hamujących aktywność kory nadnerczy. **Wnioski.** Leczenie Hydrokortyzonem jest nieskuteczne w ACRD, gdyż jest on metabolizowany do kortyzonu. W przypadku leczenia deksametazonem u naszego pacjenta osiągnęliśmy równowagę pomiędzy supresją nadnerczowej produkcji androgenów a prawidłowym rozwojem i wzrostem pacjenta.
Słowa kluczowe
deksametazon, pozorny niedobór reduktazy kortyzonu, dzieci

Introduction

The crucial pathway in glucocorticoid metabolism is the interconversion of hormonally active cortisol and inactive cortisone catalysed by two isozymes of 11b-hydroxysteroid dehydrogenase (11-HSD). *In vivo* 11-hydroxysteroid dehydrogenase type 1 (11b-HSD1) acts mainly as an oxo-reductase using NADP(H) as a cofactor generated by hexose-6-phosphate dehydrogenase (H6PDH) activity to produce cortisol. 11b-HSD1 is located in the endoplasmatic reticulum in cells of glucocorticoid target tissues for example liver, brain, adipose tissues, skeletal muscles, testis [1]. By contrast, 11-hydroxysteroid dehydrogenase type 2 (11b-HSD2) is a NAD-dependent dehydrogenase and utilises NAD to inactivate cortisol to cortisone in mineralocorticoid receptors (MR) responsive tissues (for example distal nephron, colon). Thereby it protects the nonselective MR from activation by glucocorticoids andenables access of aldosterone to the receptor [2].

The impaired activity of 11b-HSD1 leads to 'true' cortisone reductase deficiency (CRD) caused by inactivating mutations in HSD11B1 and 'apparent' (ACRD) as a result of inactivating mutations in H6PD, which encodes the hexose-6-phosphate dehydrogenase (H6PDH) enzyme. The first case of CRD/ACRD was described in 1984, and there have been around 16 cases of CRD/ACRD reported in literature so far [2–12]. For many years, the functional mutations in the coding regions of HSD11B1 gene have not been discovered. Thereafter, the attention of the researchers was focused on the study of the H6PD gene, which encodes H6PDH, the enzyme responsible for NADPH generation playing critical role in 11b-HSD1 activity. This resulted in a characterization of the first inactivating mutations in H6PD, which abolished the H6PDH activity and thereby led to the lack of NADPH cofactor [8,10]. The first cases of patients with normal H6PD gene and dominant negative mutations in the coding sequence of the HSD11B1 gene causing CRD were reported in two boys in 2011 [11]. Both, CRD and ACRD are characterised by an increased metabolic clearance rate of cortisol, due to a defect in cortisone to cortisol conversion. Decreased cortisol concentration through the negative feedback mechanism activates hypothalamic-pituitary-adrenal (HPA) axis to increase cortisol levels, and in result it leads to excessive ACTH-mediated adrenal androgen secretion [1]. The clinical manifestation of CRD and ACRD in patients is presented by premature adrenarche, pseudopuberty in childhood and females with features of hyperandrogenism (acne, hirsutism, oligo-amenorrhoea, infertility), occuring in adolescence or early adulthood [2–12]. In biochemical studies, CRD and ACRD are diagnosed through the assessment of urinary cortisol and cortisone metabolites and consist of measuring the tetrahydrocortisol (THF) plus 5-THF/tetrahydrocortisone (THE) ratio (THF5-THF/THE ratio). Furthermore, a recent study has definied the differentiation between ACRD and CRD by steroid profile analysis of a 24-h urine collection [12].

In 2003, our patient was described as the first male among children (6 years-old) with ACRD [9];so far we have not found another case of a boy with ACRD in literature. In this study we would like to analyse the process of the disease, efficacy of long-lasting treatment with glucocorticoids and possible physiological implications of defective 11ß-HSD1 activity throughout childhood and adolescence.

Case presentation

A 23 year-old male patient was admitted for the first time by the Department of Pediatrics, Endocrinology, Diabetology with Cardiology Divisions in Białystok at the age of 6.9 years old. He is the first-born child of nonconsanguineous parents, born to a 39-year-old mother, who previously experienced a spontaneous abortion. The causes of admission were precocious pubarche manifested by the occurrence of pubic hair and its accelerated growth. The boy's anthropometric measurements are: height: 136 cm (under 97th percentile), weight: 31 kg (between 85 and 97th percentile), body mass index 16.8 (between 50 and 75th percentile), bone age: 11.5 years old (Greulich and Pyle). Growth analysis based on medical documentation was made retrospectively. It showed rapid growth from the age of 2. On admission, pubic hair and genitalia with testicular volume of 2 ml on both sides indicated the pubertal Tanner 2 stage.Blood test revealed normal level of cortisol and ACTH, the plasma androgen was increased, with slightly elevated 17-hydroxyprogesterone concentration (table I). Serum gonadotropins concentrations confirmed the prepubertal stage. Thyroid hormone (T3, T4) concentrations were normal, the same as serum TSH and TSH, after a standard stimulation with TRH. The level of prolactin was normal. Dexamethasone suppression test was performed – using a low-dose(first 48h, 0.5 mg p.o. every 6h) and a high-dose(next 48h, 2 mg p.o. every 6h), which showed suppression of plasma androgens and cortisol after the low-dose administration. There were no abnormalities in adrenal ultrasound examination and magnetic resonance imaging of abdomen and head. A 24-h urine collection for steroid profile

Table I. Serum hormone values in our ACRD patient during first year of treatment. In contrast to hydrocortisone treatment, two months of dexamethasone treatment significantly decreased the concentrations of androgens. HC – hydrocortisone, Dx – dexamethasone, ACTH – adrenocorticotropic hormone, DHEA-S – dehydroepiandrosterone sulfate, 17-OHP – 17-hydroxyprogesterone, HPLC – high-pressure liquid chromatography, RIA – radioimmunoassay

Tabela I. *Wartości stężeń hormonów w surowicy naszego pacjenta w trakcie pierwszego roku leczenia. W przeciwieństwie do leczenia hydrokortyzonem, dwa miesiące leczenia deksametazonem znacząco wpłynęły na obniżenie stężenia androgenów. HC – hydrokortyzon, Dx – deksametazon, ACTH – hormon adrenokortykotropowy DHEA-S – siarczan dehydroepiandrosteronu, 17-OHP – 17-hydroksyprogesteron, HPLC – wysoko sprawna chromatografia cieczowa, RIA – metoda radioimmunologiczna*

Duration of treatment (Czas leczenia)	**Before treatment (Przed leczeniem)**		**2 months of HC (2 miesiące HC)**	**2 months of Dx (2 miesiące Dx)**	**1 year of Dx (rok Dx)**	**Reference values (prepubertal age)** (Wartości referencyjne dla wieku przed okresem dojrzewania płciowego)
Age (Wiek)	**6 9/12**	**7 6/12**	**7 8/12**	**7 10/12**	**8 8/12**	
Dose (Dawka)			**17.5mg/24h**	**0.375mg/24h**	**0.375 mg/24h**	
ACTH, pg/ml	40	13		13		10-60
DHEA-S, μmol/l	16.85	11.41	10.5	<0.027	1.59	0.024–1.96
Androstendione, nmol/l		5.7	11.9	0.73	1.8	0.28-1.75
Testosterone, nmol/l	1.46	3.47	1.36	<0.17	0.20	<0.1-0.35
Cortisol, nmol/l	197 (RIA)	213.2 (HPLC)	2493 (HPLC)	35.2 (HPLC)	5.5 (RIA)	137.7-551
Cortisone, nmol/l		90.3 (HPLC)	82.5	16.8		23.8-47.4
17-OHP, nmol/l	6.04				<0.15	0.15-3.47

Table II. Excretion of androgen metabolites (5,6), conjugated cortisol (1–4) and corticosterone (7) metabolites (μg/24 h) in our ACRD patient during treatment with hydrocortisone. Therapy with HC was ineffective in suppression of urinary adrenal androgen metabolite and elevation of THF+alloTHF ratio to THE to normal values; THE – tetrahydrocortisone, THF – tetrahydrocortisol, THA – tetrahydro-11-dehydrocorticosterone

Tabela II. *Stężenie metabolitów androgenów (5,6), sprzężonych metabolitów kortyzolu (1–4) i kortykosteronu (7) (μg/24 h) u naszego pacjenta w trakcie leczenia hydrokortyzonem. Terapia hydrokortyzonem była nieefektywna w hamowaniu produkcji nadnerczowych androgenów oraz w podniesieniu stosunku THF+alloTHF do prawidłowych wartości. THE – tetrahydrokortyzon, THF – tetrahydrokortyzol, THA – tetrahydro-11-dehydrokortykosteron*

	Metabolites (Metability)	**Before treatment (Przed leczeniem)**	**2 months of treatment with HC 17.5mg/24h (2 miesiące leczenia hydrokortyzonem 17.5mg/24h)**	**Reference values (boys aged 6–9) (Wartości referencyjne dla chłopców w wieku 6-9 lat)**
1	THE	5604	11007.9	545.4–2048.6
2	THF	139	468.8	260.6–554.4
3	allo-THF	40	94.3	299–820.2
4	ß-cortolone	755.5	501.2	48.1–329.1
5	etiocholanolone	218.9	177.4	37.1–166.1
6	androsterone	1132.2	1812.2	85.8–363
7	THA	351	200.9	26.4–108.5
THF+alloTHF/THE		0.021	0.051	0.7–1.2

and steroid biomarkers by gas chromatography/mass spectrometry was performed. The excretion of free cortisol was 19.7 Ìg/24 h (normal range 5–80 Ìg/24 h), cortisone was 40 Ìg/24h (normal range 20–150 Ìg/24 h) and tetrahydroaldosterone 27.1 Ìg/24 h (normal range 8–60 Ìg/24 h), stayed normal. Measuring the conjugated cortisol and cortisone metabolites showed the way to the diagnosis. Tetrahydrocortisone (THE) was significantly increased and accompanied by decreased tetrahydrocortisolmetabolites (THF + allo-THF). TheTHF + allo-THF/THE ratio was significantly reduced, which is typical for CRD patients (reference range 0.7–1.2, in ACRD patients the ratio is lower than 0.1) (table II). An increase in androgen metabolites' excretion was comparable to the excretion of cortisol and corticosterone. This would lead to the conclusion that there is the same mechanism (ACTH-dependent) responsible for the production of both steroid groups. The results indicate a decreased 11ß-HSD1 activity. At the age of 7.6 years old, the patient was admitted by the Department of Endocrinology of Children's Memorial Health Institute in Warsaw. Laboratory studies showed raised plasma testosterone level in comparison to the condition 7 months earlier. Plasma cortisone concentration was elevated (determined by HPLC). Blood test revealed again normal level ACTH beside the elevated level of cortisol metabolites in urine (tables I,II). Dexamethasone suppression tests revealed decreased plasma androgen and cortisol levels after a low dose. The patient's bone age progressed to 13 years old (biological age: 7.6 years old), and the height went up to 146 cm (+3.7 SD). A decision regarding oral administration of hydrocortisone (17.5 mg daily) was instigated with the control of urinary and plasma steroids during treatment. After one month a 24-h urine collection for steroid profile showed improvement of the [THF + allo-THF] to THE ratio from 0.021 to 0.055. Within the next month of hydrocortisone medication, no improvement in THF to THE ratio was observed, androgen metabolites in urine did not decrease (table II). There was no progression in treatment. Treatment with hydrocortisone was ceased. After five days CRH-stimulation test was accomplished. Blood samples were collected after 5, 15, 30, and 60 min in order to measure ACTH, cortisol, and cortisone levels. The test showed a pathological ACTH response (0 min: 49.6 pg/ml, 5 min: 173 pg/ml), which equaledto the increased F response (0 min: 249.3 nmol/l, 30 min: 562 nmol/l). Oral administration of dexamethasone (0.375 mg/day, two doses, 0.25mg in the morning and 0.125 mg in the evening) was instituted. After two months blood and urine tests revealed androgen suppression (table II).

Dexamethasone was administered. At that time, the patient was 7 years and 10 months old, his height was 147.6 cm (97 percentile), weight: 36.7 kg (between 85 and 97 percentile), BMI 16.7 kg/m^2 (between 50 and 75 percentile). The condition of the patient who did not receive a proper treatment for more than year remained the same, he did not develop any other symptoms caused by 11ß-HSD1 deficiency. During that year his bone age progressed from 11.5 years old to 13 years old (Greulich-Pyle). Dexamethasone treatment decreased his growth velocity, consequently, from 6.5 cm/year before treatment, to 2.4 cm / year after one year of treatment to the total growth inhibition for a few months, which resulted in reduction of the dexamethasone dose to 0.25mg per day. The lowest dose of dexamethasone was at the patient's age of 10 years and 6 months, when the boy was entering puberty (0.125mg/ per day in the morning). This dose was maintained for over a year. Thereafter, the doses of dexamethasone have been

Table III. Serum hormone values in our ACRD patient during continued treatment with dexamethasone which suppressed excessive adrenal androgen synthesis
Tabela III. *Wartości stężeń hormonów w surowicy naszego pacjenta w trakcie dalszego leczenia deksametazonem, który zahamował nadmierną syntezę androgenów przez nadnercza*

Duration of treatment with dexamethasone (Czas leczenia deksametazonem)	**3,5 years (3,5 roku)**	**7 years (7 lat)**	**10 years (10 lat)**	**Reference values (Wartości referencyjne)**
Patient's age (Wiek pacjenta)	**11 2/12**	**14 8/12**	**18**	
Dose (Dawka)	**0.125mg/24**	**0.250mg/24**	**0.250mg/24**	
ACTH, pg/ml	23		83.4	10–60
DHEA-S, ng/dl	1207	858		800–5600
Androstendione, ng/dl	111	105		80–300
Testosterone, pg/ml	79	1514		2362–9965
Cortisol, μg%	4.77HPLC	0.92	16.28	4.75–23.3

Table IV. Excretion of androgen metabolites (5,6), conjugated cortisol (1–4) and corticosterone (7) metabolites (μg/24 h) in our ACRD patient during treatment with dexamethasone (Dx). Therapy with Dx never suppressed the cortisol excretion in urine, what resulted in increased concentrations of cortisone metabolites. Dx treatment lead to significant improvement of urinary adrenal androgen metabolites suppression

Tabela IV. *Stężenie metabolitów androgenów (5,6), sprzężonych metabolitów kortyzolu (1–4) i kortykosteronu (7) (μg/24 h) u naszego pacjenta w trakcie leczenia deksametazonem. Terapia ta nigdy całkowicie nie zahamowała wydzielania kortyzolu w moczu, co skutkowało podwyższonymi wartościami stężeń metabolitów kortyzonu. Leczenie deksametazonem znacząco wpłynęło na hamowanie wydzielania metabolitów androgenów w moczu*

Duration of treatment with Dx (Czas leczenia deksametazonem)		**4 years (4 lata)**	**7 years (7 lat)**	**10 years (10 lat)**	**11 years (11 lat)**	
Dose of Dx (Dawka deksametazonu)		**0.125mg/24h 0.250mg/24h (every 2nd day – co 2 dzień)**	**0.250mg/24**	**0.250mg/24h**	**0.250mg/24 0.375mg/24 (every 2nd day – co 2 dzień)**	
						Reference values (Wartości referencyjne)
1	THE	9148.1	984.5	6980.7	7368.2	1193–6760
2	THF	211.9	26.8	189.7	235.5	615–2997
3	allo-THF	54.3	11.3	26.1	52.4	414–2599
4	ß-cortolone	1310.2	1249.2	1658.3	3127.6	738–5204
5	etiocholanolone	918.1	497.7	1207.9	2545.8	652–3387
6	androsterone	2938.6	197.8	1292.1	2030.1	242–1180
7	THA	763.7	45.3	278	289.9	44–328
THF+alloTHF/THE		0.036	0.04	0.03	0.04	0.7–1.2

changed depending on the patient's condition. A 24-hour urinary steroid profile analysis showed that treatment never lead to a definitive suppression of the cortisol excretion, what resulted in an intensified conversion to cortisone and increased cortisone metabolites in urine. We also never got the THF + allo-THF/THE ratio in normal values (in our patient urinary profile – around 0.04; norm: 0.7-1.3) (tables III,IV). Despite that, dexamethasone causes the inhibition of androgen metabolites excretion and suppresses or stopsprecocious pubarche. The patient's height became proper to his age after approximately 3 years of treatment (90 percentile at the age 11 years and 2 months). Bone age was equal to the biological age when the boy was 14 years old. Dexamethasone is a strong steroid, but the patient did not develop any serious side effects. He was under a steady ambulatory care, and had a steady control of blood pressure, serum glucose, lipid profile and Hba_1c level. In tests, only cholesterol was slightly elevated, low-cholesterol diet was recommended at the patient's age of 18. Testicular volume was evaluated with the Tanner scale during every visit and the volume increased appropriately to the patient's pubertal stage (age 11 – testicular volume 6 ml, age 12 – 11ml, age 13 – 15 ml – Tanner 5, age 17 – 18 ml). Stretch markson hips and abdomen, and mild acne on face and back were the only visible symptoms. In his medical history, the patient had a few fractures, but the connection with steroidotherapy was not proved. Imaging usingthe DXA method was performed at the age of 17, it showed a properbone mass (z-score +1,87), in prophylaxis vitamin D3 in dose 700 I.U. was administered. Regularly performed ultrasonography has not revealed any abnormalities, besides one ultrasound which showed an enlarged liver (148 mm – age 17). These tests have never shown any deviations from norm in adrenal glands. At the age of 18 the patient was 184 cm height (between 75 and 90 percentile), his weight was 74 kg (BMI – 21.9 kg/m^2) without any signs of hyperandrogenism.

Discussion

CRD and ACRD are extremely rare disorders and before describing our patient in 2003 there were found only several cases of adult women with ACRD in literature [4–7]. The fact that the patient became the first male child with ACRD caused that the treatment was challenging. Because of cortisol deficiency and to suppress excessive adrenal androgen synthesis by blocking pituitary ACTH secretion, the administration of glucocorticoid substitution was necessary. Excess of glucocorticoids can lead to side effects including growth failure, weight gain and iatrogenic Cushing's disease, and therefore our goal of treatment was to use the lowest doses of glucocorticoids

to prevent hypercortisolism, suppress androgens and provide normal puberty and growth [13]. In prepubertal children hydrocortisone as physiological cortisol is chosen as the first-line treatment. It has the least impact on growth suppression as a short-acting glucocorticoid [14]. In our case, administration of oral hydrocortisone (17.5 mg daily) was discontinued after two months due to the lack of significant improvement of suppression of adrenal androgen production. This observation showed that hydrocortisone was rapidly metabolized to cortisone without subsequent regeneration to cortisone by 11ß-HSD. It indicated impaired activity of this enzyme though functional mutations in the HSD11B1 gene were not found. The diagnosis of ACRD based on clinical presentation and biochemical data was confirmed five years later by detection of inactivating mutations in the H6PD gene [10]. Comparison cases of CRD and ACRD in literature suggestthat ACRD patients present more extreme biochemical phenotype characterized by significantly lower THFC5a-THF/THE ratios and HPA axis activation is more fully developed than in CRD patients. Furthermore, inactivation of H6PDH is a cause not only of loss of 11b-HSD1 oxo-reductase activity but also it leads to the gain of 11b-HSD1 dehydrogenase activity [12]. These findings may explain the reasons of inactivation of hydrocortisone resulting in reducing its potency, thereby initial therapy was ineffective in our patient. By contrast, in CRD patients therapy with optimized doses of hydrocortisone may be satisfactory to block HPA axis activityand decrease adrenal androgen excess [12].

After the ineffective therapy with hydrocortisone, dexametasone, longer-acting synthetic formula was administered, although it is generally avoided in children because of the concerns regarding the growth suppression [15]. Traditionally, glucocorticoid equivalence doses are based on the anti-inflammatory effect. Hydrocortisone is regarded with a relative potency of 1 and dexametasone with 30 times higher. However, research studies and clinical experience showed that the androgen-suppressing effect of dexametasoneis even 70-100 times higher, and therefore the potential for over treatment remains high [16, 17]. Authors suggested an incorrect dosage because of a wrong assumption of its potency as a main cause of the myth of 'growth toxic' glucocorticoid [18].

During childhood and adolescence of our patient, the dose of dexametasone was modified depending on the present results of laboratory tests, medical history and physical examination. Doses between maximum of 0.350 mg and minimum of 0.125 mg in puberty were administered. He was 184 cm at the age of 18 (between 75 and 90 percentile), although we observed two short-term episodes of height-suppression during treatment. Furthermore, regular measurements of testicular volumes indicated values in normal range according to the Tanner Scale. The patient developed only slight side effects – mild acne and stretch marks, slightly elevated concentration of cholesterol, reduced by proper diet. The patient did not report any complaints during control appointments and hospitalizations. Control laboratory studies indicated suppression of excess adrenal androgen synthesis (table III). Unluckily, we did not gain the complete suppression of cortisol production, although dexamethasone is the most potent adrenal suppression drug. However, in our opinion, we have found the balance between the glucocorticoid treatment effects of adrenal suppression and the achievement of full height potential considering the condition of our patient. Furthermore, our case has shown how significantly the knowledge about ACRD and CRD has evaluated with the last years.

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