Hyperandrogenism in a 13-year-old girl due to glucocorticoid receptor mutation

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Introduction

Glucocorticoid resistance syndrome (GRS) is a rare genetic disorder caused by inactivating mutations of the *NR3C1* gene encoding the glucocorticoid receptor. The phenotypic spectrum is broad ,may be asymptomatic or with clinical symptoms of mineralocorticoid and /or androgen excess. So far, about 20 different mutations in *NR3C1* presenting with the GRS phenotype have been reported.

Case Report

We report a 13-year-old girl that presented with severe hirsutism increased virilization and clitoromegaly. No suppression of cortisol following short overnight dexamethasone test, repeated elevated urinary free cortisol (UFC) and elevated ACTH indicated a diagnosis of Cushing syndrome but without the stigma of Cushing syndrome. Imaging evaluation by brain and abdominal MRI revealed normal pituitary and adrenal glands. Based on the contradiction between the phenotype, with absence of manifestations of Cushing syndrome, and the laboratory findings that indicated Cushing syndrome, GRS was suspected.

Genetic Investigation

Sanger sequencing of *NR3C1* identified a previously reported heterozygous mutation, c.1759_1762dupTTAC; p.His588Leufs*5, which results in a frameshift and stop codon 5 amino acids forward, in the proband and in her father. Other family members were negative for the identified mutation. The father was asymptomatic but had elevated 24-h UFC.

Treatment:

With a Low dose of dexamethasone improved the hirsutism and her well-being, but follow-up is needed.

Conclusion

The reported case demonstrates the unique phenotype of GRS and raises awareness of this rare condition. Glucocorticoid receptor sequencing is recommended in cases with discrepancies between laboratory findings that suggest Cushing syndrome and clinical manifestations of hyperandrogenism and mineralocorticoid excess with no symptoms of glucocorticoid excess.

Table 1: Levels of hormone before and after therapy with Dexametasone.

Parameter	Age 13.5 y	Age 15.5 y	After therapy	Reference range
Basal Cortisol	21.4	39	<0.5	4-22 µg/dl
Basal 17-OH-P	0.8	6.8	0.37	<3.2 ng/ml
11-Deoxycortisol	4.5	24.9	2.6	0.11-7.2 ng/ml
24 h UFC	256	774	85	32-208 nmol/24 h
DHEAS	195	354	4.7	25-460 µg/dl
ACTH	49.8	62	0.19	0-46 pg/ml
Androstendione	20	>35	2	1-11.3 nmol/l
Testosterone	0.91	0.98	<0.5	0.2-0.81 ng/ml
Cortisol after SDST (1mg)	1.42	2.58		<1.8 µg/dl

Table 2: Clinical parameters and DNA analysis of the NR3C1 Gene

	Patient	Father	Mother	Sister	Brother
Age (years)	16	40	37	15	12
Blood pressure	Normal	Normal	Normal	Normal	Normal
Height (cm)	158	178	161	158	169
Weight (kg)	49	80	60	48	42
Onset of Puberty	Early Puberty	Unknown	Normal	Normal	Premature Adrenarche
Hirsutism and Virilization	+++ Increased	++	+	-	+
Age of Menarche	11 y		12 y	12.5 y	
Androstendione	>35	16	2	8	7
24-H UFC (138-524) nmol/24hr	774	772	250	580	223
p.His588Leufs*5 mutation	Heterozygous	Heterozygous	W.T	W.T	W.T