11-oxygenated androgens may be related to the virilization of female external genitalia due to the maternal androgen-producing adrenal tumor

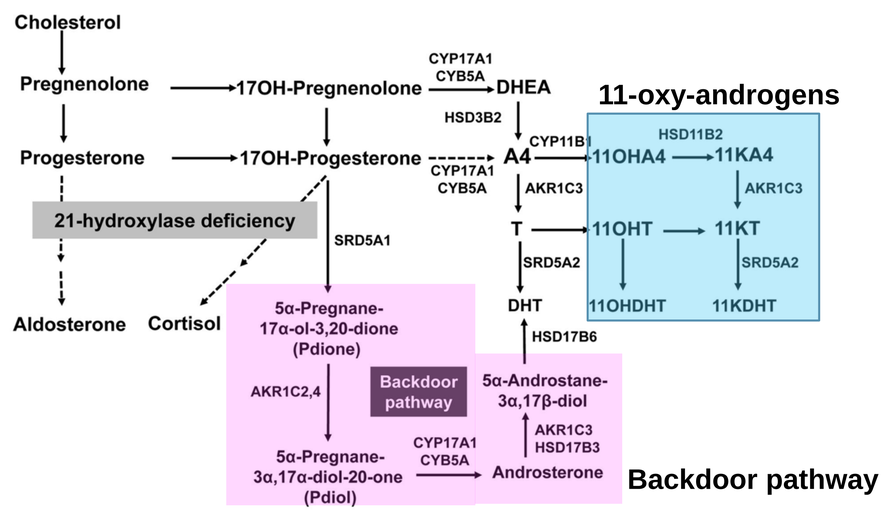
Keisuke Nagasaki[1], Kaoru Takase[2], Tomoyuki Tani[1], Hiromi Nyuzuki[1], Yohei Ogawa[1], Chikahiko Numakura[3], Keiko Homma[4], Tomonobu Hasegawa[5]

1. Division of Pediatrics, Department of Homeostatic Regulation and Development, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.
2. Department of Neurology, Hematology, Metabolism, Endocrinology and Diabetology, Yamagata University Faculty of Medicine, Japan.
3. Department of Pediatrics, Yamagata University School of Medicine, Yamagata, Japan.
4. Clinical Laboratory, Keio University Hospital, Tokyo, Japan. 5. Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan.

Background

- Masculinization of the external genitalia in humans is dependent on the formation of DHT through both the classical androgenic pathway and an alternative (backdoor) pathway. Backdoor pathway has been reported for the virilization of female patients with 21-hydroxylase deficiency (21-OHD) and cytochrome P450 oxidoreductase deficiency.
- Moreover, recent studies have demonstrated higher than normal circulating levels of 11-oxygenated 19-carbon steroids (11oxC19) in patients with 21-OHD[1,2] (Fig.1). 11-ketotestosterone (11-KT) and its 5α-reduced metabolite, 11-ketodihydrotestosterone (11-KDHT) are potent agonists of the human androgen receptor, similar to the classic androgens, testosterone (T) and dihydrotestosterone (DHT), respectively.
- The purpose of this study was to examine various androgen levels in the mother with fetal external virilization due to a maternal androgen-producing adrenal tumor.

Fig. 1 Adrenal steroidogenic pathways in 21-hydroxylase deficiency



Modified Curr Opin Endocrinol Diabetes Obes. 2017;24:252 Fig. 2

Patient 1 [3]: female child

The female patient was diagnosed as 46,XX DSD with Prader grade 3 virilization (Fig.2). Abnormal external genitalia (clitoral hypertrophy, labial fusion with a urogenital sinus, and non-palpable gonad) was recognized at birth. Her karyotype was SRY-negative 46,XX. Magnetic resonance imaging revealed a uterus, vaginal structure, and gonads in the right intraperitoneal and left inguinal region (Fig. 3). Hence, her gender was determined to be female. A neonatal screening test revealed no abnormalities. A deficiency in fetal-derived androgens, such as cytochrome P450 oxidoreductase deficiency, was considered from maternal signs of masculinization, but urinary steroid profile results were negative. No pathogenic variants were identified in 46,XX DSD-related genes such as *NR5A1, WNT4,* and *RSPO1*.

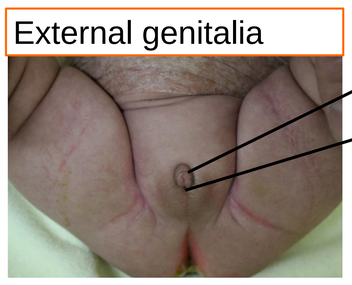


Fig.2 Prader stage III

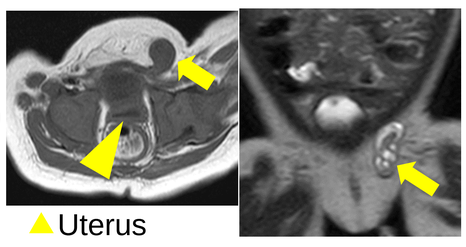


Fig.3

Patient 2 [3] : Mother

The patient's mother was 30 years old and had noticed hirsutism before and during pregnancy, without other sign of masculinization. She developed gestational diabetes mellitus and pregnancy-associated hypertension and gave birth via emergency cesarean section at 30 weeks of gestation. She was diagnosed with an androgen-producing adrenal tumor and Cushing syndrome at 8 months after delivery because of the virilization of her female infant's external genitalia and a continuation of her hirsutism. (Fig. 4) The tumor was removed by laparoscopic surgery, and the histology indicated an adrenal adenoma. Maternal androgen levels decreased after tumor removal (Table 1).

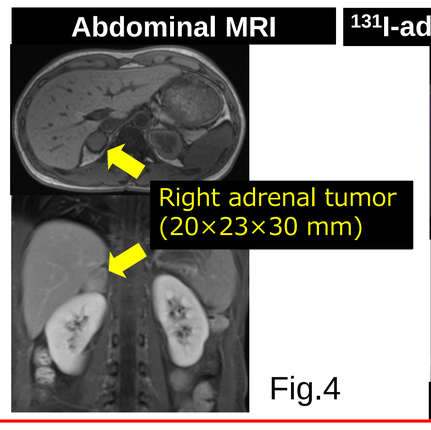


Fig.4

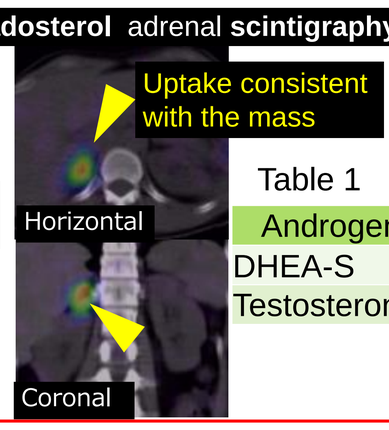


Table 1

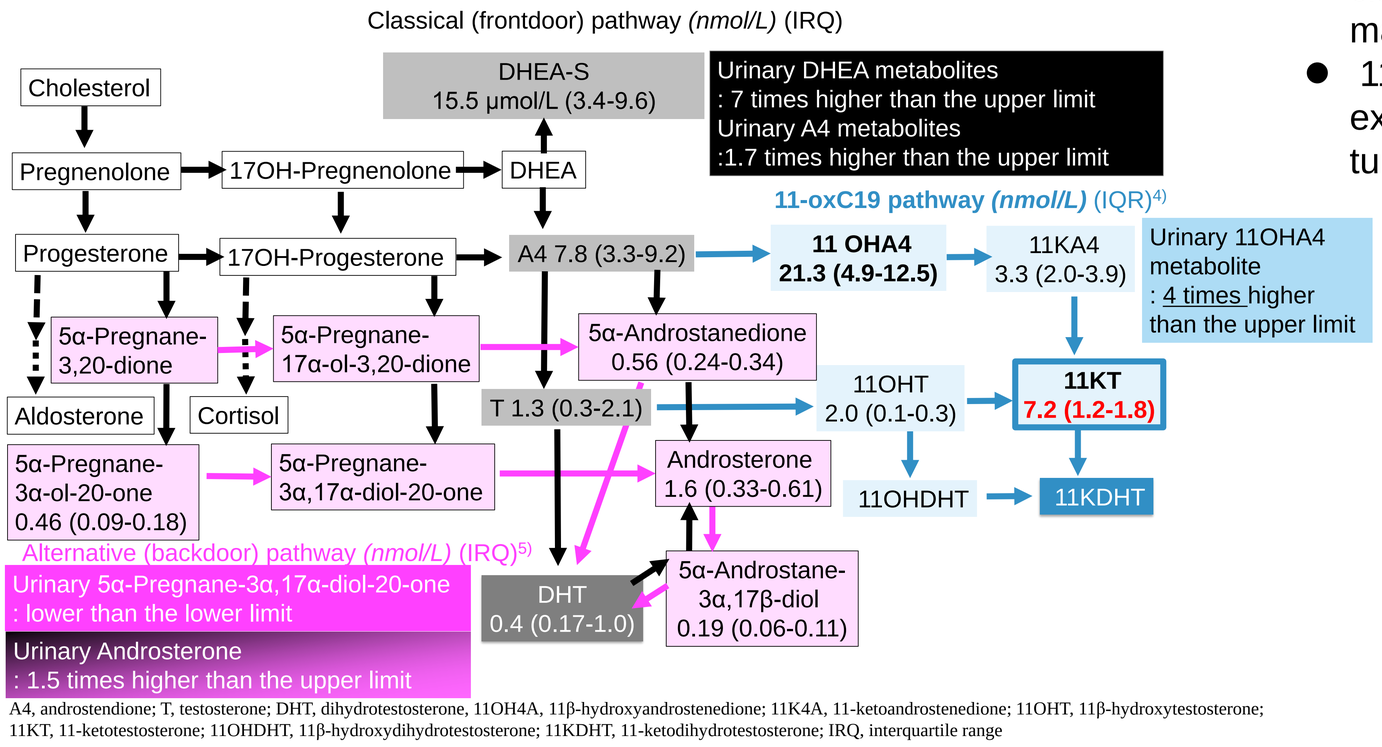
Androgens	Before	Post-op	
DHEA-S	15.5	0.16	μmol/L
Testosterone	2.8	<0.69	nmol/L

Methods

Maternal androgens measurement

- Serum DHEA-S and androstenedione (EIA)
- Urinary steroid profiles (GC/MS)
- Serum T, DHT, 11-oxC19 and backdoor pathway products (LC/MS/MS)

Results



A4, androstendione; T, testosterone; DHT, dihydrotestosterone, 11OH4A, 11β-hydroxyandrostenedione; 11K4A, 11-ketoandrostenedione; 11OHT, 11β-hydroxytestosterone; 11KT, 11-ketotestosterone; 11OHDHT, 11β-hydroxydihydrotestosterone; 11KDHT, 11-ketodihydrotestosterone; IRQ, interquartile range

As a result of various androgen measurements in the mother with an androgen-producing tumor, the two pathways for DHT biosynthesis, the classic and the backdoor pathway, were found to be slightly elevated, with the exception of the weak androgen, DHEA. However, 11KT, which has a strong androgenic action, was predominantly increased.

Discussion & Conclusions

- Placental aromatase converts excess androgen from the mother into estrogen, protecting it from fetal androgen exposure. However, 11oxC19s are nonaromatizable androgens, leading to fetal external masculinization.
- This is the first report of the involvement of 11oxC19, in addition to the classical and alternative pathways, in the fetal external masculinization.
- 11KT is the dominant androgen involved in the virilization of female external genitalia due to the maternal androgen-producing adrenal tumor.

(nmol/L)	A4	T	11OHA4	11KA4	11OHT	11KT
Patient 2	7.8	1.3	21.3	3.3	2	7.2
Control [4]	5.9	0.3	6.8	2.7	0.2	1.5
PCOs [4]	26.8	0.7	31.7	13.4	0.4	2.4

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58ESPE P2-249
Sex differentiation, gonads and gynaecology or sex endocrinology
Keisuke Nagasaki
Poster presented at: ESPE 2019 VIENNA
PosterSessionOnline.com