A case of 46,Y,dup(X)(p21.2p22.2) DSD caused by overexpressed DAX1

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1. Introduction

< DAX1 >
urogenital ridge

DAX1

SOX9

SRY

müllerian duct

< DAX1 overexpression >
urogenital ridge

overexpression

DAX1

SOX9

SRY

development müllerian duct

anti-müller hormone

follicle cell

anti-müller hormone

DAX: disorders of sex development
DAX1: dosage-sensitive sex reversal, adrenal hypoplasia critical region, on chromosome X, gene 1
SOX9: SRY (sex determining region Y)-box 9

2. Case Report

【case】 5Y8M, female socially

【physical examination】
H: 100 cm (-2.4 SD), BW: 12.7 kg (-2.1 SD)
BP: 90/53 mmHg

head: low-set ears, telecanthus and cleft palate

external genitalia: complete female (Quigley scale 6)

【laboratory data and imaging studies】

<blood examination>

ft₂ 1.20 ng/dL
TSH 8.85 μIU/dL
T< 0.03 ng/ml
LH 0.26 mIU/ml
FSH 13.26 mIU/ml
E2 19 pg/mL

< bone age > 5 years old

< steroid profile in urine > no abnormal findings

< MRI > head: no abnormal findings
pelvis: not detected ovaries, testes, and uterus.

< US > no abnormal findings

【stimulation test】

LHRH (2.5μg/kg) TRH(7μg/kg)

TLR (mIU/mL)

0min 30min 60min 90min 120min

1.16 18.00 17.50 15.58 11.12

15.14 23.75 28.41 29.48 30.88

11.8 135 93.5 74.8 58.8

hCG (3000 units) for 3days

0hr 24hr 48hr 72hr

<0.03 <0.03 <0.03 <0.03

T (ng/mL)

<0.03 <0.03 <0.03 <0.03

3. Discussion

In mice, Dax1 exposure to both low- and high-dose Dax1 can induce DSD (1). However, while the mechanisms behind Dax1 overexpression have been clarified in mice (1), details regarding the process in humans remain unclear.

No major differences have been noted between overexpressed Xp patients with or without DSD (2). While nearly all female patients with DAX1 overexpression and DSD have complete female external genitalia. Similarly, our patient also had complete female external genitalia while further exhibiting short stature. Short stature has been reported in a proportion of cases (2-4), although in our present case, the height might be due to her being small-for-gestational age (SGA) or having subclinical hypothyroidism.

The present case occurred with subclinical hypothyroidism, indicating that thyroid gland function was not normal. However, DAX1 overexpression and the region surrounding the DAX1 gene is not related to thyroid function. Therefore, we believe that the patient’s subclinical hypothyroidism was unrelated to overexpression of DAX1, occurring naturally. We need further research. Excluding her short stature, we were unable to explain the source of the patient’s symptoms.

4. Conclusion

* To our knowledge, this is the first case of DAX1 overexpression with subclinical hypothyroidism.
* Thyroid function should be ascertained to examine DAX1 overexpression in patients.