Turner syndrome with positive SRY gene and non-classical congenital adrenal hyperplasia: A case report

Mei-Nan He, Shan-Chao Zhao, Ji-Min Li, Lu-Lu Tong, Xin-Zhao Fan, Yao-Ming Xue, Xiao-Hong Lin, Ying Cao

Abstract

BACKGROUND
Co-morbidity of SRY gene turner syndrome (TS) with positive SRY gene and non-classical congenital adrenal hyperplasia (NCAH) is extremely rare and has never been reported to date.

CASE SUMMARY
In this article, we present a 14-year-old girl who was referred to our hospital with short stature (weight of 43 kg and height of 143 cm, < -2 SD) with no secondary sexual characteristics (labia minora dysplasia). Laboratory tests indicated hypergonadotropic hypogonadism with significantly increased androstenedione and 17-hydroxyprogesterone (17-OHP) levels. This was accompanied by the thickening of the extremity of the left adrenal medial limb. The patient’s karyotype was 45,X/46,X, +mar, and cytogenetic analysis using high-throughput sequencing indicated that the SRY gene was positive with compound heterozygous mutations in CYP21A2 as the causative gene for congenital adrenal hyperplasia. The sites of the suspected candidate mutations were amplified and verified using Sanger sequencing. The patient was finally diagnosed as having SRY positive TS with NCAH. The patient and her family initially refused medical treatment. At her most recent follow-up visit (age = 15 years old), the patient presented facial hair, height increase to 148 cm, and weight of 52 kg, while androstenedione and 17-OHP levels remained high. The patient was finally willing to take small doses of hydrocortisone (10 mg/d).
INTRODUCTION

Turner syndrome (TS) is the most common chromosomal abnormality in females. It has a prevalence of 1:2500, which approaches to 3% of live female births and approximately 15% of miscarriages\[^{1,2}\]. TS patients are characterized by short stature, broad chest, low posterior hairline, prominent ears, narrow and acutely arched palate, lack of pubertal onset at adolescence, and presence of streak ovaries with normal intelligence\[^{3}\]. Monosomy X is the most common karyotype observed in patients with TS (50%-60%), in addition to other structural abnormalities in the X chromosome or mosaicism karyotype reported\[^{4,5}\]. Additionally, the presence of Y chromosome material has been reported in about 10%-18% of patients. The role of the Y chromosome in human tumorigenesis remains controversial. However, the risk of virilization during puberty, gonadoblastoma, and malignant transformation increases by 7%-10% when Y chromosome material is present in gonadal tissue or peripheral blood in TS patients\[^{6,7}\].

Non-classical congenital adrenal hyperplasia (NCAH) is a common autosomal recessive disorder that manifests due to P450c21 (21-hydroxylase) deficiency. NCAH is caused by mutations in the CYP21A2 gene or microconversions between CYP21 pseudogenes and active genes\[^{8,9}\]. The disorder is a mild form of congenital adrenal hyperplasia (CAH) and may result in infertility, miscarriages, oligomenorrhea, hirsutism, acne, advanced bone age, and clitoromegaly in females. 17-hydroxyprogesterone (17-OHP) levels could be used for diagnosis, but the gold standard is the adrenocorticotropic hormone (ACTH) stimulation test and 17-OHP measurement based on several studies and guidelines. However, the optimal cutoff for baseline 17-OHP levels or post-ACTH peak 17-OHP levels for NCAH diagnosis remains controversial\[^{10-14}\]. Based on a large data set in combination with genetic diagnosis, NCAH could be diagnosed using baseline 17-OHP levels > 6 nmol/L or > 30 nmol/L after ACTH stimulation\[^{10-14}\]. The diagnosis could be substantiated using CYP21A2 mutation analysis. In contrast to CAH patients, the majority of patients with NCAH are never diagnosed due to very mild symptoms. In addition, compared to the majority of patients with classic CAH requiring life-long glucocorticoid treatment for survival, NCAH patients are seldom diagnosed and treated only when

CONCLUSION

In conclusion, upon evaluation of the patient mentioned in the report, we feel that 17-OHP measurement and cytogenetic analysis are necessary for TS patients even in the absence of significant virilization signs. This will play a significant role in guiding diagnosis and treatment.

Key Words: Turner syndrome; SRY gene; Congenital adrenal hyperplasia; Tumor; Diagnosis; Endocrinology and metabolism; Case report

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symptomatic\(^{(10)}\).

The diagnosis of CAH is difficult in females with TS. This is because of the shared common clinical features like short stature, amenorrhea, and infertility and the rare reports of the condition. Moreover, patients with a combination of TS with a positive SRY gene and NCAH have never been reported. In this article, we present a 14-year-old girl who was diagnosed with NCAH and TS with a positive SRY gene concurrently. The combination of these three factors increases the difficulty of diagnosis and treatment but provides insights into the understanding of TS. It also suggests that 17-OHP together with genetic screening is necessary for TS patients.

**CASE PRESENTATION**

**Chief complaints**
A 14-year-old girl was referred to our hospital with growth and developmental retardation.

**History of present illness**
Based on her medical history, the patient was born after a normal full-term delivery and her parents were not genetically related. She appeared to be in good health. Her height and weight were 51 cm and 3.2 kg, respectively, at birth. However, her growth rate was slow (1 cm/year) and her height was 143 cm at age 12 years (< -2 SD), which was significantly lower than normal when she visited our hospital.

**Physical examination**
On physical examination, the patient’s general status was good, her vital signs were stable, and no masculine features such as hirsutism, acne, and clitoromegaly were observed. Axillary and pubic hair was absent. Breast and labia minora dysplasia was observed.

**Laboratory examinations**
Biochemistry and electrolyte analysis showed no abnormalities (Table 1). Hormone profiles indicated hypergonadotropic hypogonadism, and karyotype analysis indicated 45,X/46,X, +mar, and mosaicism with suspected Y chromosome material (Figure 1).

**Imaging examinations**
Ultrasonic gynecopathy examinations and pelvic magnetic resonance showed no development of the uterus or ovaries (Figure 2).

**FINAL DIAGNOSIS**
The patient’s final diagnosis was SRY positive TS with NCAH.

**TREATMENT**
The patient initially refused medical treatment. At the most recent follow-up visit (one year later), the patient finally accepted low doses of hydrocortisone (10 mg/d).

**OUTCOME AND FOLLOW-UP**
At the most recent follow-up visit (patient’s age was 15 years old), the electrolytes were normal. However, the patient had facial hair, her height increased to 148 cm, and her weight was 52 kg, with androstenedione and 17-OHP levels remaining high (Table 1). Human chorionic gonadotropin (HCG) stimulation test showed absence of Leydig cell function (Table 2). We will continue to follow the patient for therapeutic effects.
Table 1 Patient electrolyte and hormone profile

| Parameter                                      | First visit | Follow-up (after 1 yr) | Reference range |
|------------------------------------------------|-------------|-------------------------|-----------------|
| Serum sodium, mmol/L                          | 138         | 140                     | 135-145         |
| Serum potassium, mmol/L                       | 3.82        | 4.38                    | 3.50-5.30       |
| Serum chloride, mmol/L                        | 102.9       | 103.9                   | 137-147         |
| Serum calcium, mmol/L                         | 2.40        | 2.40                    | 2.20-2.65       |
| Serum phosphorus, mmol/L                      | 1.36        | 1.40                    | 0.81-1.45       |
| Serum magnesium, mmol/L                       | 0.78        | 0.80                    | 0.77-1.03       |
| Follicle stimulating hormone, mIU/mL          | 60.86       | 60.83                   | 3.50-12.50      |
| Lateinizing hormone, mIU/mL                   | 19.98       | 23.88                   | 2.40-12.60      |
| Estradiol, pg/mL                              | < 5.00      | 11.96                   | 12.40-233.00    |
| Progesterone, ng/mL                           | 0.101       | 0.722                   | 0.00-0.89       |
| Testosterone, ng/mL                           | 0.200       | 0.310                   | 0.025-0.481     |
| Free testosterone, pg/mL                      | 3.48        | 4.12                    | 0.00-4.20       |
| 17Hydroxyprogesterone, ng/mL (first time)     | 24.70       | 27.26                   | 0.05-1.02       |
| 17Hydroxyprogesterone, ng/mL (second time)    | 12.10       | -                       | 0.05-1.02       |
| Dehydroepiandrosterone, µg/dL                 | 4.15        | 4.77                    | 4.30-22.40      |
| Androstenedione, ng/mL                        | 7.12        | 8.18                    | 0.30-3.30       |
| Adrenocorticotropic hormone, pg/mL            | 39.74       | 51.06                   | 7.20-63.30      |
| Cortisol (8:00), nmol/L                       | 15.32       | 13.20                   | 1.65-9.23       |
| Cortisol (16:00), nmol/L                      | 4.96        | -                       | 3.44-16.76      |
| Cortisol (0:00), nmol/L                       | 1.83        | -                       | -               |
| AMH, ng/mL                                    | < 0.06      | -                       | -               |

AMH: Anti-Mullerian hormone.

Table 2 Human chorionic gonadotropin stimulation test results

| Parameter                                      | 0 min  | 24 h   | 48 h   | 72 h   |
|------------------------------------------------|--------|--------|--------|--------|
| Testosterone, ng/mL                            | 0.250  | 0.300  | 0.260  | 0.290  |
| Androstenedione, mmol/L                        | 8.18   | -      | -      | 4.86   |
| Dihydrotestosterone                            | 35.59  | -      | -      | 28.90  |

DISCUSSION

As mentioned previously, CAH diagnosis is difficult in females with TS. The majority of previously reported cases with concomitant TS and CAH were diagnosed as TS. They had ambiguous genitalia or their NCAH was misdiagnosed as TS\[^{9,16-26}\]. Although our patient was of short stature with no virilization signs and ambiguous genitalia, Larizza \textit{et al.}\[^{21}\] reported that the frequencies of both abnormal 17-OHP response to ACTH stimulation test and \textit{CYP21} gene mutation carriers were prominently higher in patients with TS than in healthy controls. Next, Linglart \textit{et al.}\[^{27}\] found that the proportion of 21-hydroxylase deficiency carriers in TS patients was up to 21.6%, which was significantly higher than that in the general Italian population\[^{27}\]. Based on previous studies and the labia minora dysplasia observed in our patient, we measured 17-OHP levels and performed karyotyping and cytogenetic analysis. Our results demonstrated that 17-OHP levels were significantly increased and karyotype and cytogenetic analysis demonstrated 45,X/46,X,+mar with a positive SRY gene with compound heterozygous mutations in \textit{CYP21A2}, suggesting it to be the causative gene for CAH.
The reason for the absence of typical clinical manifestations despite the presence of the causative gene mutation for CAH is the wide phenotypic variability of the non-classical form. This is due to different enzymatic activity levels induced by several gene mutations in the CYP21A2, as well as microconversions between CYP21 pseudogenes and active genes. To-date, > 200 CYP21A2 inactivating mutations have been recorded in the Human Gene Mutation Database (www.hgmd.org). New et al. extensively investigated the genotype-phenotype correlation in 1507 patients with CAH and demonstrated the presence of genotype-phenotype discordance. Moura-Massari et al. investigated the correlation between genotypes and the severity of hyperandrogenic phenotype in a cohort of 114 NCAH patients. Their results demonstrated that CYP21A2 genotypes do not predict the severity of hyperandrogenic manifestation in the non-classical form of CAH.

Gonadal dysgenesis observed in TS patients is associated with gonadoblastomas and malignant transformation when Y-chromosome-derived genetic material is present in the genome. If the presence of Y chromosome fragments in TS patients

Figure 1 Computed tomography scan and Karyotype analysis indicated 45,X/46,X, +mar, and mosaicism with suspected Y chromosome material. A-D: Magnetic resonance imaging showed no uterus or ovary; E: Computed tomography of the adrenal gland indicated left adrenal hyperplasia; F: The patient’s karyotype is 45,X/46,X, +mar.
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could be detected at an early stage, the incidence of gonadoblastomas could be reduced or even prevented. Treatment of TS could be guided with prophylactic gonadectomy considered\(^2\).

Regrettably, our patient refused laparoscopic exploration to further determine the

Figure 2 The sequences of the patients and her parents. A, C, and E: The patient’s sequence; B and D: The sequence of the patient’s father; F: The sequence of the patient’s mother.
presence and nature of gonadal tissue and determine whether she was at risk for gonadoblastoma. HCG stimulation test showed the absence of Leydig cell function. We will assess disease progression during follow-up.

CONCLUSION

In conclusion, upon evaluation of the patient mentioned in the report, we feel that 17-OHP measurement and cytogenetic analysis are necessary for TS patients even in the absence of significant virilization signs. This will play a significant role in guiding diagnosis and treatment.

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