Triple-X syndrome accompanied by congenital adrenal hyperplasia: case report

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The 47,XXX karyotype is a rare sex chromosome anomaly. This karyotype is usually not associated with a characteristic physical phenotype. In the presented case, a triple-X girl patient associated with 11β-hydroxylase deficiency is identified. The case was referred to the Endocrinology Unit at six days of age because of ambiguous genitalia. The karyotype in this case was 47,XXX, an unexpected finding. Diagnosis of 47,XXX individuals remains difficult because specific clinical criteria used to identify this condition are not available. Congenital adrenal hyperplasia has not been previously reported in patients with triple-X syndrome.

Key words: triple-X, congenital adrenal hyperplasia, 11beta-hydroxylase deficiency.

By definition, triple-X syndrome (47,XXX) is a sex chromosome abnormality occurring in females that is characterized by the presence of an extra X chromosome¹. The incidence rate of the syndrome has been reported to vary between 0.73² and 1.0³ per 1,000 female births. The majority of females with triple-X syndrome appear normal at birth, and without specific congenital malformations or identifying physical characteristics⁴-⁶. We detected the 47,XXX karyotype in a six-day-old girl who was diagnosed and treated for 11β-hydroxylase deficiency and who was eventually submitted for cytogenetic examination because the external genitalia were quite virilized. To our knowledge, this is the first case report of an association of triple-X karyotype with congenital adrenal hyperplasia (CAH) due to 11β-hydroxylase (11β-HD) deficiency.

Case Report

This case was referred to the Endocrinology Unit at six days of age because of ambiguous genitalia. The child’s weight at birth was 2600 g after an uneventful pregnancy followed by a spontaneous vaginal delivery at term, and it was the first pregnancy of a 17-year-old healthy mother. There was no kinship between mother and father, no history of disease and no use of drugs before or during pregnancy. Physical examination showed ambiguous genitalia: the genital tubercle measured 2x1 cm, the urethral opening was at the perineum, and two gonads were not palpable within a bifid scrotal structure. The genitalia were hyperpigmented (Fig. 1). Bone age was 38 weeks by knee X-ray. The infant’s blood pressure was 90/65 mmHg. Blood was drawn for electrolytes, androgen levels, and karyotype. Serum sodium concentration was elevated (149 mEq/L) and serum potassium concentration was normal at 5 mEq/L. Metabolic acidosis (serum bicarbonate concentration was 16.7 mmol/L) was also present. Intravenous fluids were started, and hydrocortisone (20 mg/m²) was given perorally. Serum concentrations of adrenal steroids and their precursors before the first dose of hydrocortisone were abnormal: 17-hydroxyprogesterone was 101 ng/ml (normal 0.4 ng/ml), 11-deoxycortisol was 63.54 ng/ml (normal 0.1-1.5 ng/ml), dehydroepiandrosterone sulfate (DHEA-S) was 3575 ng/ml (normal 50-100 ng/ml), androstenedione was 41 ng/ml (normal 0.06-0.68 ng/ml), total testosterone was 5864 ng/dl (normal 75-400 ng/dl), free testosterone was 208.67 pg/ml (normal 1.5-31 pg/ml), adrenocorticotropic hormone (ACTH) was 1834 pg/ml (normal 0-60 pg/ml), and cortisol was 37.3 µg/dl). Ureterogram showed a normal uterus (Fig. 2). Cranial magnetic
resonance imaging (MRI) showed metopic craniosynostosis, and echocardiographic study showed atrial septal defect with a diameter of 7-8 mm and aortic coarctation. Ultrasonography revealed enlarged collecting system. Voiding cystourethrogram did not show vesicoureteral reflux. Treatment was started with captopril 0.5 mg/kg/24h, perorally for hypertension. This infant had classical CAH due to $11\beta$-HD. The karyotype was 47,XXX (Fig. 3). Thus, she was also diagnosed as triple-X syndrome.

**Discussion**

Females with the 47,XXX karyotype, first reported in 1959, present a tendency to be tall and thin, and many of them appear to be completely normal. Studies of inheritance and expression of X-linked genes suggest that the origin of the extra X chromosome in 47,XXX females is usually nondisjunction in meiosis I of the mother, and a maternal age effect has also been noted. In this case, all the other family members were phenotypically normal,
and the origin of the extra X chromosome could not be ascertained, but maternal age was very young. In a study of 43 infants with trisomy X, the mean birth weight at term was 2970 g. There was no recognizable phenotype at birth. These infants were identified by prospective cytogenetic screening of all newborns in Denver. Their karyotype would not have been suspected from their physical examination. Congenital heart disease was diagnosed in two infants and congenital hip dislocation in one. There was an increased frequency of epicanthal folds and clinodactyly\(^9\). The presence of such minor anomalies as these is possibly increased in 47,XXX females as compared with controls\(^10\). Cardiac ECHO demonstrated atrial septal defect and aortic coarctation, and cranial MRI showed metopic craniosynostosis in our case. The karyotype was 47,XXX. This was an unexpected finding in our case.

\(^{11}\)β-hydroxylase deficiency (HD) is the second most common form of CAH, accounting for 5 to 8% of all cases, with an incidence of about 1 in 100,000 births in the general Caucasian population\(^11\). It is clinically characterized by virilization of the external genitalia in females, rapid growth and premature epiphyseal closure, and hypertension. Biochemically it can be recognized by elevated production of 11-deoxycortisol, androstenedione, testosterone, and occasionally 11-deoxycorticosterone. Urinary concentrations of 18-hydroxylated steroids are decreased, whereas tetrahydrometabolites of 11-deoxycortisol and deoxycorticosterone are increased. Serum potassium levels may be normal or decreased; serum sodium levels are normal but plasma renin and aldosterone are low or undetectable, respectively\(^12-14\). In our case we suspected CAH due to ambiguous genitalia. Although the external genitalia were quite virilized, the internal mullerian structures were preserved in our case. This led us to investigate the karyotype. The clinical and biochemical abnormalities revealed the classic form of 11β-HD, and the 47,XXX result of her karyotype was interesting. The different options of management were discussed with the family and this child was raised as a female. She had surgery for vaginoplasty and clitoroplasty performed in the first six months of life. She is presently receiving maintenance hydrocortisone and captopril.

Our case illustrates that the proper diagnosis of a genetic disease may lead to the diagnosis of an associated disorder. To our knowledge, this is the first case of a trisomy of chromosome X with CAH. We consider that the association between CAH and X trisomy in this patient may be a random finding.

**REFERENCES**