

# Four rare cases of Turner syndrome with unusual phenotypes and genotypes

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## Abstract

Turner syndrome (TS) is the most common sex chromosome disorder, and characterized by short stature and ovarian failure. The clinical phenotype of TS is highly variable and depends on the chromosome abnormality. There have been remarkable advance in medical knowledge about TS, but there are still many areas to be investigated as to what problems will accompany them grow up. To facilitate better understanding of TS, we present four patients with TS with various genotypes and phenotypes. Iron deficiency anemia due to excessive menstrual bleeding, TBG deficiency and normal stature and ovarian failure in patients with various TS genotype were described. Patients with TS exhibits a wide spectrum of clinical symptoms and require long-term follow-up

## Case reports

### Patient 1

A 14.5-year-old girl was referred to our clinic because of short stature. Physical examination revealed hypertelorism, down-slanted palpebral fissures, micrognathia, a highly arched palate, and cubitus valgus. She was 141 cm tall (<1<sup>st</sup> percentile) and weighed 47 kg. Her Tanner stage was breast V and pubic hair II. She had no cardiac or renal anomalies. She had frequent otitis media and respiratory infections and had undergone a tonsillectomy and adenoidectomy. The growth plates were closed when she visited our clinic and she was never treated with growth hormone. Cytogenetic analysis revealed a TS karyotype with 45,X. Menarche had occurred at the age of 12 years and her menstrual cycle was irregular. One year earlier, she visited a local gynecology clinic with oligomenorrhea and took ethinyl estradiol for about 6 months. Subsequently, she had excessive menstrual bleeding and took iron supplements for anemia. These symptoms persisted even after stopping the ethinyl estradiol. In our hospital, the initial laboratory findings were hemoglobin (Hb) 13.6 g/dL, ferritin 42.7 ng/mL, total iron-binding capacity (TIBC) 290 µg/dL, iron 112 µg/dL, transferrin saturation 38.6%, luteinizing hormone (LH) 9.85 mIU/mL, follicle-stimulating hormone (FSH) 6.58 mIU/mL, and estradiol (E2) 104.50 pg/mL. Thyroid function tests revealed a euthyroid state, and antithyroid antibodies were all negative. Coagulation studies were normal. Gynecological ultrasound revealed a normal uterus and ovaries. Two months later, she visited our clinic complaining of dizziness and persistent menstrual bleeding for more than 2 weeks. Laboratory tests showed Hb 7.1 g/dL, ferritin <0.5 ng/mL, TIBC 341 µg/dL, iron 16 µg/dL, and transferrin saturation 4.7%. There was no evidence of hemolysis. She was diagnosed with iron deficiency anemia (IDA) due to menometrorrhagia. After transfusing packed red blood cells (PRBC), the Hb increased to 10.1 g/dL. Subsequently, she has been taking oral iron supplements and estradiol valerate. After 3 months, the iron supplements were discontinued. She has a regular menstrual cycle on estradiol valerate, and continues to have pediatric endocrinology and gynecology checkups.

### Patient 2

A 58-month-old girl was referred to our clinic because of short stature. On physical examination, she was 97.2 cm tall (<1<sup>st</sup> percentile) and weighed 17.5 kg. She was prepubertal and has no dysmorphism of TS, except short stature and cubitus valgus. She had no cardiac or renal anomalies. Cytogenetic analysis of 25 blood lymphocytes revealed a TS mosaicism karyotype, 45,X (18 cells)/47,XXX (7 cells). Serum laboratory tests were T3 67.5 ng/dL (normal 58–159), free T4 0.66 ng/dL (normal 0.7–1.48), TSH 2.658 µIU/mL (normal 0.35–4.94), and negative antithyroid antibody. Thyroxine-binding globulin (TBG) was <1.0 µg/mL, indicating TBG deficiency. She was treated with growth hormone and her progress was monitored. Because she has been living in Philippines since she was 3 years old, she visited our hospital once a year. At age 5 years, she was prepubertal, and laboratory tests revealed LH 4.4 mIU/mL, FSH 3.1 mIU/mL, and E2 <5.0 pg/mL. At age 7 years, 10 months, breast budding occurred and her bone age was 10.5 years. In that time, she was 117.3 cm tall and weighed 33.9 kg. Menarche occurred at age 11 years; her bone age was 13 years and she was 137.0 cm tall and weighed 49.8 kg. Tanner stage was breast IV and pubic hair II. When she visited our clinic at the age of 13, she looked pale and anemic. She had a regular menstrual cycle, but complained of menometrorrhagia.

The initial laboratory findings were Hb 4.4 g/dL, ferritin <0.5 ng/mL, TIBC 490 µg/dL, iron 8 µg/dL, and transferrin saturation 1.6%. No evidence of hemolysis was found. She had LH 7.39 mIU/mL, FSH 5.42 mIU/mL, and E2 300.3 pg/mL. Coagulation studies were normal. Gynecological ultrasound revealed a normal uterus and ovaries. She was found to have IDA due to menometrorrhagia. After a PRBC transfusion, the Hb increased to 8.0 g/dL. She took iron supplements and medroxyprogesterone acetate. After 3 months, she appeared healthy and had a regular menstrual cycle without excessive bleeding. Laboratory tests revealed Hb 13.8 g/dL, ferritin <1.8 ng/mL, iron 121 µg/dL, 33.8% transferrin saturation, LH 0.95 mIU/mL, FSH 7.64 mIU/mL, and E2 43.0 pg/mL. Her height and weight were 141.6 cm and 48.7 kg, respectively, and the growth plates were completely closed. Tanner stage was breast V and pubic hair III.

### Patient 3

A 17-year-old girl was referred because of recent amenorrhea lasting more than 1 year. Her menarche had occurred at the age of 16 years; this was followed by one episode of oligomenorrhea and no menstruation since then. On physical examination, her height was 160 cm (ca. 50<sup>th</sup> percentile) and she weighed 50 kg. She has never been treated with growth hormone. Her Tanner stage was breast IV and pubic hair II. She had no cardiac murmurs. There was no suspicious dysmorphism of Turner syndrome. Serum laboratory tests were LH 26.83 mIU/mL, FSH 99.36 mIU/mL, and E2 <5 pg/mL. Thyroid function tests revealed normal T3, mildly increased TSH (5.13 µIU/mL), and positive thyroglobulin (TG) antibody (436.20 IU/mL, normal 0–115 IU/mL). Her bone age was 12.5 years. Gynecological ultrasound revealed a small uterus and ovaries with invisible follicles. Cytogenetic analysis of 30 blood lymphocytes revealed a karyotype of TS with 46,X,del(X)(q24). Her parents do not want to tell her that she has TS until she enters college. She is not receiving growth hormone therapy or sex hormone therapy, and is undergoing periodic outpatient follow-up.

### Patient 4

She was born via cesarean section due to oligohydramnios at gestational age 36 weeks. Her birth weight was 2,160 g. She was admitted to the neonatal intensive care unit for cyanosis after delivery. No lymphedema or webbed neck was observed. Cytogenetic analysis revealed TS mosaicism, 46,X,i(X)(q10)/45,X. She was treated with levothyroxine for congenital hypothyroidism and referred to another clinic. At the age of 5 years, she revisited our clinic for short stature. On physical examination, her height was 101.9 cm (<3<sup>rd</sup> percentile) and she weighed 16.2 kg. Her growth velocity was 4.1 cm per year. She had no dysmorphism of TS, except short stature and cubitus valgus. Her parents said, she had frequent otitis media and respiratory infections. Echocardiography revealed no heart problems. Thyroid function tests were normal without levothyroxine supplementation. She is on growth hormone therapy and we are tracking her growth and pubertal progress.

Serum LH, FSH, and estradiol (E<sub>2</sub>) were measured only in the patient group. Serum MKRN3 concentrations were determined using a commercially available Human MKRN3 ELISA Kit (MyBioSource, San Diego, CA, USA), with a detection limit of 7.8 pg/mL. The intra- and inter-assay coefficients of variation (CVs) listed by the manufacturer were < 8% and < 12%, respectively. The test worked as stated by the manufacturer. Serum NPTX1 levels were determined using a commercially available Human MKRN3 ELISA Kit (MyBioSource, San Diego, CA, USA), with a detection limit of 0.10ng/mL. The intra- and inter-assay coefficients of variation (CVs) listed by the manufacturer were < 10%, respectively.

## Conclusions

TS has a variety of underlying X chromosome abnormalities, and its clinical manifestations are even more varied and extensive. Because short stature and ovarian failure are hallmarks of TS, one cannot overemphasize the importance of considering TS in patients with short stature or ovarian failure. In addition, clinicians should be aware that TS exhibits a wide spectrum of clinical symptoms and approach it with a long-term perspective and deep understanding

**The authors have no conflicts of interest to declare**

