A classical turner syndrome in 16 years old girl

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ABSTRACT

Turner syndrome (TS), a disorder of female is characterized by the absence of all or part of second sex chromosome. TS is associated with amount of potential abnormalities in many organ systems. Important to recognize a classical case of TS and its management. A 16 year old girl who was referred with delay puberty, short stature and hearing loss. She had prepubertal pattern genital development, no distribution of axillary and pubic hair, high arch palatum, low posterior hair line, low set ears and short neck. Laboratory examination showed high concentration of lutein and follicular stimulating hormone, and low concentration of estradiol, with the karyotyping (45,XO). We planned to give growth hormone but it wasn’t covered by insurance. Low ethinylestradiol started with gradually increment and after 6 month therapy, she had minimal pubic hair and breast development, 0.5 cm height increment and got grommet insertion to treat the hearing loss. Recognizing TS in many organ systems was important to make a proper management.

Keywords: Turner syndrome, hypergonadotropic hypogonadism, short stature, delay puberty.

INTRODUCTION

Turner syndrome (TS) is a disorder of female. It was first described in 1938 by Turner. TS recognized from the loss of an X chromosome or essential part of it. Approximately half TS have monosomy X (45, XO), 20 – 30% may have mosaicism structural abnormalities and 20 % have isochromosome. The prevalence of TS is still unknown. It has been roughly estimated among live born females is 1 in 2000 to 1 in 5000.1-3

Turner syndrome is associated with a constellation of potential abnormalities involving many organ system and the presentation of TS varies throughout life stage. The classic phenotypic presentation of TS most commonly includes short stature and puberty delay. Additional features are webb neck, low posterior hair line, misshapen or rotated ears, high arch palatum, broad chest with widely spaced nipples, cubitus valgus, pubertal delay, micrognathia, short fourth metacarpal and metatarsals, scoliosis, cardiac malformation, kidney anomalies, sensorineural hearing loss and recurrent otitis media.4

Diagnosis TS is based on clinical features, laboratory and chromosome analysis. The chromosomal analysis of Turner syndrome was first recognized by Ford et.al and has been gold standar for definitive diagnosis. After TS was diagnosed, it is important to screen other congenital anomaly related to the syndrome.1,4,5,7
A multidiscipline approach is needed to improve the quality of life patient with TS. We are report the sixteen-aged female patient who had the classical morphology features of Turner syndrome.

DS, A 16-year-old girl was referred to endocrinology outpatient clinic with chief complain primary Amenorrhea. Here other complaint were not breast development, pubic dan axillary hair. She was also short statured and had hearing loss.

During childhood, there was also no prior history of receiving hormonal therapy, narcotics, corticosteroid or chemotherapy, and never had head trauma. She was born by spontan delivery at 37 weeks of gestation to a non-consanguineous parents. The mother and father was 25 and 30 years old respectively. She has 23 years old brother with normal phenotype. Both of her parents were phenotypically normal. But she has a cousin from her father’s family with the same abnormal phenotype and diagnosed with TS. Other illness genetic disorder, mental retardation has never occurred in her family. (Pedigree showed at figure 1)

Physical examination revealed an alert girl, who looked active. The pulse was regular at 98 beats per minute, respiratory rate 22 beats per minute and axillaries temperature 36.8°C. Her body weight, body height and upper arm circumference were 30 kg (< 3rd percentile, CDC 2000; severely underweight), 140 cm (< 3rd percentile, CDC 2000; severely stunted) and 19 cm respectively. The ideal body weight was 35 kg and her potential height was 160.5 ± 8.5 cm. Thus, according to the waterlow criteria, her nutritional status was 85% (under-nourished).
CASE ILLUSTRATION

Physical appearance with low hair line, low set ears, rotated ears, high arched palate, webb neck and shield chest. She had absence of secondary sexual characteristics, lack of axillary hair, pubic hair and no breast budding. Tanner stage of breast and pubic hair development was stage 1.

Based on anamnesis and physical examination working diagnosis for the case was hypergonadotrophic hypogonadism et causa suspic turner syndrome differentiated with constitutional delay of growth and puberty and hypogonadotropic hypogonadism. We planned for further examination such as measurement of lutein hormone (LH), follicular stimulating hormone (FSH), liver function (LFT), tiroid stimulating hormone (TSH), free thyroid (FT4), karyotyping, ultrasound abdomen and gynecology, echocardiography, bone age measurement, and consult patient to otolaryngology head and neck surgery department for hearing loss analysis.

Gynecological ultrasonography revealed 3x0.5 cm uterus, ovaries were non visualized, no adnexal masses and gall bladder, absent of calculus and neoplasm. The FSH level and LH was very high 143 mIU/L and 30.8 mIU/L respectively compare to normal females (FSH 0.96–12.9 mIU/L and LH 0.5-9.8 mIU/L ). The estradiol level was very low 1.32 pg/ml compare to normal female (estradiol >45 pg/mL). Echocardiography, liver fuction test, TSH and FT4 were normal. The karyotyping result consistent with turner syndrome 45, X0.

Then ethinylestradiol was given after the diagnosis was established. She has been treatment low dose ethinylestradiol, started from 2 µg and increased until the feminization is adequate. Growth hormone (GH) was not given in that patient because it is not covered by insurance. She also had grommet insertion to treat the hearing loss. In our last follow up, after 6 months therapy, we found minimal pubic hair with breast development (Tanner stage 2) and increased body height until 0.5 cm. (figure 7).

DISCUSSION

Turner syndrome is a rare case with known genotype variability that affect females in a ratio of 1: 2,000 to 1 : 5,000 live births. This syndrome is caused by partial or total deletion of sexual chromosome. A 45, XO karyotype has been observed in 1- 2% of human conception, 10% aborted at first trimester pregnancy, more than 99% aborted by 28 weeks gestation, and just 1% still alive. About half of the subject have a karyotype monosomy (45, X0), 20-30% have mosaicism structural abnormalities (45,X/ 46,XX) and 20% have isochromosomy (46 XiXq/46 XdelXp/XrX). Turner syndrome is unrelated with maternal age, and not preferentially linked to maternal meiotic error. The missing chromosome more typically related with paternal meiotic error in early embryonic division. The current genes implicated in TS are located on X chromosome, termed as pseudoatosomal that ensure X-Y meiotic pairing. In our case, the patient karyotype was 45, XO. Patient also has a cousin from her father family with the same phenotype.

The presentation of TS varies throughout a patient’s life. The diagnosis TS can be suspected prenatally with specific ultrasound finding such as hydrops, increased nuchal translucency, cystic hygroma or lymphedema. Additional finding suggestive TS include coarctation of the aorta, cardiac anomaly, brachycephaly, renal anomaly, polihydramion, oligohydramion, and growth retardation. Approximetally, 20–30% identified during neonatal period due to lymphedema, webb neck, low posterior hair line, misshapen or rotated ears, high arch palatum and crowded teeth, broad chest...
with widely spaced nipples, cubitus valgus, micrognathia, short fourth metacarpal and metatarsals, scoliosis, cardiac malformation, kidney anomalies. Approximately 35% of girls are diagnosed in childhood due to short stature, lack of breast development, amenorrhea with elevated FSH by 14 years of age, sensorineural hearing loss and recurrent otitis media. Turner syndrome typically have normal intelligence, but they may have difficulty with nonverbal, social and psychomotor skills.\textsuperscript{3,4,6,12}

In our case, the clinical presentation of patient are amenorrhea, no breast budding, short stature, low posterior hair line, misshapen ears, high arch palate, broad chest with widely spaced nipples, recurrent otitis media and elevated FSH.

The diagnosis TS, relies on clinical features and documented X chromosome abnormalities. Prenatally diagnosis TS detected by abnormal fetal ultrasound and amniocentesis, but it was difficult to acquire reliable data on predictive value of the test with regard to clinical outcome. Postnatal diagnosis of TS can be made by chromosomal karyotype. It has been the “gold standard” for definitive diagnosis of TS for the past several decades. At the time of diagnosis, all individuals with TS need to have comprehensive screening evaluation like echocardiography, renal ultrasound, hypertension screening, thyroid and liver function, eye, ear, nose and throat examination, audiometry testing, bone age and growth evaluation.\textsuperscript{4,5,9,10} In our case, the chromosomal karyotype was 45, XO, the echocardiography, renal ultrasound, blood pressure, thyroid and liver function and eye examination within normal limit. Patient had severe hearing loss and recurrent otitis media.

A multidisciplinary approach to treatment is important to improve the quality of life adolescent with turner syndrome. Almost 90% will require hormone replacement therapy (HRT) either to initiate or to ensure progress in puberty, maintain secondary sexual development, and promote bone health. The optimal timing, type and dose of estrogen administration route for puberty induction in TS remains controversial.\textsuperscript{10}

The main goal of sex steroid replacement therapy in puberty are to ensure adequate breast development, pubertal growth spurt, adequate uterine development and peak bone mass. The best time to start induction puberty is at 12–15 years old, with low dose estrogen started from 2 µg oral ethinylestradiol daily or conjugated estrogen 0.3 mg daily or 6.25 µg patch 17β oestradiol nightly. There were similar metabolic effect (body composition, lipid oxidation and lipid concentration between oral and patch estrogen treatment in TS. Estrogen treatment is gradually increased every six months to mimic the physiological rise level to ensure adequate breast development and pubertal growth spurt. At the end of this period, progesterone such as medroxyprogesterone is added monthly or three monthly to allow endometrial shielding and bleeding cyclic.\textsuperscript{5,8,20} In our case, patient got oral fix dose ethinylestradiol daily, started from 2 µg and gradually increased every 6 months until pubertal development adequate.

Estrogen therapy required until of normal menopause (52–54 years old) to maintain the normal feminization and prevent osteoporosis. Common forms of post induction puberty are oral contraceptive and combine transdermal patch. Estrogen replacement therapy associated with higher risk of hypertension, stroke, venous thromboemboloy and coronary heart disease in women. The contraindication of estrogen use in TS are similar to women in general, like gynecological cancer, history of thrombosis or cloting disorder, and familial breast cancer risk.\textsuperscript{5,20}

Hypergonadotropic hypogonadism associated in TS, as consequence of premature ovarian failure. The ovary develop but tipically degenerate due to accelerated follicular atresia during fetal life, childhood or later in life. Approximately 30% girls with TS have spontaneous pubertal, 4% reach menarche, and 2% get spontaneous pregnancy. The likelihood of functional ovarian tissue and fertility in women in TS relies on the presence of 46, XX germ cells in ovaries. It is more likely in women with mosaicism. Spontaneous pregnancy in monosomy TS are hardly ever seen. Advance reproduction medicine, like in oocyte donation have increased possibility of childbearing in infertile women with TS. However pregnancies in TS remain challenging due to high prevalence of serious cardiovascular complication such as aorta dissection, fetal malformation, spontaneous abortus, intra uterine growth retardation, low birth weight, and perinatal death.\textsuperscript{5,8,20}

Short stature is the most common clinical feature of TS that is thought to be related to the haplo insufficiency of the SHOX gene. Turner syndrome may reduce growth hormone sensitivity and pertubation of growth hormone (GH) – insulin like growth factor (IGF) - IGF binding protein (IGFBP) system. Growth hormone is administrated subcutaneous daily with dose started from 30µg/kg/week. Growth should be monitored 3–6 months and individualized dosing should be considered if the response GH is not adequate. The GH of TS dose was higher than growth hormone deficiency dose. The most predictive factor of increment height in TS related to parental height, age at initiation of therapy, response GH during first year. Optimal age to initiation of GH therapy is when height drop below 5th
percentile on growth chart, usually on the average age of 9 years. If the height already far below 5th percentile of normal growth curve in older TS girls, the treatment need to added non-aromatizable steroid, such as oxandrolone with dose 0.05mg/kg/day. Continue monitoring of IGF-1 is important to prevent the side effect of GH therapy, including benign intracranial hypertension, scoliosis, and impaired glucose tolerance. Introducing combine therapy of ultra low dose estrogen and GH in childhood, will improved final height and bone maturation. In our patient, although the mature height base on skeletal age was 99.3% closed to 100% of mature adult skeletal age, the patient still need GH treatment. But unfortunately it was not covered by insurance.

Approximately 10% TS will get osteoporosis and increased risk of fracture, commonly during adolescence. Estrogen is crucial treatment to reach maximal peak bone mass in TS by reduce bone remodelling, reduce bone resorption and stimulate endocortical bone formation. Strabismus, amblyopia, and ptosis are common in TS. Ophthalmological evaluation should be part of the regular physical examination, with referral when appropriate.

Women with TS also have increased risk for aortic dilatation and aorta dissection. Monitoring for aortic root dilatation should be guided by the type and severity of the underlying cardiac problem. If patient does not show congenital heart disease, a repeat cardiovascular physical examination and echocardiography, with particular attention to the aortic root, should be conducted sometimes.

Congenital malformations of the urinary system are present in up to 30% of patients with TS. Rotational abnormalities and double collecting systems are found most frequently. TS with congenital renal malformation increased risk for hypertension, urinary tract infection, or hydronephrosis. Between 10 – 30% of TS will develop primary hypothyroidism because of the antithyroid antibody. Often, there is no overt clinical symptom. Level TSH and total of free T4 should be measured at diagnosis and intervals 1 – 2 years thereafter.

Hypertension is common in TS even in the absence of cardiac or renal malformation, therefore blood pressure should be monitored at each regular check up. Turner syndrome also have a predisposition to obesity, it altered and atherogenic of lipid profile. Altered lipid fluxes in obesity lead to lipid accumulation in abdominal viscera, and metabolic dysregulation.

Middle ear disease (chronic otitis media, cholesteatoma) and hearing loss are very frequent in TS, with prevalence about 54%. Cranio-facial dysmorphism (abnormal of eustachian tube, hypertonic tensor veli palatine, cochlea malformation and hair cell defect of organ corti) and lymphatic insufficiency associated with hearing loss in TS. Chronic otitis media, often requiring grommet insertion (typanostomy tube insertion) to maintain a ventilator port for the middle ear space for approximately 1-2 years. In our case, patient with mix hearing loss and recurrent otitis media. Patient got aggressive treatment and insertion of ventilation tube from otolaryngology head and neck surgery department.

The psychological impact of TS, may be effect caused by infertility, short stature, impairment of secondary sexual characteristic and lack of libido. They should have individualized access to psychologist and educational support.

CONCLUSION

Turner syndrome is a rare case, affect females in ratio 1: 2000 live births and caused by partial or total deletion of sexual chromosome. The clinical features key of TS are lack of breast development and amenorrhea with elevated FSH at puberty stage. Turner syndrome must be confirmed based on chromosome analysis. At the time of diagnosis TS, comprehensive screening evaluation need to be done, to find another congenital anomaly related the syndrome. Hormon replacement therapy is used to stimulate the development of secondary sexual characteristics and routine check up is needed to follow up and prevent the complication related to the syndrome.

REFERENCES


