

A basic understanding of Turner syndrome: Incidence, complications, diagnosis, and treatment

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Summary

Turner syndrome (TS), also known as Congenital ovarian hypoplasia syndrome, occurs when the X chromosome is partially or completely missing in females. Its main clinical manifestations include growth disorders, reproductive system abnormalities, cardiovascular abnormalities, and autoimmune diseases. TS is highly prevalent in China. Timely diagnosis is crucial, and non-invasive prenatal DNA testing can identify TS and other diseases. Treatment of TS mainly involves administration of growth hormone combined with very low doses of estrogen to increase the patient's height. This article describes the incidence, complications, diagnosis, and treatment of TS.

Keywords: Turner syndrome, clinical features, diagnosis, treatment, complication

1. Introduction

Turner syndrome (TS) occurs when the X chromosome is completely or partially missing in females. This is the only monomer syndrome that humans can survive. TS is a relatively common type of human chromosomal aberration (*I*) that occurs in 1:2,500 female live births. The features of TS were first described by Turner in 1938, pathogenicity X chromosome monosomy was identified in 1959 (2). Monosomy 45,X is present in about 45% of cases, the remaining TS patients show a variety of chimeras and structural abnormalitie (3). The main phenotypic characteristic of patients with TS is a short stature, which is common to all patients. Other characteristics include a short neck, a broad chest, genu valgum, and nail dysplasia. The overall mortality rate for patients with TS is higher than that for normal people because of the higher incidence of cardiovascular disease and autoimmune diseases. This article mainly describes the epidemiology, diagnosis, treatment, and complications of TS.

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2. Epidemiology of TS

TS is a disease that affects females. The genetic background of the phenotype is highly variable, and analysis of the karyotype can improve understanding of the disease. The "classic" karyotype for TS is 45,X. In a recent study, the classic karyotype was only found in 45% of patients; the remaining patients had a mosaic karyotype (*i.e.* 45,X/46,XX or 45,X/47,XXX), a karyotype with an X chromosome structural abnormality (*e.g.* i(Xq) or i(Xp)), or a karyotype that included the Y chromosome or fragments of the Y chromosome (4). A karyotype analysis of 67 patients with TS in Suzhou, China identified the 45,X karyotype in 44.7%, a mosaic karyotype in 17.9%, a karyotype with a chromosomal structural abnormality in 31.4%, and a karyotype that included the Y chromosome or fragments of the Y chromosome in 6.0% (5). A karyotype analysis of 62 patients with TS in Linyi identified the 45,X karyotype in 40.3%, a mosaic karyotype in 8.1%, a karyotype with a structural abnormality in 43.5%, and a karyotype that included the Y chromosome or fragments of the Y chromosome in 8.1% (6). The 45,X karyotype was the main karyotype in those areas. Karyotypes of patients with TS in several Chinese cities are listed in Table 1.

Based on a number of cytogenetic studies, the incidence of TS is estimated to range from 25 to 210

Table 1. Karyotypes in patients with Turner syndrome in several Chinese cities

Karyotype	Monosomy (45,X)		Mosaic (45,X/46,XX;45,X/47,XXX)		X chromosome structural abnormality (isochromosome of the long arm, ring, or translocation)		Includes the Y chromosome or fragments the Y chromosome		Ref.
	total	%	total	%	total	%	total	%	
Suzhou	30/67	44.7	12/67	17.9	21/67	31.4	4/67	6	(5)
Linyi	25/62	40.3	5/62	8.1	27/62	43.5	5/62	8.1	(6)
Zhengzhou	8/18	44.4	5/18	27.8	5/18	27.8	/	/	(7)
Fuzhou	13/58	22.4	10/58	17.3	30/58	51.7	5/58	8.6	(8)
Ningbo	23/44	52.0	22/44	48	/	/	/	/	(9)
Dalian	32/78	41.0	16/78	20.5	30/78	38.5	/	/	(10)
Beihai	20/73	27.4	22/73	30.1	18/73	24.7	13/73	17.8	(11)
Liuzhou	16/31	51.6	6/31	19.4	8/31	25.8	1/31	3.2	(12)

per 100,000 women (13). According to study from 1999 to 2004, the incidence of TS in 119,158 births was 1/1,180 or 0.85% (14). The incidence rate of Chinese (0.90% or 1/1,111) is higher than that of Malays (0.72% or 1/1,389) and India (0.38% or 1/2,632). The incidence of TS has increased according to a study in Denmark (15), and the known number of surviving patients with TS steadily increased during that study. Mortality due to TS has also increased. In a UK cohort study, the relative risk of death increased to 4.2 due to an increased risk of diseases of the nervous system, digestive system, cardiovascular system, respiratory system, or genitourinary system (16).

3. Complications of TS

3.1. Cardiovascular abnormalities

An epidemiological study indicated that the overall mortality rate for patients with TS was 3 times that for the normal population (17). Cardiovascular events are a major risk factor and occur in 41% of patients. Patients with TS have congenital cardiovascular abnormalities more often than normal people. Heart valve disease is a prevalent abnormality, and patients with TS have a significantly higher incidence of aortic bicuspid deformity. Patients with TS have a risk of dying mainly from an aortic dissection aneurysm, young people with TS have a significantly smaller aortic diameter than the general population, and aortic surgery is indicated for patients with TS over the age of 18 with an ascending aortic size index $> 2.5 \text{ cm/m}^2$ to prevent aortic dissection (18). Due to the limited number of patients and ethnic differences, the exact incidence of cardiovascular disease in patients with TS is unclear and needs to be studied further.

3.2. Autoimmune diseases

Secondary autoimmune disease is one of the most prominent features of TS due to aneuploidy of the X chromosome (19). TS causes a variety of autoimmune diseases such as thyroiditis, colitis, celiac disease, type

1 diabetes, and psoriasis, though the most common is autoimmune thyroiditis (20). Follow-up studies have indicated that the incidence of autoimmune thyroiditis in patients with TS is 3.2% (21). Chinese (Han) patients with TS are prone to Hashimoto's thyroiditis (22); the prevalence of Hashimoto's thyroiditis in the general population in China is about 0.4-1.5%. The incidence of Hashimoto's thyroiditis in children with TS is significantly higher than that in other regions (23). Compared to the general population, patients with TS have an increased incidence of celiac disease; depending on the number of patients studied, its prevalence varies from 2.2 to 8.1%. Celiac disease may aggravate the manifestation of short stature, hypogonadism, and osteoporosis (24,25). The incidence of other autoimmune disease impacts the lives of patients with TS to an extent.

3.3. Skeletal abnormalities

Fractures are considered to be one of the major complications of TS. However, there is currently no evidence of an increased risk of fracture in children and adolescents with TS, but there is evidence that women with TS have about a 25% increased risk of fracture, mainly in the form of forearm fractures (26). However, tomographic data from patients with TS are disputed, and especially those from studies of elderly patients who have never received estrogen or who have received delayed and suboptimal therapy, and the prevalence of fractures may be overestimated (15). Landin-Wilhelmsen *et al.* found that osteoporosis and fractures are related to age in patients with TS; of 70 patients with TS, 16% had suffered a fracture and 50% were over the age of 45 (27). Timely diagnosis and treatment can help to keep bone healthy in patients.

4. Diagnosis of TS

Prenatal counseling is important, and in some countries a fetus diagnosed with TS is electively aborted. An increasing number of patients are diagnosed with TS during a prenatal examination. Some babies are

diagnosed with TS in the womb or at birth based on the results of an ultrasound examination or signs of lymphedema or congenital heart disease (such as aortic coarctation) (28,29). Next-generation sequencing technologies (such as genomes, whole exomes, and gene panel sequencing) are likely to identify more diseases during newborn screening than other methods (30,31). However, errors do occur during prenatal examinations, so a complete karyotype analysis needs to be performed to verify those results. The gold standard for diagnosis is karyotype analysis (32). Real-time polymerase chain reaction (PCR) gene quantification can be used to diagnose TS. CpG methylation sites specific to X-chromosome inactivation that are widely distributed on the X chromosome may be a marker of TS (33).

Attention should also be paid to other signs of TS: *i*) conductive and sensorineural deafness; regular hearing tests should be conducted every 1-3 years; *ii*) hyperopia; a regular eye examination should be performed at age 1.0-1.5; *iii*) strabismus, a normal eye examination should be performed at 4 months to 5 years of age; *iv*) abnormal kidney or liver function; a renal ultrasound should be performed, and at the age of 10 or so urea and creatinine levels, liver function, and the total blood cell count should be measured; *v*) hip dislocation and feeding difficulties; these manifestations should be monitored until infancy; *vi*) otitis media and delayed adolescence; these manifestations should be monitored throughout childhood; *vii*) scoliosis/kyphosis; these manifestations should be monitored during adolescence; and *viii*) dysplasia; this manifestation should be monitored during the entire growth process (34). Methods of diagnosing TS are listed in Table 2.

In short, timely diagnosis is very important. In addition to genetic testing, manifestations of TS should be monitored during the entire developmental process so that TS can be treated in a timely manner.

5. Treatment of TS

5.1. Growth hormone therapy

A study has indicated that growth hormone therapy

can increase the adult height of patients with TS (35). A study administered growth hormone to 16 girls with TS in India over a prolonged period; the patients' height SD score and body mass index indicated that patients with TS did benefit from growth hormone (36). A large number of studies have indicated that administration of high doses of biosynthetic human growth hormone can significantly increase the lifelong height of children with TS, so growth hormone therapy is currently the treatment of choice. The sensitivity of an individual to recombinant human growth hormone (r-hGH) is known to vary (37); it causes significantly accelerated growth in the first year, but the response gradually diminishes over time (38,39). The patient's lifelong height is related to the age at treatment, time, and dose (1) and the administration of growth hormone (40). Various combination therapies are better than therapy with growth hormone alone. Long-term growth hormone therapy has a positive effect on craniofacial development in girls with TS, and its greatest impact is on posterior facial height and the height of the mandibular ramus (41).

5.2. Estrogen therapy

Retarded adolescent growth is related to a deficiency of estrogen in patients with TS, so estrogen is administered (42). In the past, estrogen replacement therapy started when the patient was 15 years old to avoid premature closure of the epiphysis, thus affecting the patient's lifelong height. The general recommendation is that patients be started on small doses of estrogen at age 12, enabling the patient to begin developing secondary sexual characteristics and the uterus and to improve liver function, cognitive function, and quality of life (43). A recent trial administered r-hGH and low-dose estrogen to patients with TS for 20 years (44). Results clearly indicated that administering very low doses of estradiol and r-hGH in adolescence produced estrogen levels close to those of healthy girls in puberty; as adolescent girls with TS mature, increasing the dose of estradiol greatly increases their final adult height. Many forms of estrogen can be used to treat patients,

Table 2. Several methods for diagnosing Turner syndrome

Method of diagnosis	Characteristics	Ref.
Next-generation sequencing technologies (such as genomes, whole exomes, and gene panel sequencing)	Noninvasive prenatal test; allows the identification of more diseases.	(30,31)
Karyotype (gold standard)	Labor intensive, unrealistic for large-scale population or high-throughput testing.	(32)
Molecular methods (Southern blotting, polymerase chain reaction (PCR), restriction fragment length polymorphism (RFLP), fluorescent PCR genotyping, GeneScan-based genotyping, and real-time PCR)	Cannot effectively detect individuals with mosaic or partial X chromosome deletions.	(33)
Developmental process (hearing, vision, liver function, kidney function, and spine)	Can help with diagnosis.	(34)

Table 3. Treatment of Turner syndrome

Treatment of Turner syndrome	Characteristics	Ref.
Growth hormone therapy	Individual sensitivity is variable. Lifelong height is related to age, time, and dose of treatment.	(1,37)
Estrogen therapy	The general recommendation is to start a low dose of estrogen replacement therapy at the age of 12. Increasing the dose of estradiol given to girls with TS will greatly promote final adult height.	(43,44)
Oxymetholone treatment	Marked effect when used in combination with growth hormone. Adverse reactions may occur, so this treatment should be used with caution.	(45,46)
Other methods	Traditional Chinese medicine treatment; vitamin D supplementation; active lifestyle.	(27,48-50)

the most common of which is oral estrogen followed by transdermal patches. However, whether young patients with TS should take oral estrogen or use estradiol transdermal patches needs to be verified further (43).

5.3. Oxandrolone therapy

In 1986, a trial administered r-hGH alone or in combination with androgen for the first time; once the trial was complete and patients with TS reached their final height, this combination therapy significantly increased growth and final adult height (45). However, the possibility of adverse reactions (such as masculinization (e.g. an enlarged clitoris, deeper voice, hirsutism, and acne), a delay in breast development, and lower HDL cholesterol levels) has prompted caution in the clinical use of androgens (46). Currently, oxytocin is seldom used because hormone replacement has proven to be a more effective treatment when using estradiol in combination with r-hGH (47).

5.4. Other treatments

Liao *et al.* administered nandrolone phenylpropionate in the early stages of TS to promote the synthesis of protein, and they also administered a traditional Chinese medicine – Liuwei Dihuang pills – to aid the kidneys (48). This alleviated the lack of estrogen and it also prompted the patient's genital organs and secondary sexual characteristics to develop to an extent, resulting in limited menstruation. Fractures are one of the major complications of TS. The mechanism of bone injury in patients is not clear, but an estrogen deficiency and X chromosome abnormalities are key factors. Several studies have noted a low level of vitamin D in the serum of patients with TS, and this may lead to lower bone mineral density (27,49). Therefore, vitamin D supplementation and an active lifestyle including weight-bearing activities and regular sports are of great benefit to the health of bone in patients with TS (50). Forms of treatment are listed in Table 3.

6. Prospects for diagnosis and treatment of TS

TS is a rare disease in which all or part of the X

chromosome is missing, and patients' growth and lives are heavily affected. Timely diagnosis and treatment is crucial. The incidence of cardiovascular diseases and bone abnormalities in TS is currently being studied. In addition to unusual physical phenotypes, patients with TS exhibit characteristic neurocognitive features that involve deficits in visual spatial processing. Cognitive deficits that have been found in TS seem to persist into adulthood. Whether this is caused by genetic mechanisms or only by hormones and other biological factors is unclear. Genetic and hormonal effects may need to be studied in the same patient. Further research is needed in this area to determine how genes, karyotypes, and the brain are linked to cognition (51). The latest structural and molecular biology techniques need to be used in post-mortem studies, modern genomic strategies need to be adopted, and medical histories need to be routinely reported (52).

Given trends in biomedical development, the next generation of treatment will be based on stem cells and regenerative medicine. Stem cell research has become an area of interest. Stem cells are cells that have the potential to proliferate, differentiate, and self-renew. Somatic cells are dedifferentiated into pluripotent stem cells by introducing foreign genes, and those stem cells are known as induced pluripotent stem (iPS) cells. The major advantage of iPS cells over embryonic stem (ES) cells is that iPS cells can be derived from a patient's own somatic cells, thus avoiding immunological rejection and ethical issues (53). For rare diseases such as TS, the somatic cells of patients can be extracted and their dedifferentiation into stem cells can be induced to create a model of the disease in order to study its pathogenesis and to develop new methods of studying and treating that disease.

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