Turner syndrome

Managing a multisystem disorder

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Turner syndrome may present in females at any age and with a range of different features. A multidisciplinary healthcare team co-ordinated by the general practitioner and general paediatrician is key to providing appropriate surveillance and management of patients with Turner syndrome.

Key points

- **Affecting about one in 2500 live female births, Turner syndrome is caused by the chromosomal abnormality 45,X or mosaicism with 45,X.**
- **Turner syndrome may present in females of any age. In newborns, webbed neck, lymphoedema and coarctation of the aorta are common presentations. During childhood and the teenage years, short stature and delayed puberty may become apparent.**
- **Turner syndrome is a disorder that may affect many organ systems to varying degrees and at different stages of life.**
- **A multidisciplinary approach to management and regular surveillance throughout life is essential for the wellbeing of patients with Turner syndrome.**

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Turner syndrome may be diagnosed in females of any age from the prenatal period to adulthood. It is caused by the complete or partial absence of the second sex chromosome, resulting in multisystem features. It occurs with an incidence of about one in 2500 live births but the true incidence is much greater due to the high rate of fetal demise with the chromosomal abnormality monosomy X (see Figure).

Girls with Turner syndrome may be diagnosed incidentally on prenatal chorionic villus sampling or amniocentesis performed to detect autosomal trisomy. In all of these cases, chromosomes should be re-evaluated postnatally. Prenatal counselling for parents should include discussion on the broad clinical spectrum of Turner syndrome, including variable physical features, likelihood of IQ scores in the normal range but with specific types of learning difficulties, and the likelihood of short stature and infertility. Although lifespan may be decreased in people with Turner syndrome compared with the general population, many affected women lead happy, healthy and fulfilling lives with appropriate medical management.

In the newborn period, girls with Turner syndrome may present with webbed neck, lymphoedema of the hands and feet and coarctation of the aorta. In mid-childhood other features may become apparent such as short stature, cubitus valgus, low hairline, low set ears, nail hypoplasia, multiple pigmented naevi, short fourth metacarpal or chronic otitis media. In teenage years, additional presenting features may be pubertal delay and primary or secondary amenorrhoea. Some women with a Turner mosaic karyotype may only be diagnosed following investigation of infertility or recurrent miscarriage. In all cases, testing for Y chromosome material is important in view of the risk of gonadoblastoma.

Girls and women with Turner syndrome are ideally managed within a multidisciplinary team, including an endocrinologist; cardiologist;

Table. Screening and monitoring by age in girls and women with Turner syndrome

At diagnosis (usually childhood)	During childhood and adolescence	During adult life	Other referrals as required
• Genetic studies and counselling • Clinical review: height, weight, blood pressure, general physical check including pubertal status, skeletal system including spine and skin check • Bone age x-ray of left hand and wrist • Blood tests: UEC, glucose, lipids, LFTs, thyroid function, coeliac screen, IGF-1, pubertal hormones if >10 years • Cardiac review with echocardiogram and ideally MRI, electrocardiogram • Renal ultrasound • Pelvic ultrasound (if >10 years old) • Hearing test and ENT review • Ophthalmology review • Dental and/or orthodontic review • Educational and psychological review	• Clinical review, including height measurement every six months • Blood tests as previously every 12 months • Bone age x-ray annually when on growth hormone treatment • Pelvic ultrasound if not carried out at diagnosis, and again in late teenage years • Bone mineral density in mid-teenage years • Renal ultrasound if previously documented structural abnormalities • Cardiac review every five years (or more frequently if needed) • ENT review and hearing test every one to five years as needed • Ophthalmology review as needed • Dental and/or orthodontic review at least once after age 7 years • Educational and psychological review as needed	• Clinical review every 12 months • Blood tests as previously every 12 months (coeliac screen every two to five years) • Bone mineral density, early adulthood and then as needed • Hearing test and ENT review every one to five years • Cardiac review every five to 10 years or more frequently if indicated • Full cardiac evaluation including MRI and detailed medical evaluation before pregnancy	• Podiatrist • Dermatologist • Orthopaedic surgeon • Dietitian • Psychologist • Educational support • Plastic surgeon

Abbreviations: ENT = ear, nose and throat; IGF-1 = insulin-like growth factor-1; LFT = liver function tests; UEC = urea, electrolytes, creatinine.
Reproduced from Ambler GR. Turner Syndrome. Pfizer Endocrine Care patient booklet.

audiologist; geneticist; ear, nose and throat surgeon; ophthalmologist and psychologist. Not all patients require input from all team members. The general paediatrician and GP have key roles in co-ordinating care and should be kept up to date with all progress. Young women with Turner syndrome are at high risk of loss to multidisciplinary follow up during transition to adult services. Women with Turner syndrome need ongoing annual medical review. There are few co-ordinated multidisciplinary services for adult women with Turner syndrome and GPs therefore play a vital role in surveillance and co-ordinating subspecialty care. Recommended monitoring through childhood, adolescence and adulthood is summarised in the Table.

Cardiovascular system

Features

Congenital cardiovascular malformations occur in up to 50% of girls with Turner syndrome. Residual neck webbing is predictive of cardiac malformations. The spectrum of anomalies ranges from nuchal cystic hygroma causing fetal demise to coarctation of the aorta (which may present at any age) to bicuspid aortic valve (which is often clinically silent). Coarctation of the aorta occurs in approximately 11% of girls with Turner syndrome. It may be detected in the neonatal period following investigation of cardiac failure or on routine screening at an older age. Bicuspid aortic valve occurs in approximately 16% of girls with Turner syndrome and can be complicated by endocarditis, aortic stenosis or regurgitation, dilation of the ascending aorta, and aortic aneurysm and dissection. Coarctation of the aorta, bicuspid aortic valve and systemic hypertension are all risk factors for rare but often fatal aortic dissection. It is therefore important to screen for cardiac malformations and hypertension from infancy to adulthood.

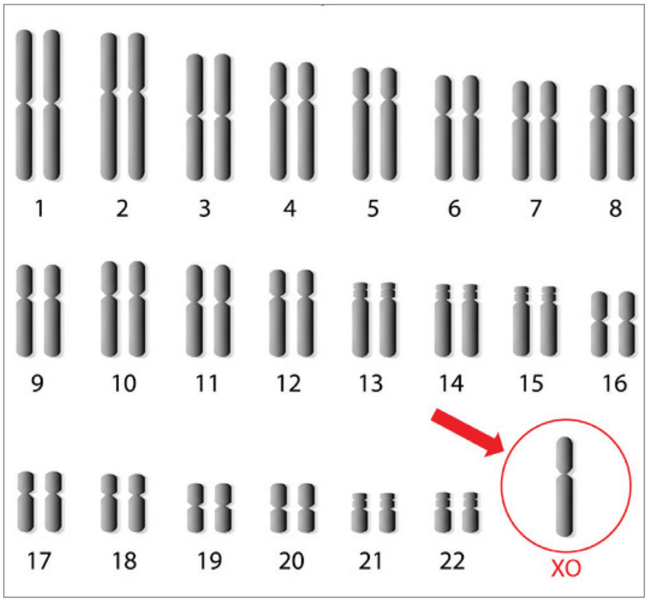

Figure. Karyotype of Turner syndrome.

Hypertension occurs in about 25% of paediatric patients with Turner syndrome and is more frequent in adulthood. Conduction defects, including prolonged QTc, are also more common in patients with Turner syndrome.

Management

All newly diagnosed patients with Turner syndrome should have a baseline evaluation by an experienced cardiologist, including comprehensive physical examination, ECG and echocardiography. MRI may be required for further detailed evaluation but this requires sedation in young children. Cardiac review, ideally including MRI, should again be performed in all young women with Turner syndrome before transition to adult services. Blood pressure should be monitored frequently and hypertension treated vigorously in patients with Turner syndrome of all age groups.

Frequency of cardiac review in adulthood depends on individual circumstances. Aortic dimensions are monitored on echocardiography every five to 10 years even if no significant cardiac malformations or hypertension are present. Patients at risk of aortic dissection should be counselled about the risk of pregnancy and intensive exercise.

Lymphoedema that is present at birth usually resolves in infancy. However, it may occur at any age and may be precipitated by initiation of growth hormone therapy or oestrogen therapy. Patients are treated with decongestive physiotherapy including the use of compression stockings.

Skeletal system

Features

Nearly all girls with Turner syndrome have mild intrauterine growth retardation and childhood short stature with slow growth despite normal growth hormone production. This is due to haploinsufficiency of the short stature homeobox-containing gene found on the X chromosome. Without treatment, final adult height is about 20 cm less than target height.

Other skeletal abnormalities include wide body compared with height, relatively large hands and feet, short neck, cubitus valgus, genu valgum and short forth metacarpal. Madelung deformity of the wrist is infrequently seen. Girls with Turner syndrome also have a higher risk of congenital dislocation of the hips, scoliosis and kyphosis.

Management

Growth hormone therapy is effective in increasing final height. Greater final height is achieved in girls who are taller at the start of treatment, in girls with taller parents, and in those who undergo a longer duration of treatment and at higher doses. Age appropriate pubertal induction with physiological doses of oestrogen and progesterone (see below) does not counteract the effect of growth hormone therapy. Monitoring for exacerbation of scoliosis or kyphosis should occur during growth hormone therapy and consultation with an orthopaedic surgeon if required.

Reproductive system

Features

Due to ovarian dysgenesis, over 90% of women with Turner syndrome ultimately have gonadal failure but up to 30% undergo some spontaneous puberty and 2 to 5% may achieve a spontaneous pregnancy. Women with mosaic karytopyes (e.g. 45,X/46,XX or 45,X/47,XXX) have higher rates of spontaneous puberty and pregnancy. Girls with Turner syndrome have a normal vagina and uterus that respond to pubertal induction hormones.

Most women with Turner syndrome are not fertile; however, with appropriate hormone induction, the uterus may be able to carry a pregnancy following implantation of a fertilised donor egg. The rate of miscarriage is similar to that in women who have used assisted reproductive techniques for other causes of infertility. However, maternal complication rates, including caesarian section, hypertension, diabetes and life-threatening aortic dissection, are higher.

Women with Turner syndrome whose karyotype includes Y chromosome material (e.g. 45,X/46,XY mosaicism) are at higher risk of gonadoblastoma, with reported cumulative risk rates of 8% by 25 years and overall prevalence of gonadal malignancy of 15 to 40%.

Management

Pubertal induction should occur at an age-appropriate time to maximise psychosocial wellbeing. Serum gonadotropins are checked and pelvic ultrasound performed before induction of puberty.

Commencing low-dose oestrogen therapy at age 12 years does not interfere with growth hormone effects on final height and allows girls with Turner syndrome to proceed through puberty with their peers. Pubertal induction should occur over a two- to three-year time frame to mimic physiological development. Low-dose oestrogen is commenced either transdermally (patch, gel) or orally. The dose is gradually increased every six months. After two years or with spontaneous vaginal bleeding, a progesterone is added to regulate menstrual cycles and protect the uterus from unopposed oestrogen. Therapy with oestrogen and progesterone is long term and should continue until age of normal menopause to prevent symptoms of oestrogen deficiency and osteoporosis. The oral contraceptive pill is not recommended for pubertal induction because the synthetic oestrogen component in most oral contraceptive pills is too high and the progestin component may not be optimal for breast and uterine development. Furthermore the 'pill-free' week during use of the oral contraceptive pill is not appropriate for women who have primary gonadal failure who require oestrogen and progesterone replacement until the time of age-appropriate menopause.

Fertility options are best discussed in a centre with expertise in managing women with Turner syndrome. A comprehensive cardiac evaluation is needed, including an MRI to evaluate aortic dilatation and dissection risk. After appropriate hormonal preparation of the uterus, implantation with either a donated embryo or fertilised donor oocyte is possible. Pregnant women with Turner syndrome should then be cared for by a multidisciplinary team in a high-risk pregnancy facility. The small group of women with spontaneous ovarian function should ideally have planned pregnancies with the option of prenatal diagnostic techniques because of the higher rate of chromosomal abnormalities or other congenital problems in the offspring. Ovarian cryopreservation for adolescents with Turner syndrome is an area of considerable research and may offer the possibility of pregnancy with the patient's own oocytes in the future. Frozen embryo storage for a young woman with Turner syndrome with oocytes and a partner is another option that may be offered by fertility centres.

Renal system

Features

Of patients with Turner syndrome, 30 to 40% have congenital malformations of the urinary system. The most common are collecting system malformations (20%), horseshoe kidney (10%) and malrotation (5%). The presence of a renal malformation increases the risk of urinary tract infections and hypertension.

Management

All patients with Turner syndrome should have a renal ultrasound at diagnosis. Blood pressure monitoring is part of routine clinical review.

Autoimmune system

Features

Autoimmune hypothyroidism (25%) and coeliac disease (5%) are more prevalent in people with Turner syndrome.

Management

Thyroid antibodies and thyroid function tests are screened for annually in all girls with Turner syndrome and treatment with thyroxine commenced as soon as hypothyroidism is detected. Coeliac disease screening should occur regularly (every two to five years or earlier if symptomatic). Patients with a positive coeliac screen need referral to a gastroenterologist.

Metabolic system

Features

There is an increased long-term risk of type 2 diabetes and dyslipidaemia in individuals with Turner syndrome. Coupled with hypertension, these add to the cardiovascular risk profile.

Management

Girls with Turner syndrome are encouraged to lead active lifestyles with healthy eating to maintain a healthy weight. Monitoring fasting glucose levels and lipid profile should occur from adolescence and the oral glucose tolerance test should be considered in those at high risk of type 2 diabetes (e.g. obesity, strong family history of metabolic syndrome).

Bone health

Features

Women with Turner syndrome may have an increased rate of osteoporosis especially if female hormone replacement therapy has been suboptimal.

Management

Appropriate oestrogen therapy from the time of puberty until normal age of menopause minimises the risk of osteoporosis. Adequate calcium and vitamin D intake together with weight-bearing exercise should be encouraged.

Ear, nose and throat

Features

Girls with Turner syndrome have a higher rate of conductive hearing loss. Base of skull abnormalities can lead to abnormal alignment between the Eustachian tube and middle ear, predisposing to chronic otitis media. Progressive sensorineural hearing loss can occur with age but may also be present in younger girls with Turner syndrome.

Management

Regular otoscopy, tympanometry and audiology evaluation is required for all girls with Turner syndrome. Early referral to an ear, nose and throat surgeon is needed in cases of recurrent or prolonged episodes of otitis media.

Eyes

Features

Strabismus, hypermetropia and red-green colour blindness are more frequent in girls with Turner syndrome than in the general population. Many girls with Turner syndrome also have abnormalities of the external ocular adnexa, including epicanthal folds, upward slanting palpebral fissures, hypertelorism and ptosis.

Management

Review by a paediatric ophthalmologist at 12 to 18 months of age is needed in girls with Turner syndrome and then as indicated.

Dental and orthodontic problems

Features

Girls with Turner syndrome are at higher risk of dental and orthodontic problems due to craniofacial malformations.

Management

Early and regular review by a dentist and orthodontist is recommended for girls with Turner syndrome.

Psychological and educational issues

Features

Individuals with Turner syndrome have normal intelligence apart from those with a small ring X chromosome who have an increased risk of cognitive delay. However, many have selective nonverbal skill impairment that may affect their performance in mathematics and visuospatial and executive function tasks. Girls with Turner syndrome display normal behaviour patterns but can have higher rates of social isolation, immaturity and anxiety. This may contribute to delayed sexual milestones compared with their peers. Adults with Turner syndrome report normal self-perceived physical and mental health apart from some who report lower self-esteem in social situations.

Management

Individualised educational intervention aimed at specific deficits (e.g. mathematics, problem solving and visuospatial tasks) should be offered to school-aged girls with Turner syndrome. Medical management (e.g. age-appropriate pubertal induction) is aimed at minimising differences from peers, which can contribute to social anxiety. It is important to have open and honest age-appropriate discussions with the patient and her family about the diagnosis and consequences of Turner syndrome.

Patient information booklets are a useful resource for families who often face information overload at diagnosis. Many girls with Turner syndrome and their families also benefit from patient support groups (e.g. Turner Syndrome Association of Australia who provide educational and social forums).

Malignancy risk

As discussed previously, women with Turner syndrome and with Y chromosome material are at higher risk of gonadoblastoma. Population-based studies, although with small numbers, suggest that the overall risk of cancer for women with Turner syndrome is not increased, but site-specific risks were increased for meningioma, childhood brain tumours and bladder and uterine cancer (but not breast cancer) when compared with the general population.

Other causes of early mortality

Premature and unexpected causes of death in people with Turner syndrome are often linked to underlying cardiovascular conditions, such as aortic dissection, congenital cardiovascular disease, and ischaemic heart and cerebrovascular disease. Deaths due to noncardiac causes, including epilepsy, diabetes, chronic renal disease, pneumonia, chronic liver disease and malignancy, also occur with increased frequency.

Summary

Turner syndrome may present at any age and with a range of features. Most girls are diagnosed by karyotype analysis in childhood following investigation of short stature or pubertal delay. A multidisciplinary healthcare team co-ordinated by the GP and general paediatrician is key to providing appropriate surveillance and management, enabling girls and women with Turner syndrome to lead happy, healthy and fulfilling lives. **ET**

Further reading

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