Diagnosing Turner Syndrome

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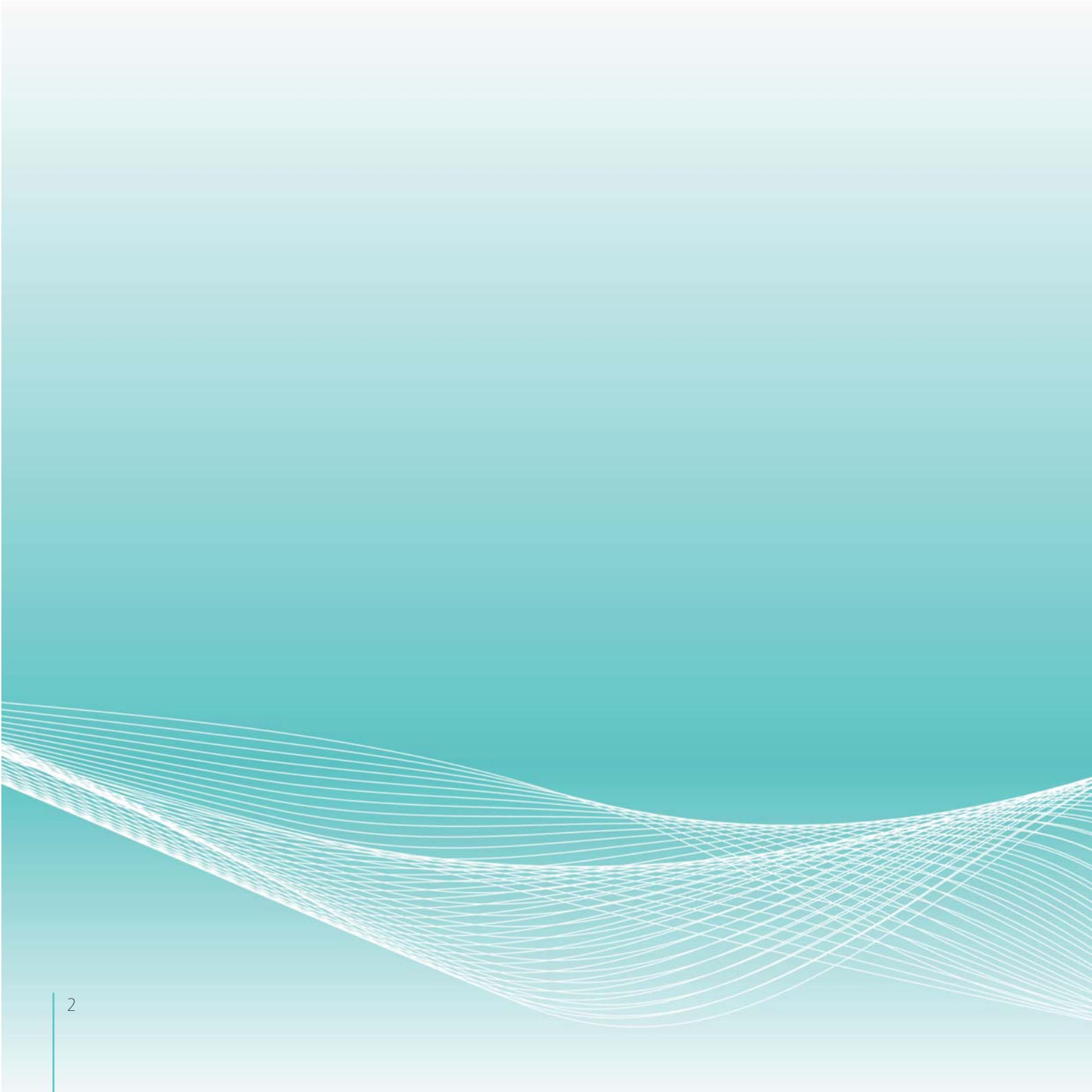

Foreword

The majority of girls and women with Turner syndrome live long, healthy lives. However, some are susceptible to a number of chronic conditions and so diagnosis as early as possible is important. Although Turner syndrome is diagnosed by chromosome analysis or karyotype, the condition presents with a number of physical features and clinical characteristics which may suggest the diagnosis.

Many girls are diagnosed in early childhood when growth starts to slow down. Some are diagnosed later when there is no puberty growth spurt or development of secondary sexual characteristics. However, by this stage, associated medical problems such as congenital lymphoedema and renal malformation may be established and there is also a risk of other problems developing such as sensorineural hearing loss, osteoporosis, obesity and diabetes.

Turner syndrome should therefore be diagnosed as early as possible after birth to ensure that the child has the best care throughout childhood and beyond.

I hope that health professionals who may encounter children with Turner syndrome i.e. general practitioners, paediatricians and community child health workers will find this booklet a useful aid to the diagnosis of the condition.

Professor Martin Savage

Professor of Paediatric Endocrinology

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Introduction

In 1938, an American endocrinologist Dr Henry Turner first described Turner syndrome, which is one of the most common chromosomal abnormalities. More than 95% of adult women with Turner syndrome exhibit short stature[1] and over 90% have signs of ovarian failure[2].

Turner syndrome affects many systems in the body. In the neonate, mortality may be increased because of coarction of the aorta and in the adult patient mortality may also be increased because of cardiovascular disease, particularly aortic dissection. Turner syndrome is also associated with obesity, type 2 diabetes, sensorineural hearing loss and osteoporosis is also common. Renal anomalies may be present and result in a predisposition to urinary tract infections or hypertension. Hypertension may occur in the absence of cardiac and renal anomalies.

Turner syndrome presents the clinician with a challenging array of genetic, developmental, endocrine, cardiovascular, psychosocial and reproductive issues.

Incidence

The incidence of Turner syndrome varies from one in every 2,000 to 2,500 live female births[1,2]. Turner syndrome causes 10% of all first-trimester miscarriages[1,3]. Unlike Down's syndrome, maternal age does not increase the risk of Turner syndrome and there are no clearly established risk factors. Recurrence of Turner syndrome in subsequent pregnancies is rare[3]. Turner syndrome affects 15,000 females in the UK; however 60% of affected children are not diagnosed during childhood.

Genetics

The chromosome defect in Turner syndrome is present at conception and remains throughout life. It consists of the partial or complete absence of one X chromosome (45,X karyotype), with or without cell line mosaicism. In addition to monosomy X (45,X), a similar clinical picture is found with a 46,XXiq karyotype and in some individuals with mosaic karyotypes.

Methods of diagnosing Turner syndrome

Turner syndrome is diagnosed by the demonstration of an abnormal chromosome analysis or karyotype. It is confirmed by the presence of a 45,X cell line or the deletion of the short arm of the X chromosome.

Under-diagnosis and delayed diagnosis of Turner syndrome remains a major problem[2]. Early detection ensures that any cardiovascular malformations are detected and treated[2]. In addition, early diagnosis facilitates prevention or remediation of growth failure, hearing problems and learning difficulties[2].

Pre-natal

Genetic counselling is a pre-requisite to any prenatal diagnostic procedure.

Pre-natal diagnosis is sometimes made by chorionic villous sampling (CVS) or amniocentesis. Certain ultrasound findings indicate an increased likelihood of Turner syndrome.

A karyotype should be obtained if the ultrasound of the fetus shows increased nuchal translucency, a nuchal cystic hygroma, lymphoedema, horseshoe kidney, left-sided cardiac abnormalities or non-immune fetal hydrops.

A useful resource for parents at this stage is: www.antenataltesting.info

Birth

All babies with suspected Turner syndrome should have a post-natal karyotype performed instead of amniocentesis or CVS. This is recommended if human chorionic gonadotrophin, oestradiol or alpha-fetoprotein values are abnormally raised during pregnancy.

Although the gonadotrophins, particularly follicle-stimulating hormone (FSH) may be elevated at birth, this finding alone is not reliable enough for use in the diagnosis.

Childhood

Children usually present with short stature, but some girls under the age of 11 years have heights within the normal range. Typical physical features, when recognised, also suggest the diagnosis.

Adolescence and adulthood

In older adolescents and adults, the presenting symptoms usually involve issues related to puberty and fertility, as well as short stature.

Diagnosis of Turner syndrome should be considered in girls with primary or secondary amenorrhea, lack of breast development and with elevated FSH levels by 14 years of age.

Adult women may present with unexplained infertility, particularly when they are also short in stature.

Features of Turner syndrome

Girls with Turner syndrome may have only a few or several of the features, but short stature and infertility are nearly always present. Adults are short due to a slower growth rate in childhood and absence of the growth spurt in adolescence.

Ovarian failure should be considered if a girl has no breast development by the age of 12 years, or absence of the menses by the age of 14 years. Elevated levels of luteinising hormone and FSH confirm ovarian failure. However, pubic hair development is normal.

The presentation of Turner syndrome varies throughout a patient's life and it may be difficult to recognise clinically because the characteristic facial features can be subtle.

A suspected diagnosis can be made by noting some or all of the typical features shown in Table 1.

Table 1: The typical features of Turner syndrome

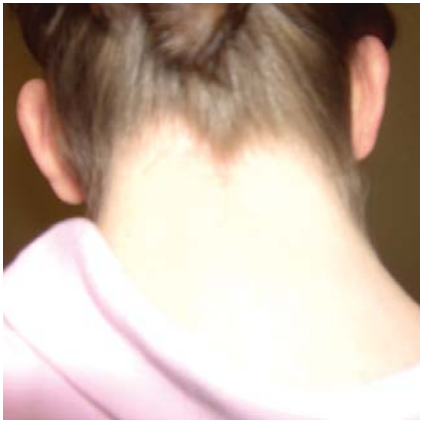
Characteristic	Baby	Child	Adolescent	Adult
Borderline small for gestational age	✓			
Short stature		✓	✓	✓
Lymphoedema *(of hands and feet)*	✓	✓	✓	✓
Poor feeding in infancy	✓			
Poor weight gain	✓			
Poor sleeping pattern	✓	✓		
High activity levels	✓	✓		
Heart murmur	✓	✓	✓	✓
Behavioural difficulties		✓	✓	
Exaggerated fearfulness		✓	✓	✓
Ear infections		✓	✓	✓
Hearing loss		✓	✓	✓
Tendency to obesity	✓	✓	✓	✓
Specific learning difficulties *(maths, visuo-spacial tasks)*		✓	✓	✓
Social vulnerability			✓	✓
Gonadal dysgenesis causes absent or incomplete puberty			✓	✓

Physical features

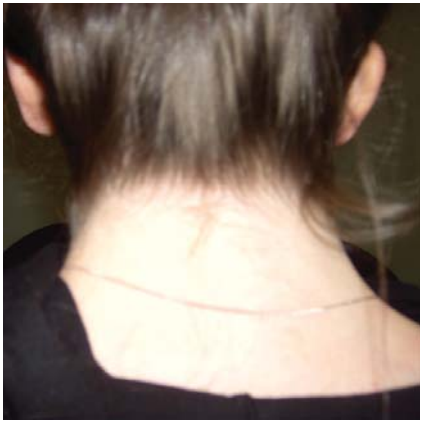
There are several physical features of Turner syndrome; not all of which will be present in one person (see Table 2). Some of these features are illustrated in Photographs 1 to 12 *[reproduced with the kind permission of members of the Turner Syndrome Support Society]*.

Table 2: Summary of the physical features of Turner syndrome

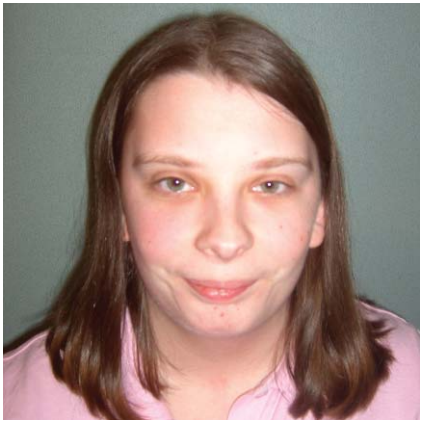
- Short stature
- Broad chest with widely spaced nipples
- Webbed or broad neck
- High arched palette with crowded teeth
- Low posterior hairline
- Deep forehead
- Misshapen or rotated and low set ears
- Swelling of the hands and feet
- Abnormal finger and toe nails: hyperconvex or hypoplastic
- Short 4th metacarpal or metatarsal
- Cubitus valgus; wide carrying angle of the arms where it is difficult to straighten the elbow
- Abnormal bone development e.g: hands and elbows
- Larger number of naevi compared to other members of the family
- Ptosis, strabismus, amylyopia and cataracts are more common
- Red-green colour blindness



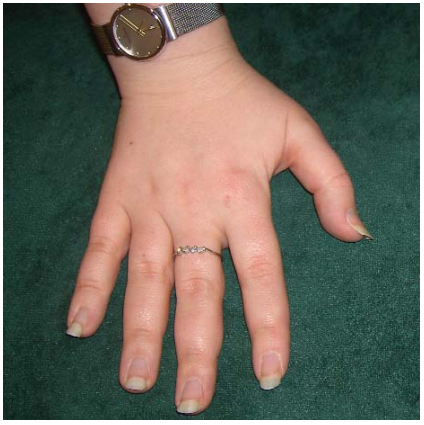
The young girl has a webbed or broad neck. Lymphoedema in utero causes this feature. Her hairline is also low at the neck which is another feature of Turner syndrome.

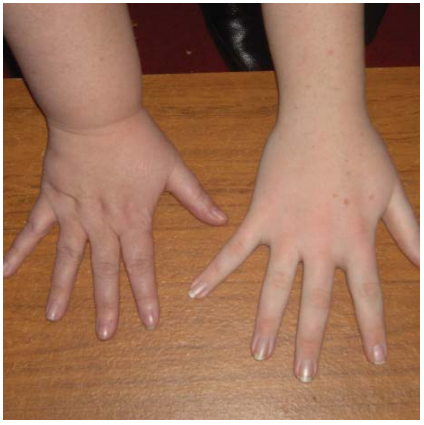


The hairline is low at the neck and the ears are low set.

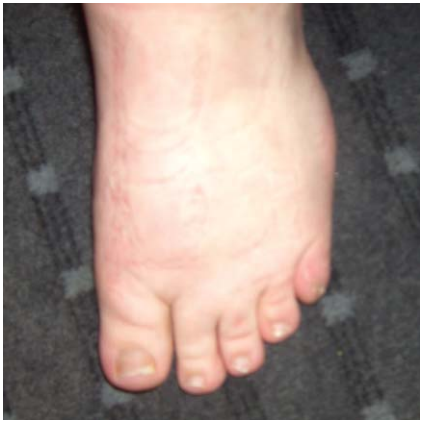


Both these girls have a deep forehead.

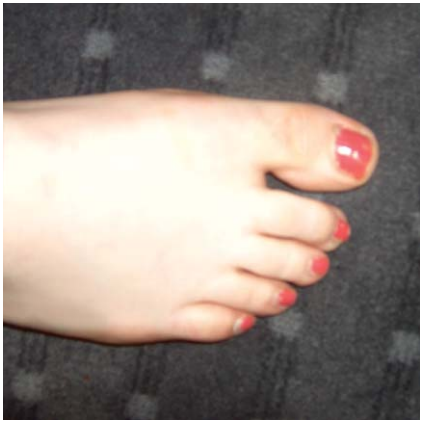




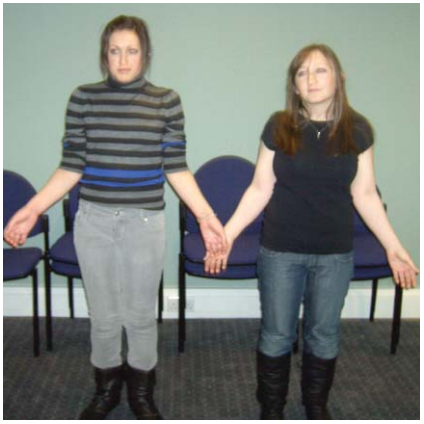
The hands are often very wide. The 4th metacarpal or metatarsal is shorter than normal and can be a clue to the presence of Turner syndrome.



This girl's feet are swollen and puffy ; lymphoedema can be present at any age. The hands may also be swollen.

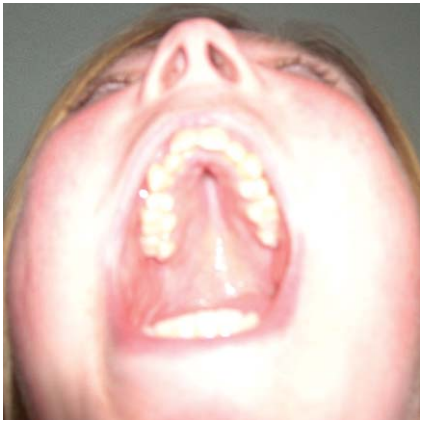


The finger and toe nails are hyperconvex and hypoplastic.



Notice the wide 'carrying angle' of the arm; it is often difficult to straighten the elbow. This is a common skeletal anomaly.

Droopy eyelids or ptosis is more common in Turner syndrome. This makes the eyes look almond-shaped.



The palette is abnormally high and arched; this can lead to feeding problems in babies.

Look carefully at these girls. Which one(s) have Turner syndrome? See page 22 for the answer

Communicating the diagnosis

Communicating the diagnosis should not be a 'one-off' event. The patient and the family will need careful education and counselling. Communication of the initial diagnosis will be a single point in the clinician/patient relationship that will continue through to treatment and overall management of the condition.

If the girl is under 16 years of age her parents will usually be present when the diagnosis is discussed. If the girl is over 16 years of age the clinician should recommend that the parents attend the appointment in order to provide support to their daughter.

Communicating a diagnosis can be a difficult process for both the clinician and the parents and/or patient. The successful communication of the diagnosis and the genetic information involves a number of important skills and considerations. The challenges involved in communicating medical information cannot be successfully addressed with universal, 'one-size-fits-all' recommendations.

A number of factors will influence the success or otherwise of communicating the diagnosis including the personality of the clinician, parents and child. Health professionals should take into consideration that different people react differently to the diagnosis and they should tailor their communication accordingly. In addition it is important to take note of the people involved and their ability to understand medical information. All information should be presented in an easy-to-understand manner.

Pre-diagnosis

Before the diagnosis has been confirmed, it is assumed that communication between the health professional and the parents and/or patient has already commenced in relation to the possible diagnosis. The clinician will have described Turner syndrome in terms that are positive and described what is involved in the diagnostic test.

The clinician should assume that the parents will have probably done some research whilst waiting for the diagnosis to be confirmed and that this may have frightened them.

At diagnosis

As soon as the diagnosis is confirmed, the clinician should speak to the parents and/or patient in person. A quiet, private room is required to convey the diagnosis with time to communicate at the parents' or patient's pace and with no interruptions. The language should be as simple as possible, medical jargon should be avoided.

Printed materials about the condition should be available and information about the Turner Syndrome Support Society should be provided at the same time.

A plan of action should be discussed so as to reassure the parents and child that they will receive the best possible care. The action plan will include treatment options which should be explained in small pieces of information.

The parents and child should be given time to ask any questions that they may have and further support provided by other health professionals if required.

Post-diagnosis

The care plan should be revised as the girl gets older and management of the condition continues. The parents and child need to be continually updated and encouraged to attend regular check-ups so that any associated medical problems (see Table 3) are identified quickly and receive the best possible long-term care.

Turner syndrome is a complex condition and there are various associated medical problems which need to be monitored throughout the life of the patient (see Table 3).

Table 3: Summary of the medical problems associated with Turner syndrome

System	Clinical Problem
Auditory	Sensorineural hearing loss. Annual hearing assessment is required; more frequently if the child has recurrent otitis media.
Bones	Osteoporosis occurs in adulthood due to a lack of oestrogen as a result of ovarian failure. Osteopenia may also occur.
Cardiovascular	One-third of patients with Turner syndrome have a cardiac malformation; 75 % of these have coarction of aorta or a bicuspid aortic valve. Hypertension is common and blood pressure should be routinely measured at each visit.
Dental	Various orthodontic anomalies may occur.
Digestive	Incidence of Crohn's disease and ulcerative colitis is increased.
Hepatic	Liver enzymes may be elevated.
Immune	About 10-30 % of girls with Turner syndrome develop hypothyroidism, generally associated with antithyroid antibodies. Coeliac disease may occur.
Lymphatic	Lymphoedema may be present.
Metabolic	Abnormalities of glucose metabolism, including Type 2 diabetes are more common than in the unaffected population.
Ophthalamic	Strabmismus and ptosis may occur. Amblyopia and cataracts are more common.
Psychological	Girls with Turner syndrome typically have normal intelligence, however they may have difficulty with nonverbal, social and psychomotor skills. Self-esteem may also be a problem.
Renal	33 % have renal abnormalities which may cause a predisposition to urinary tract infections. Renal malformations can occur e.g. horseshoe kidney, duplicated or cleft renal pelvis.
Reproductive	Puberty, pregnancy, infertility and oestrogen deficiency are key issues associated with gonadal dysgenesis. Spontaneous puberty can occur in 5-15 % of girls. Most patients are infertile, however, spontaneous unassisted pregnancy has occurred. Pregnancy, when achieved, is usually via IVF.
Skeletal	Infants have a higher incidence of congenital hip dislocation. Short stature is a key issue (i.e. more than two standard deviations below normal) and scoliosis occurs in 10 % and may contribute to short stature.

Management

At diagnosis, patients should be referred to a centre with an expertise in Turner syndrome and a multidisciplinary approach to treatment.

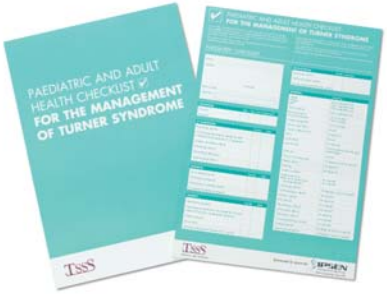
The young person with Turner syndrome should have an overall care plan which should be managed by the paediatric endocrinologist in a regional growth clinic. The paediatric endocrinologist will assess the patient regularly to monitor growth, puberty development and arrange referral to the relevant medical speciality for treatment as necessary.

Treatment focuses on the problems that occur. Some features of the condition will not require any intervention and others may be improved or treated with surgery, medicine or other relevant therapies.

Paediatric and adult health checklist

There is a Paediatric and Adult Health Checklist available from the Turner Syndrome Support Society **(www.tss.org.uk)**. The Health Checklist is a useful record for people with Turner Syndrome and their parents and is designed to slot into the patient record and act as a 'prompt' to ensure that the each girl or woman is treated according to her individual needs.

The Health Checklist is a prompt to check various aspects of development such as growth and puberty and will help to supervise and coordinate other aspects of care. It is also a useful audit tool.



Key considerations

Tables 4 and 5 outline the key management considerations for the young person and the adult.

Table 4: Key management considerations for paediatric care

- Measurement of height, weight and BMI at each outpatient visit
- Cardiovascular monitoring i.e. blood pressure at each outpatient visit
- Annual monitoring of thyroid function, IGF-I, glucose and HbA1c
- Growth hormone treatment to augment linear growth
- Oestrogen treatment for sexual development and maintaining bone mineral density

Table 5: Key management considerations for adult care

- Measurement of weight and BMI at each outpatient visit
- Cardiovascular monitoring i.e. blood pressure at each outpatient visit
- Annual monitoring of thyroid, renal and liver function, IGF-I, glucose and HbA1c
- Bone density measurement
- Hearing deficit awareness
- Ongoing ENT problems
- Sex steroid replacement therapy related to fertility and sexual development

Management of short stature

To increase adult stature, most girls with Turner syndrome are now treated with growth hormone (GH)[2]. The aim of GH treatment is for the patient to attain normal height for age as early as possible, progress through puberty at a normal age and attain a normal adult height[2]. It is well established that GH therapy is effective in increasing adult height[2]. However, the optimal age for initiation of GH therapy has not been established[2]. Some clinicians recommend that treatment should be considered as soon as the patient with Turner syndrome has dropped below the fifth percentile of the normal female growth curve[1].

The general consensus of opinion is that GH therapy should be offered to most girls at around six years of age. In older girls, or those with extreme short stature, consideration may be given to using higher doses of GH and adding a nonaromatizable anabolic steroid, such as low dose oxandrolone[2].

Hormone replacement

Oestrogen is administered as a replacement for the oestrogen that would normally have been produced by the ovaries. Oestrogen treatment induces pubertal development. Recent evidence suggests that some treatment regimens using oestradiol that begin replacement at the age of 12 years permit a normal pace of puberty, without interfering with the positive effect that GH has on final adult height[2].

It is recommended that women with Turner syndrome also receive progesterone in order to induce monthly menstrual cycles.

References

1. Saenger P, Albertsson Wikland K, Conway GS *et al*. Recommendations for the diagnosis and management of Turner syndrome. *J Clin Endocrinol & Metab* 2001;**86**:3061-3069

2. Bondy C, for the Turner syndrome consensus group. Clinical practice guideline. Care of girls and women with Turner syndrome: a guideline of the Turner syndrome study group. *J Clin Endocrinol & Metab* 2007;**92**(1):10-25

3. Morgan T. Turner Syndrome: diagnosis and management. *Am Fam Physician* 2007;**76**:405-410

Further information

Turner Syndrome Support Society

The Turner Syndrome Support Society is a national charity caring for the needs of those with Turner Syndrome throughout the UK. The Society offers support and information to both girls and adult women with Turner syndrome, their families and friends.

13 Simpson Court
11 South Avenue
Clydebank Business Park
Clydebank G81 2NR

T: 0141 952 8006
Helpline: 0845 230 7520
W: www.tss.org.uk

Answer to the question on page 14: The girl second from the left does not have Turner syndrome.

Child Growth Foundation

The Foundation is the UK's leading charity relating to children's growth. It supports and encourages all persons (either children or adults) who have growth disorders, and their families.

2 Mayfield Avenue
Chiswick
London W4 1PW

T: 020 8995 0257
W: www.childgrowthfoundation.org

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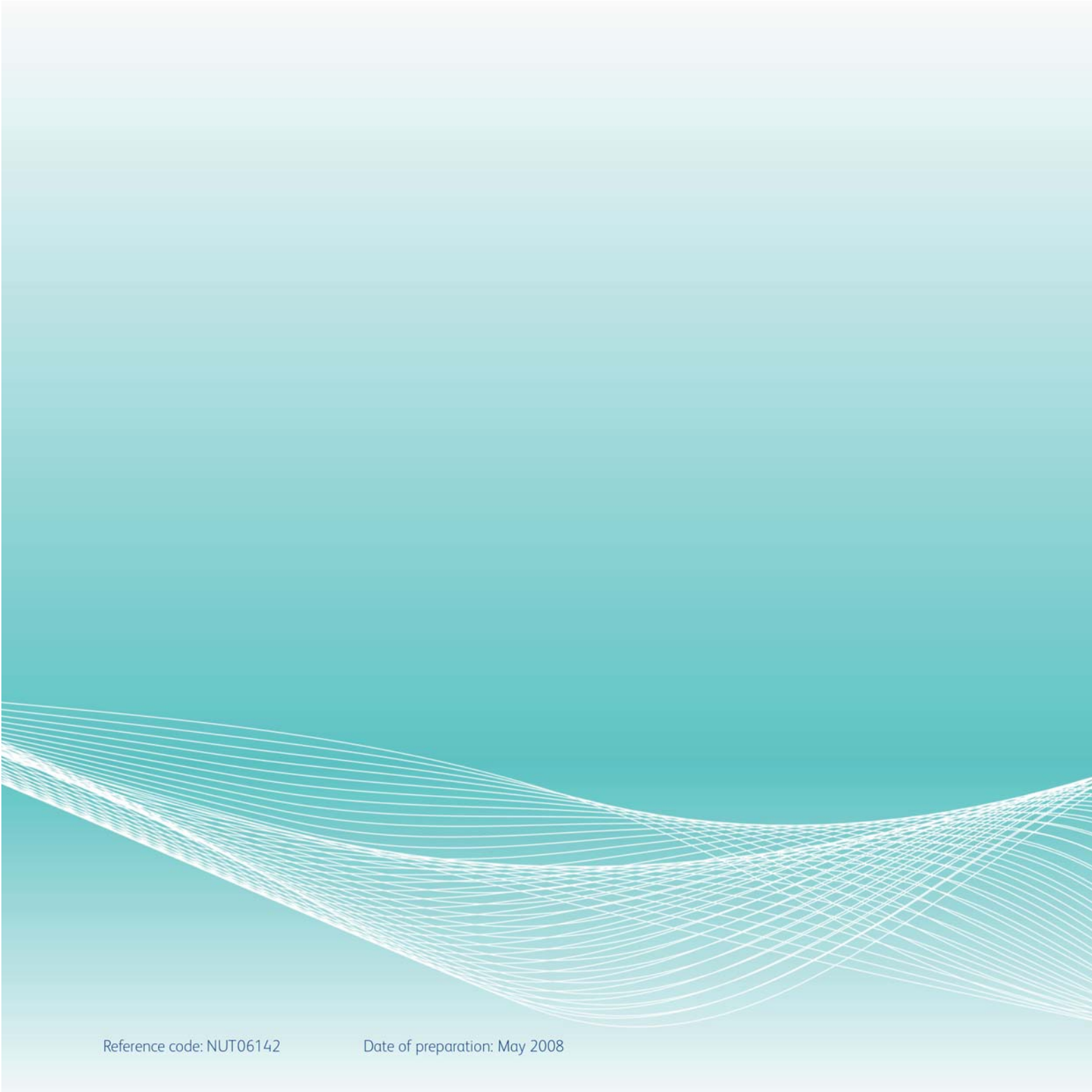

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