Turner
– know your body!

AN INFORMATION BOOK ON TURNER SYNDROME

EDITOR

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Turner – know your body!

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Foreword

Dear reader

Turner syndrome is a complex condition that can, and should, be considered from many perspectives so that all aspects of the syndrome are observed and acknowledged. Girls and women with Turner syndrome can, and should, live a life that is as close as possible to a "normal" life. This may necessitate help from several sources. Thus, expert help may be needed from various branches of medicine such as genetics, paediatrics, gynaecology and obstetrics, endocrinology, cardiology, thoracosurgery, ENT, and other specialists. There may also be a need for psychological and social assistance.

Turner syndrome should therefore be approached from a holistic standpoint, and the focus should be on the life-long expression of the condition. Recent years have taught us much about Turner syndrome, and now there is plenty of new knowledge on "Turner syndrome from the cradle to the grave".

The book you are holding in your hand is the result of the dedicated interest of many parties in girls and women with Turner syndrome, and a large number of people's help and enormous efforts. As the Contents indicate, many authors from Europe and the US have contributed to the book.

The book can be read as a whole, or as free-standing chapters that can be read independently of the rest of the book.

The book is intended as an inspiration, information and an aid to everybody with an interest in Turner syndrome.

The book has been written for girls and women with Turner syndrome, for their families, for the GP who has a patient with Turner syndrome, for the paediatrician who meets the child with Turner syndrome, and for all doctors, nurses and care providers who come into contact with people with Turner syndrome. One goal has been to disseminate the most recent scientific knowledge to all laypersons with an interest in Turner syndrome.

The book is *not* intended to be the first source of information on Turner syndrome, but the source that you turn to when you cannot find relevant information in leaflets or on the internet. In other words, the desire has been to create a specialised and detailed book containing chapters each of which are dedicated to one particular aspect of Turner syndrome. The ambition is for it to be a source of the latest research-based knowledge. Consequently, some of the chapters are written in a slightly difficult language. All the authors have been given freedom to write their chapters within the framework of the Consensus Conference on Turner Syndrome in Washington DC, USA in 2006, and of the consensus paper that was drawn up here. The information in the individual chapters thus reflects the available knowledge in these areas.

I hope that this book will meet the majority of the readers' need for information. The desire has been to create the definitive information book on Turner syndrome based on what we know *now*.

Common for all the authors is a genuine interest in Turner syndrome. Most of the authors are medical professionals, doctors and psychologists, but women with Turner syndrome and relatives have also been able to contribute with their personal experiences of having and living with Turner syndrome. All specialists who have participated in the creation of the book are involved professionally with Turner syndrome.

CLAUS H. GRAVHOLT
editor

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Childhood with Turner syndrome and genetics

Turner syndrome in childhood

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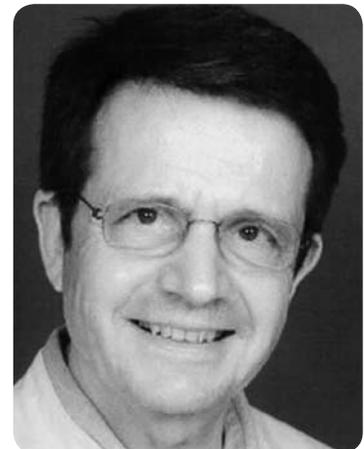
Many parents of girls with Turner syndrome experience the waiting time until the final diagnosis as stressful. Experiencee shows that the diagnosis is often made late in childhood, in adolescence or even as late as adulthood (see chapter 9 on epidemiology), and often only after the lack of growth becomes apparent, or other symptoms indicate the diagnosis.

Toddlers

In infants and toddlers, the characteristic features can be very mild; however, there will often be problems with thriving from birth. The birth weight is often lower with subsequent lack of weight gain, and feeding problems. Parents who have lived through this period tell stories of lack of support and understanding from the healthcare personnel with whom they have contact, and even of a reproving attitude that they are not looking after their child. Once the diagnosis has been made, and an explanation for the problems has been given, the parents often feel that a huge weight has been lifted, and relate that this has been a very stressful period of their and their child's life.

In those cases in which the diagnosis is made early, it is important for parents to understand that girls with Turner syndrome follow their own growth pattern, and there is nothing to be gained by forcing the child to eat. Frequent small meals will often be sufficient when eating problems are very pronounced, only rarely will more serious measures such as tube feeding be necessary.

It must be underscored that all girls who in early childhood display long-term problems to thrive must be assessed for Turner syndrome.

Lymphatic oedema and neck fold

In a newborn girl, the classic symptoms of Turner syndrome are swelling of the hands and tops of the feet, and retention of fluid (oedema) in the neck region (Figure 1). This swelling can vary greatly from child to child, and can come and go during childhood. The presence of this swelling at birth provides strong indications for Turner syndrome. The swelling is caused by an accumulation of lymph that does not drain off through the lymph canals as normal because the lymph vessels are inadequately developed. The nails are often small and poor and, due to the swelling around them, it can be difficult to avoid irritation and infection.

During the baby's time in the womb, the swelling in the neck can be more pronounced and can stretch the skin so much that at birth there is a fold of skin from the neck to the shoulder. The fold can be compared to a wing or an old-fashioned yoke. If the fold is very tight, it can mean that movement of the neck is restricted. Cosmetically, the fold can also be a problem but often we wait to see how things develop before actually making a decision to operate.

The inadequate development of the lymph vessels can be accompanied by incorrect development of the aorta. Anomalies in the

Figure 1

Congenital swelling of the hands and the tops of the feet due to inadequate development of the lymphatic system

aorta are discussed in more detail elsewhere (chapter 11). Here we will only mention the constriction (coarctation), that can be present at the exit of the aorta from the heart, and which can cause symptoms in childhood. This constriction can result in reduced blood supply to the legs and increased blood pressure in the arms. The anomaly can be found in all newborn, and therefore all newborn are checked to determine whether a pulse can be detected in the groin. If this is not the case, ultrasound scans of the heart should be performed (echocardiography) and, if necessary, other investigations. In very severe cases, an operation may be necessary.

Middle ear infection

Another important reason for early diagnosis is the increased risk for repeated middle ear infections which in the long-term can increase the risk for loss of hearing. This is because the passageway from the mouth to the middle ear, the Eustachian tube, is inadequately developed. The lack of air exchange in the middle ear results in an accumulation of fluid which can be painful and cause infection. Treatment with a drain may be necessary. Under all circumstances, regular follow-up by an ENT specialist is advised, and hearing should be checked in connection with this (see in addition chapter 18). Impaired hearing can result in poor speech perception and inhibit speech development.

Sight

Attention must also be paid to the eyes as some girls with Turner syndrome suffer from squints.

Because there is an increased tendency for the squint to be accompanied by long-sightedness, regular checks at an ophthalmologist are recommended to avoid any permanent sight impairment.

Kidneys and urination

All children who in childhood suffer frequent bladder infections or pelvic infections should be investigated for urinary tract anomalies. In most cases, an ultrasound scan is all that is needed to clarify this. Urinary tract anomalies are found frequently in girls with Turner syndrome, most frequently due to changes in the pelvis and constriction of the ureters. Partial fusion of the lower region of the kidneys may be the cause (Figure 2). Operation is seldom

Figure 2

The figure presents the anatomy of the normal kidney, and the "horse-shoe" kidney that can be seen in Turner syndrome.
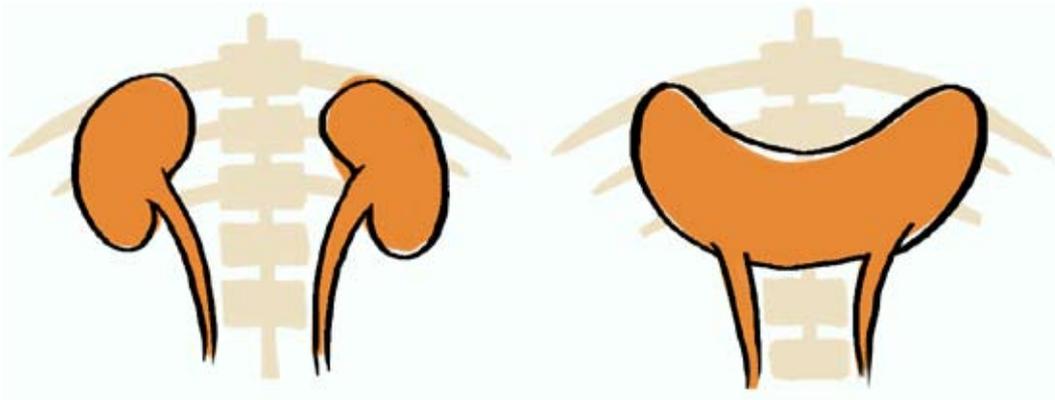
necessary, but depends on the frequency of urinary tract infections and the severity of the anomaly. Girls with repeated urinary tract infections and anomaly of the urinary tract should always be followed up regardless of whether Turner syndrome is present or not.

Growth

A characteristic symptom in Turner syndrome is the slow growth that is detected by a deviation from the normal growth curves for children. Often this deviation will be apparent at birth, but from 6 years of age most girls with Turner syndrome will lie below the normal growth curve. Special curves have been compiled for girls with Turner syndrome because it has been shown that growth in Turner syndrome follows a common and unique pattern. The deviating growth pattern is so characteristic that it should give immediate suspicion of Turner Syndrome if this diagnosis has not already been made.

The growth pattern is discussed in more detail elsewhere (chapter 2). Here we will simply mention that early diagnosis here is also important, because treatment with growth hormone can be started with good effect early in childhood. This treatment can increase the final height considerably.

The cause of the growth inhibition is not lack of growth hormone, which with treatment would simply result in increased growth, but must be looked for in a genetically-determined change in bone development. In addition to the inhibition of growth, this change can result in abnormal bending of the spine (kyphoscoliosis) with a broad chest, and incorrect position of elbows, knees and wrists. The changes are seldom obvious, but can in pronounced cases require investigation and treatment by an orthopaedic surgeon.

Metabolism

The thyroid gland in the front of the throat produces thyroid hormone that is necessary for normal bone development and growth. Girls with Turner syndrome can lack this thyroid hormone. This results not only in an increased inhibition of growth but also in tiredness and weight gain. In some cases, this lack of thyroid hormone is due to changes in the immune system that produces antibodies, which results in the production of antibodies that attack the body's own tissues (autoimmunity). Diagnosis is easy to make by taking a blood sample, and treatment with tablets is simple. Autoimmune diseases occur slightly more frequently in Turner Syndrome and are discussed elsewhere (chapters 13 and 16), however, lack of thyroid hormone is mentioned here because early diagnosis and early treatment are important for well-being and growth.

School and learning

Girls with Turner syndrome have normal intellectual capacity. However, some girls may have particular learning problems within maths, while their language skills are normal. Concentration problems can occur, and there may be problems with spatial perception that indirectly can be expressed as problems with movement patterns. Some girls state that in periods they have felt cut off and isolated and that this causes problems with social contact in school. There are support and contact groups nationally and internationally that play a very important role in providing information to parents and girls with Turner syndrome. They are invaluable in gaining acceptance and

understanding of the problems that might occur, and can contribute to overcoming these difficulties thereby helping most girls with Turner syndrome to lead a completely normal life. It is essential that healthcare providers involved in treating the Turner syndrome patient are aware of the problems mentioned above, which are best resolved by collecting and coordinating the necessary input from other specialists.

Spontaneous growth in girls with Turner syndrome

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Slower growth rate and short height are the characteristic traits of girls with Turner syndrome, as nearly all (more than 90%) of the girls are affected in this way. The cause of this short stature is not a lack of growth hormone or other hormones, but is due to a change in the growth zones of the bones. This change is expressed as a reduced sensitivity to growth hormone, and much more growth hormone is needed than in other girls to stimulate bone growth. However, this is not the entire explanation, because even treatment with high doses of growth hormone only partially normalises growth. The underlying genetic cause is that the child only has one copy of a gene designated "SHOX"(Short-stature HOmeoboX-containing gene). The SHOX gene is located on the outermost tip of the short arm of the X chromosome, and the gene produces a protein that plays a particularly important role in the growth and maturation of the bones in the arms and legs.

The reduced sensitivity of the growth zones and the absence of the SHOX gene causes girls with Turner syndrome to grow "with the handbrake on" throughout their grow-

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Figure 1

Turner height curve with normal curves for comparison.

Height (cm)

Legend:
— Normal girls
— Turner girls +/-2 SD
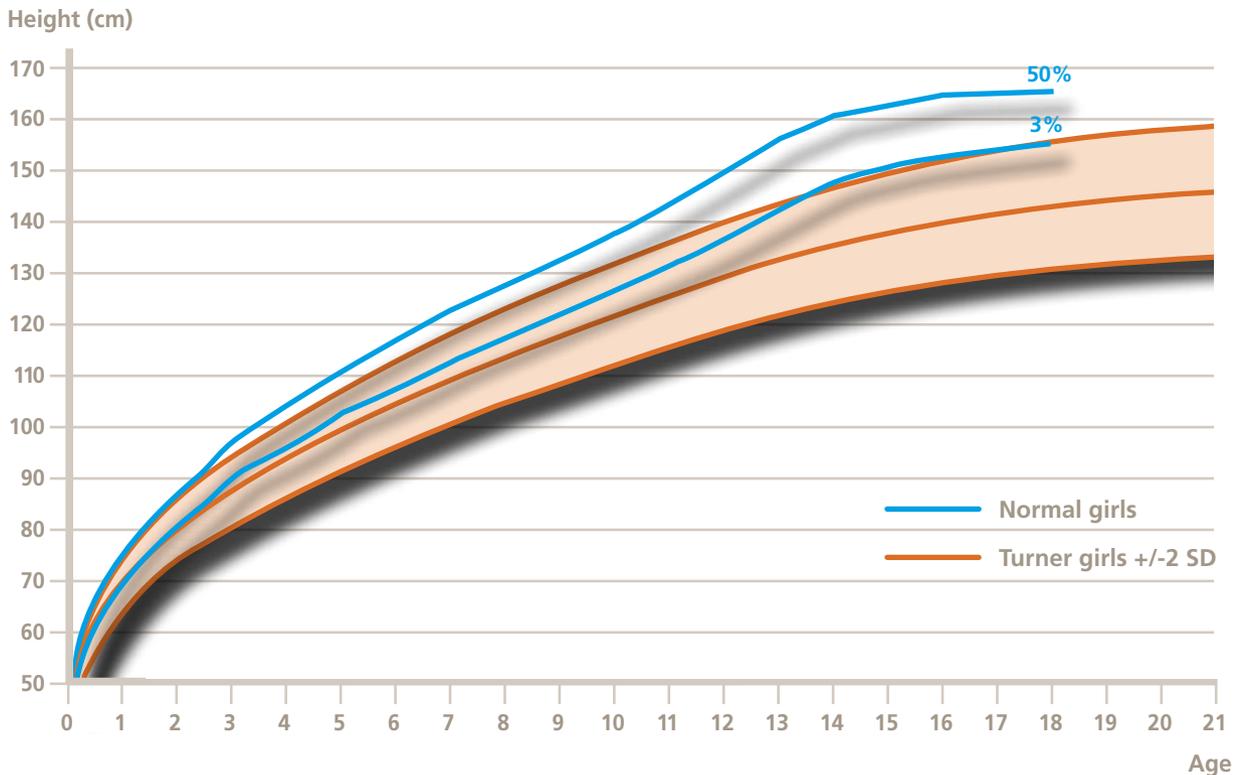
ing period. In addition, most girls do not get a growth spurt in puberty due to lack of the female hormone (estrogen).

Newborn girls with Turner syndrome are often smaller than other newborn girls. On average, a Turner girl born at term weighs about 2 800 g compared to the normal average of 3 300 g, and measures about 48 cm compared to the normal 51 cm. This reduced growth is already seen from an early stage of pregnancy. Premature girls with Turner syndrome down to week 32 have a slightly lower length and weight (2). The slower growth is particularly noticeable in the last three months of preg-

nancy and affects length and weight equally (2). After birth, the growth rate during the first years is only slightly less than in other girls, but later it is clearly slower (Figure 2). At 12 years of age, a girl with Turner syndrome is smallest compared with other girls, but she will catch up again slightly. The reason is that at the start of puberty girls normally have a fast growth rate. Most girls with Turner syndrome do not enter puberty and therefore do not have this pubertal growth spurt. However, they continue to grow for several years after other girls have stopped growing.

Figure 2

Progression of Turner girls' rate of growth.

HV in cm per year

Age in years
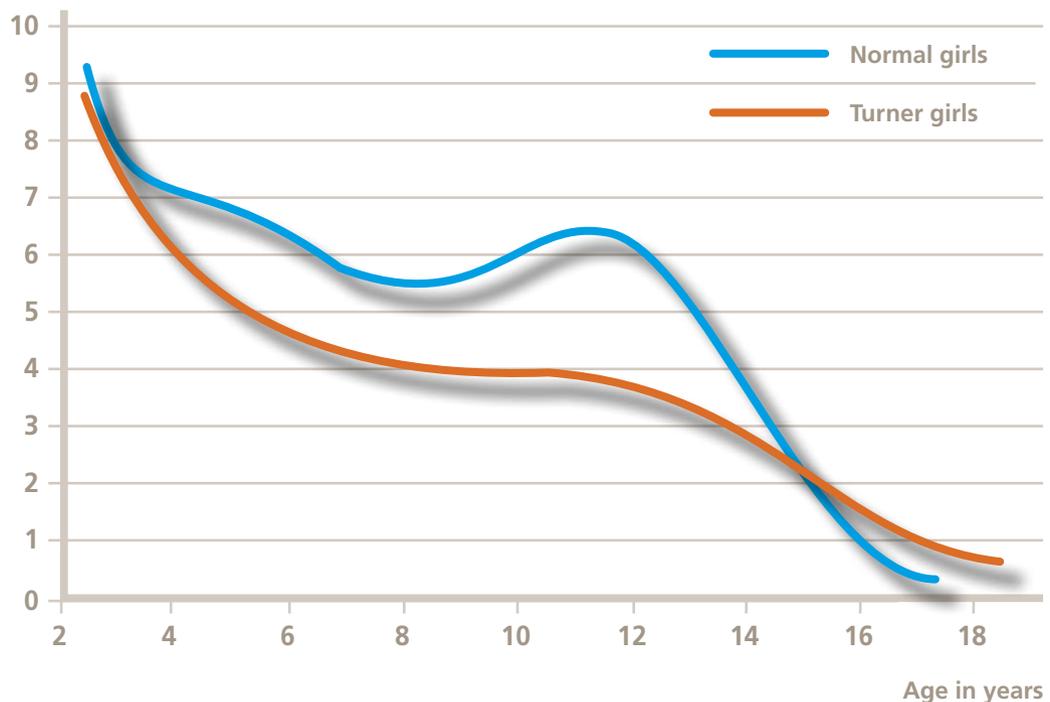
Adult women with Turner syndrome are about 20 cm shorter than other women. However, each woman's final height is just as dependent on their parent's heights as that of other girls. If a woman with Turner syndrome has tall parents, she will usually be taller than other Turner women, but will still be about 20 cm shorter than her sisters. This also means that girls with Turner syndrome from differing ethnic groups with differing normal average heights are not the same height. For example, a woman with Turner syndrome in Northern Europe is on average 147 cm, in the USA 143 cm and in Japan 139 cm.

This growth disturbance not only affects height but also body proportions. The woman with Turner syndrome typically has short legs, a broad body and a short and broad neck, but her hands and feet are the correct size in relation to her height. The growth of specific bones can be affected, but this is not normally significant. For example, the two outermost bones in the hand (metacarpals) and the foot (metatarsals) are often shorter. In addition, when a girl with Turner syndrome stretches her arms out, she has a typically larger carrying angle between her upper arm and lower arm than other girls, which means she cannot straighten her arms completely. The palate is of-

ten high, which may not mean anything other than a more nasal tone to her voice. The increased tendency to middle ear infections in girls with Turner syndrome is most probably due to effects on the growth of the facial bones (see the chapter on hearing). Smaller growth of the lower jaw often results in a receding chin, and can cause orthodontic problems. Curvature of the spine, which also occurs more frequently, is another condition that may require treatment.

In the developed countries, growth hormone therapy has slightly changed the typical characteristics of women with Turner syndrome, especially with regard to height. You can read more about this in the section on growth hormone therapy.

Figure 3

Progression of height of a typical Turner girl as a percentage of normal girls' height.

Relative height (%)

Age in years
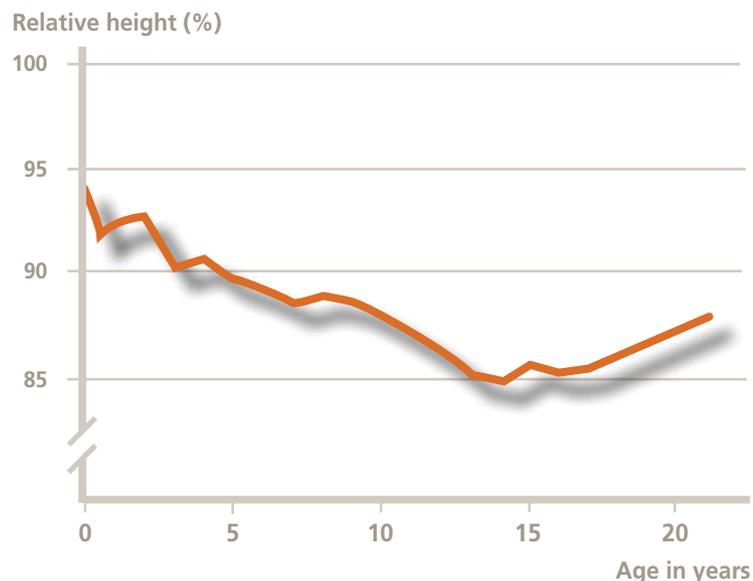
Growth hormone treatment

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Why is growth hormone offered to girls with Turner syndrome?

Most girls with Turner syndrome do not spontaneously achieve their genetic target height. Short stature in itself is, of course, not a disease, but it may affect some people severely, both psychologically and with respect to ordinary daily activities. It is still a matter of debate, whether short stature has any influence on social standing, educational standard and employment. However, attaining normal height and development now appears to be beneficial for the quality of life of Turner girls (1). In the 1980s and 1990s, many studies were conducted worldwide that investigated whether girls with Turner syndrome could attain a greater final height after administration of growth hormone, and the results were positive.

Do Turner girls lack growth hormone?

Most girls with Turner syndrome do not lack growth hormone, but appear to be less sensitive to the effects of growth hormone in the body. If the spontaneous growth curve is poorer than expected for Turner girls, e.g. if growth has stopped completely, the doctor in charge will often test whether the girl suffer from additional diseases, including lack of growth hormone. This is important in order to ensure that the appropriate treatment can be initiated first.

What is growth hormone?

Growth hormone is a protein that is produced in the pituitary of every human being. Growth hormone is produced in short pulses several times a day, but especially at night when we are asleep. As the name indicates, it is an important hormone for growth in children and adolescents. But, in fact, growth hormone is produced throughout our lifetime. The hormone also plays a very important role for metabolism. It strengthens bones, muscles, the heart and circulation, and also has effects on the metabolism of fats and carbohydrates. Growth hormone stimulates the liver to produce a so-called growth factor, IGF-I (insulin-like growth factor I), which is one of the most important factors for bone growth. (Figure 1).

In the early days, growth hormone for treatment had to be extracted from the pituitaries of dead people. Using biotechnology, growth hormone can now be manufactured in unlimited quantities. This growth hormone is an exact chemical copy of natural growth hormone. There are now several pharmaceutical companies that manufacture growth hormone, and their products are all completely comparable with regard to effect and efficacy.

What is the effect of growth hormone on final height?

Growth hormone treatment of girls with Turner syndrome increases the growth rate and the expected final height. There are large differences in the reported gains in final height, and there are few studies with good control

Figure 1

Growth hormone is produced in the pituitary, and is regulated by stimulating and inhibiting factors. Growth hormone causes the liver to produce a growth factor, IGF-I, that affects bones, muscles and fatty tissues in the body.
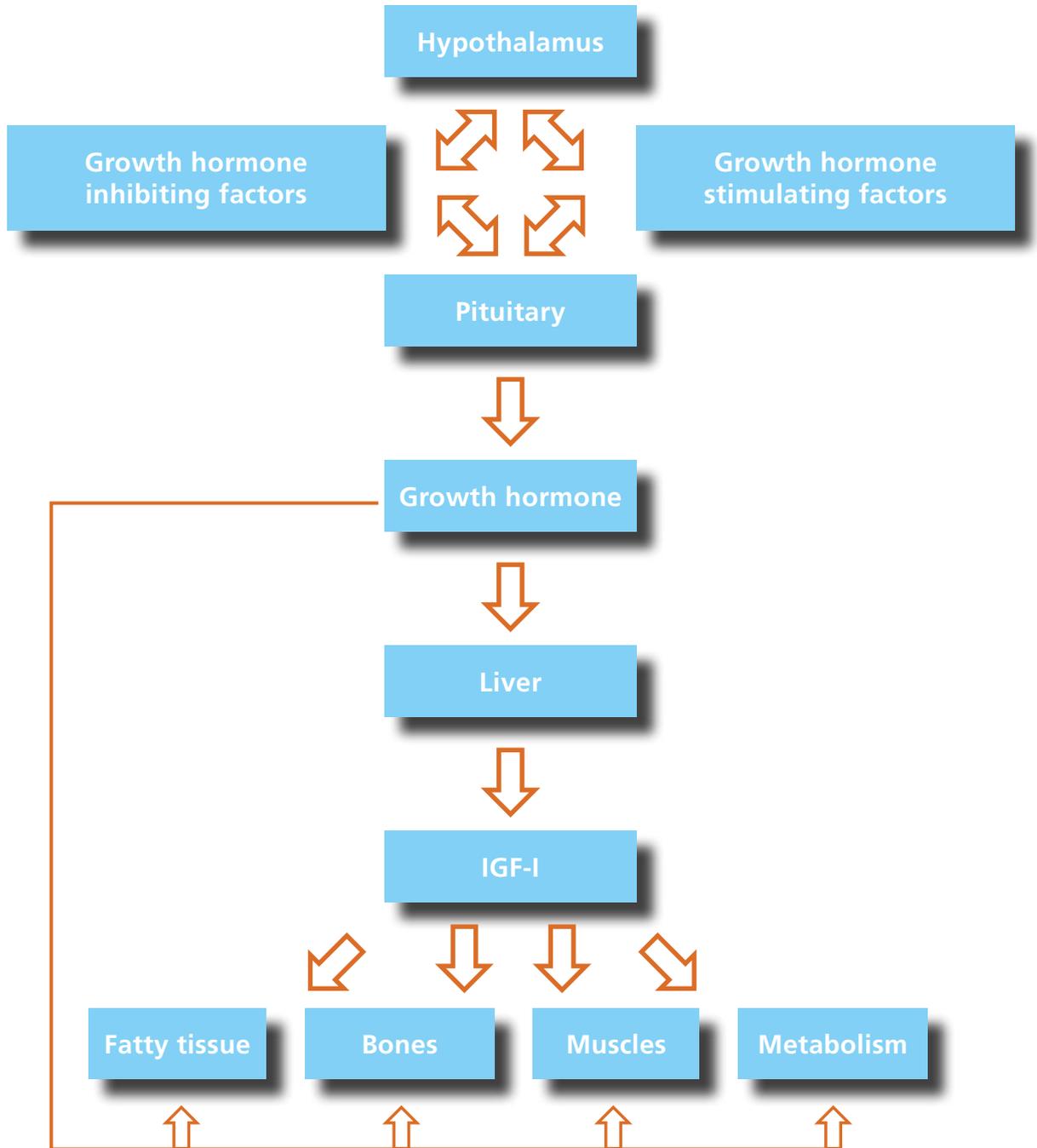
groups. The gain appears to be between 6 and 8 cm after 5–7 years of treatment. This gain is dependent on age and height at start of treatment; the dose of growth hormone; the duration of treatment; and the parents' height as an expression of the genetic target height. Some Turner girls benefit more, while others benefit less from this treatment, but it is not possible to predict the outcome with any certainty (2).

In general, Turner girls are treated with a larger dose of growth hormone than the dose given to children with growth hormone deficiency, who receive 27 µg/kg/d on average. International recommendations suggest starting doses of 54 µg/kg/d. These doses are subsequently adjusted to reflect the effect on growth and the level of growth factors in the blood. There appears to be a clear dose-effect relationship: The more growth hormone administered, the greater the benefit on final height. At doses 3 times higher than those given to children with growth hormone deficiency (90 µg/kg/d), final heights that are greater by 16.9 cm than expected, have been reported (3). Some treatment centres are reluctant to give large doses of growth hormone because these induce higher than normal blood levels of growth factors. No side effects have yet been observed after this treatment, but women with Turner syndrome continue to be followed up.

How is the treatment administered?

Treatment is given as an injection under the skin once a day. It is recommended to inject growth hormone at bedtime in order to optimally mimic the natural rhythm of growth hormone production. All growth hormone preparations use "smart pens", which make it easy to administer growth hormone. The needles used for injecting are so small that you most often do not notice the injection. The parents will normally inject their smaller children, while older children and teenagers can manage this themselves after they have received instruction from healthcare personnel. Experience shows that even patients who are very afraid of needles or having blood samples taken can manage this treatment themselves at home.

When do you start and stop treatment, and do you need to come for check-ups?

In most cases, treatment starts at around 5–6 years of age and continues until the girls have stopped growing at around 15–16 years of age. But treatment can of course stop earlier if the achieved height is satisfactory. Treatment can also start earlier, if growth in early childhood is considered to be very poor (4).

Some Turner girls are only diagnosed late in childhood or around puberty, and here an individual assessment must be made as to whether or not growth hormone treatment

is still relevant. The longer growth hormone can be given, the better the overall gain on final height.

During treatment, the child will be seen every 3 to 4 months with measurement of their height and weight, and blood samples will be taken. Occasionally, X-rays of the left hand will be taken for determination of the so-called bone age: A measurement of the maturity of the bones' growth zones. The bone age, not the child's chronological age determines how long she can continue to grow. It is important that, during growth hormone treatment, this maturation does not take place too quickly.

Are there any side effects?

Even though growth hormone affects many processes in the body, it has been shown that side effects during treatment are extremely rare and often temporary. As synthetically manufactured growth hormone was only first introduced in the 1980s, we still do not know of long-term side effects in adulthood. At the start of growth hormone treatment, oedema, in particular, can occur: Retention of fluid in the body which can be seen in the hands, feet and eyelids. Children with kidney disease and heart disease appear to experience this more frequently. This is a temporary and harmless phenomenon, which can often be avoided completely if treatment is started with a half dose for the first 2–4 weeks.

At any time during treatment, "Pseudotumor cerebri" (Benign Intracranial Hypertension) can occur: A sudden, severe headache possibly with vomiting and disturbed vision. The symptoms are similar to those seen in meningitis, aneurysms or brain tumours. Therefore the child must be seen as an emergency in A&E to exclude these conditions. If there is no obvious cause, the symptoms may be due to growth hormone and a pause in treatment will result in disappearance of all symptoms within a short time. It is believed that "Pseudotumor cerebri" is triggered by an acute fluid imbalance in the brain. After pausing, growth hormone treatment can normally be resumed without problems. "Pseudotumor cerebri" is an extremely rare side effect.

Legg-Calve-Perthes' disease is a disease of the hip bone growth zones, which at rapid growth can become unstable, move slightly, and thus cause pain. The disease can affect all children, particularly during puberty, and occurs more frequently in boys. The risk for this disease is slightly increased during growth hormone treatment. Treatment comprises rest until healed, but in some cases operation is necessary.

The risk for cancer: Growth hormone does not appear to be associated with an increased risk for cancer, or relapse of previous cancer disease.

All children can experience "growth pains" spontaneously during childhood and puberty. The cause of this phenomenon has not been completely clarified. Growth pains are expressed typically as pain or unrest in the legs at night that can be helped by gentle massage, heat, or mild pain-killers if necessary. Some

Figure 2

Examples of three growth patterns in girls with Turner syndrome (45X). E: Estimated height, M: Mother's height, F: Father's height, T: Family's expected potential (Target height), SD: Standard Deviation (O SD = average)

a) Start of growth hormone treatment as a 4-year old; treatment is adjusted based on measurements of IGF-I. Bone age represented as horizontal lines (point to the left if bone age is younger than chronological age, and to the right if older). The graph presents the height of healthy Danish girls at the top, and acts as a reference for Danish girls with Turner syndrome, who have not received treatment, presented at the bottom. Estrogen supplement in the form of plasters is started at the age of 11.

b) Growth rate for the same girl as (a) during treatment with growth hormone (GH) and estrogen in puberty.

c) Progression of growth when growth hormone treatment is started at 5 years of age, and Oxandrolone treatment at 9 years of age.

d) Growth rate for the same girl as (c) during treatment with growth hormone (GH) and Oxandrolone (Ox)

e) Increase in weight-for-height from childhood to adulthood. This patient was also treated with growth hormone and estrogen during this time.

Height (cm)

c

Age

Growth velocity (cm/year)

d

Age

Weight (kg)

e

Height (cm)
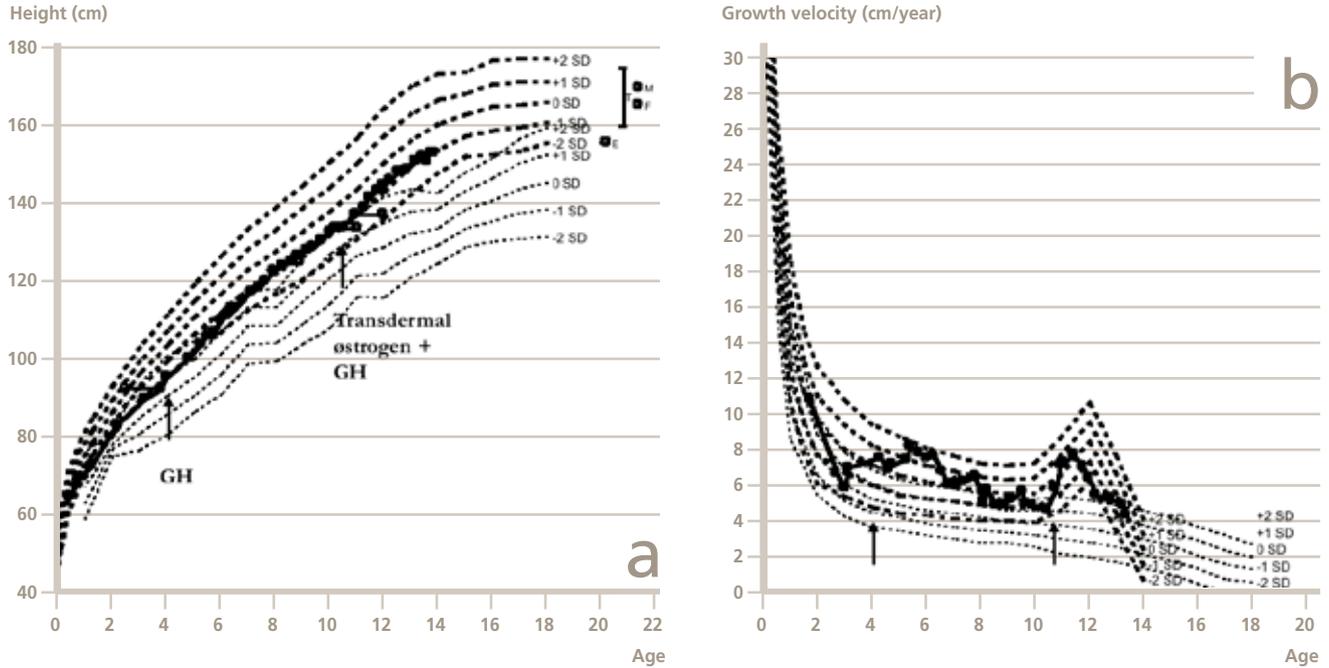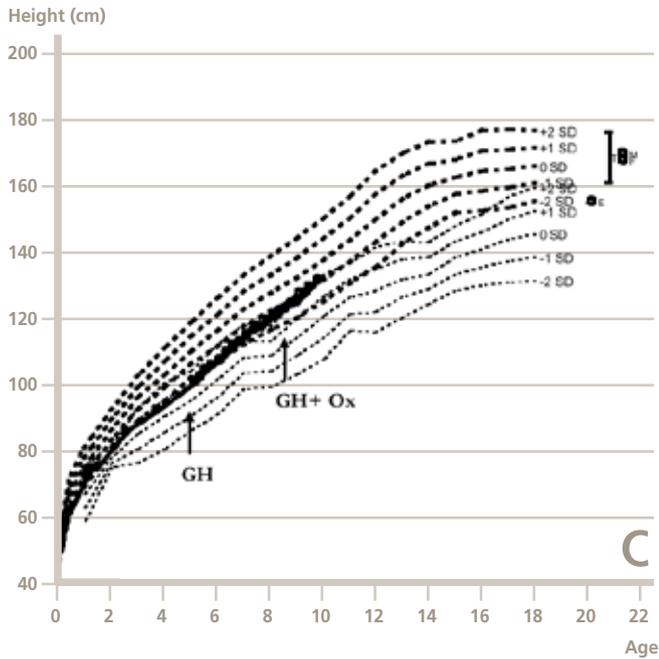
children experience them during growth hormone treatment, especially if it is having a good effect. Normally, this is temporary.

Joint and muscle pain: Many Turner girls experience diffuse pain and stiffness in muscles and joints, often without being able to find any typical signs of disease. In some children and adolescents, growth hormone treatment can cause similar symptoms. In these cases, it is important to exclude that the child has a rheumatic disease.

Growth hormone lowers insulin sensitivity and can thereby increase blood sugar levels. Therefore, glucose metabolism is monitored
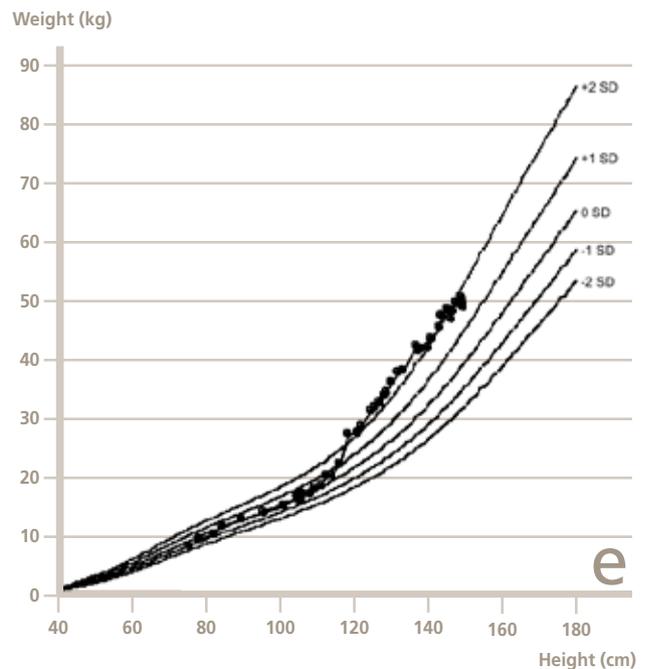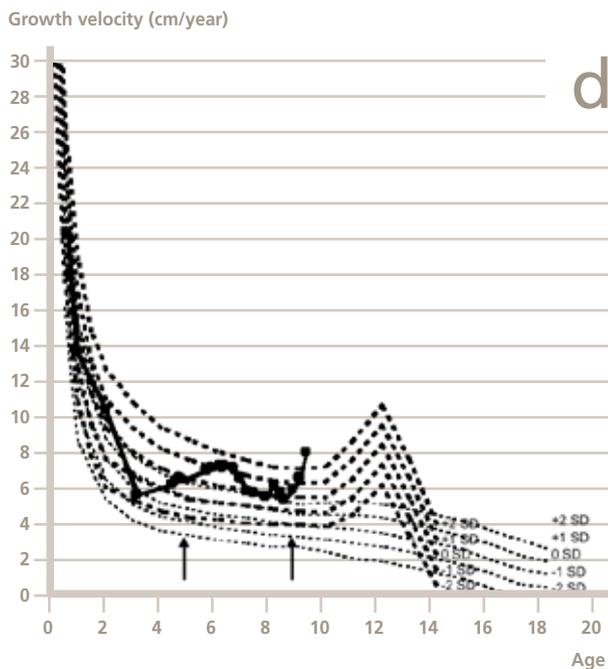
carefully during treatment. An increased incidence of diabetes (type 2 or "old man's diabetes") has been observed in adults undergoing growth hormone treatment, but this is extremely rare in children.

Growth hormone does not appear to negatively affect the heart, blood pressure or blood fats. Currently, studies are looking at whether long-term growth hormone treatment could be beneficial for cardiovascular diseases in women with Turner syndrome.

The family of a child with Turner syndrome should seriously consider whether treatment with growth hormone places too much focus on height. The treatment could negatively affect endeavours to help the child accept that growing up short in stature is perfectly OK. Expectations must not be unrealistic; growth hormone is not a "miracle cure" that enables "modelling" of the final height.

Can all girls with Turner syndrome receive growth hormone treatment?

In Western Europe and in many other countries, growth hormone treatment of Turner syndrome girls is approved by the health authorities. This means that the authorities have reviewed all results from available studies and have found that the treatment is useful and safe. This also means that in most countries the treatment, which is very expensive, is covered by the national health insurance scheme. In addition, some private insurance schemes will cover the costs of treatment. In Denmark, all growth hormone treatment of Turner girls takes place at paediatric outpatient clinics in hospitals, and the families are given the medicines/devices free of charge.

Do all girls with Turner syndrome have to take growth hormone?

Growth hormone treatment is offered to all girls with Turner syndrome, but there may be situations in which one can, correctly, consider whether or not to choose this treatment. Turner girls with tall parents can in some cases spontaneously achieve a final height that lies within the lower normal range for healthy girls. Some families would therefor not feel that growth treatment was necessary. In other cases, the parents consider that the treatment itself, with injections and follow-ups, would be too stressful for the girl, and would therefore outweigh the benefit.

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Transition – from Turner girl to Turner woman

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What is meant by transition?

Transition means "passage from one status to another". With regard to Turner syndrome, transition means that one moves from follow-up in a Department for children to follow-up in a Department for adults. This is not a sudden and rapid transition, but takes place over several years, during which the young person with Turner syndrome and her parents together with the paediatrician prepare closure in the Children's department and plan the future follow-up in the Adults' department.

Why do we need to know anything about this transition?

Transition is important. You have Turner syndrome for life, and it is associated with an increased risk for a number of complications. Some complications you can be born with, others arise in childhood, and some only later as an adult. Whether or not you get these complications, which ones, and how severely they affect you varies from girl to girl. When you have finished in the Children's department, you may have complications that still need to be followed-up and treated, and there may be complications that you will need investigated as an adolescent and an adult. The transition period is therefore an important bridge between the Children's department and the Adults' department, and the transition period must accommodate each girl and her wishes and desires.

How does the transition take place in Turner syndrome?

At the moment, there is no common transition plan that applies to all girls with Turner syndrome, regardless of which country they live in. In Denmark there are local guidelines in the various Children's departments, but they may well vary greatly from each other. This means that follow-up for an adult today is carried out by many different types of doctors for adults such as gynaecologists, fertility specialists, endocrinologists, or general practitioners.

Doctors in other countries have studied and written articles about transition in Turner syndrome (1–5). In 2006, several of the world's leading doctors within research into Turner syndrome met and discussed the best methods of treatment. This resulted in international guidelines that include when and how the transition should take place, and what the transition period should involve (6).

When should the transition take place?

Transition in Turner syndrome should be planned in detail both with regard to how long it should last and what it should include. It should be started early in puberty, i.e. around 12–13 years of age, at the time of the start of treatment with female sex hormones, and when treatment with growth hormone is about to finish (5). The final closure with the Children's department for most girls will be around 16–18 years of age when they have stopped growing in height, and puberty has finished.

How should the transition take place?

Height growth and treatment with growth hormone in childhood is one of the most important aspects to be followed-up in the Children's department for the majority of girls with Turner syndrome. In the beginning of the transition period, at 12–13 years of age, puberty replaces height growth as the most important aspect, i.e. development of breasts, growth of sexual hair and the first menstruation (5). During the transition period, it is natural for parents to withdraw more and more into the background, and for the young person to learn, at their own rate, to take responsibility for their health and the complications they may have as a result of the syndrome (6). After many years of visits to the Children's department and, in many cases, daily injections with growth hormone, most children with Turner syndrome are looking forward to being free and independent. It is, however, important that the young person understands why she still has to go to the doctor's and to follow-up appointments, and that she learns how to look after herself and keep healthy and well (6).

Figure 1

Communication during transition.

The paediatrician

The parents

The Adult doctor

The child with Turner Syndrome
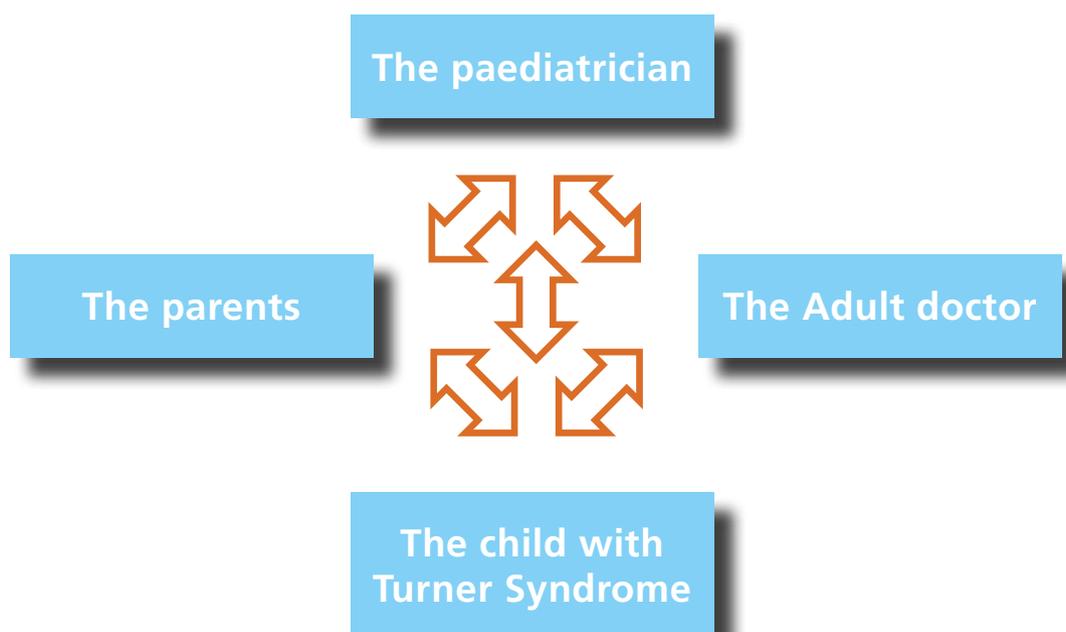
What should the transition include?

During the transition period, each girl's status is assessed in respect of:

- Function of her ovaries in relation to pubertal development and need for treatment with female sex hormones.
- Complications that have arisen in childhood that require continued follow-up and treatment (e.g. congenital heart disease, congenital kidney anomalies, chronic middle ear infections, swelling of feet and legs).
- Risks for complications in adulthood (overweight, diabetes, abnormally low metabolism, elevated fatty substances in the blood, coeliac disease (gluten allergy), elevated blood pressure, dilation of the aorta, impaired hearing, osteoporosis).
- Psychosocial functioning (maturity, self-esteem, school, education, friends, boyfriends).

Based on the results, relevant investigations and treatments are initiated and, at the end of the transition period, the girl with Turner syndrome, the paediatrician, and the adult doctor who will undertake future follow-up, will together prepare a personal health plan. A personal health plan, which the young person has been involved in writing, increases the chances that she will adhere to it and continue with follow-up visits into adulthood. This will also result in her attaining the best possible health as an adult (5).

In addition to this, there will be an ongoing need for advice and information during transition, which must be continuously adapted to the girl's maturity and needs. This could include topics such as:

- What does it mean to be an adult with Turner syndrome.
- The benefits of continued follow-up as an adult.

Figure 2

Communikation after transition.

The Adult doctor

The child with Turner Syndrome

Collaboration partners other specialists
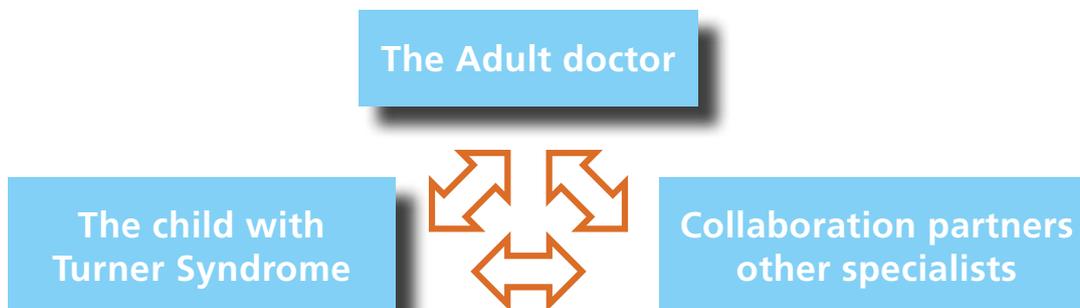
- The advantages and disadvantages of treatment with female sex hormones.
- Involuntary infertility and treatment options (egg donation, adoption).
- Sex, contraception (as required), sexually transmitted infections.
- Options for moving away from home, education and work in the future.
- Social relationships (male and female friends, boyfriends).

What is important for a good transition?

Turner syndrome is not simple, and can be highly complex, with a number of complications that affect women with Turner syndrome throughout their life time. It is therefore best to consider the syndrome and transition period as a whole and to understand that, often, the expertise of several different doctors will be required (2). Areas important for a good transition are coordination and communication (Figures 1 and 2). The Adult doctor who takes over from the paediatrician must be a specialist with an interest in Turner syndrome, and they must also coordinate each woman's present and future needs for investigations and treatments with other specialists. Therefore the specialty of the Adult doctor is not critical (7). It can be discussed whether adult follow up is best performed at multi-disciplinary clinics centrally located in major hospitals, or decentralised within various specialties in smaller regional hospitals or private practices. Regardless of the location, it is important that the coordinating Adult doctor has comprehensive knowledge of the local network of cooperation partners within relevant specialties and, similarly, which of the complications will require future referral to a major, central hospital.

Is there a need for a common national or international plan for transition in Turner syndrome?

Studies from abroad have revealed that if an overall health plan is not compiled for the young girl with Turner syndrome during the transition period, there is a high risk that she will not attend follow-up appointments as an adult (4). Furthermore, many adult women with Turner syndrome state that they have symptoms of a number of complications (3). Lack of follow up is therefore very unfortunate, and can result in treatment of complications being delayed because they are discovered later. In turn, this can result in lowered quality of life, more and perhaps worse diseases and, finally, a greater risk of dying as a consequence of some of the complications (4). Studies are not available from all countries on transition in Turner syndrome, so we cannot say with certainty what happens to women with Turner syndrome after closure in the Children's department. It is not known whether as an adult they continue to go to a doctor's for follow up, how often they go for follow up, and which diseases they are examined for. It is absolutely essential that more information about transition is provided for girls and women with Turner syndrome, and their families. It is also important that doctor's and others are familiar with the desires and needs of women with Turner syndrome, and with

their quality of life. Therefore, the compilation of common national guidelines for the transition period in Turner syndrome that are based on the international guidelines (6) would be beneficial for girls and women with Turner syndrome, their families, their doctors, and for ensuring good treatment for girls of all ages with Turner syndrome.

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Puberty – the transition between childhood and adulthood

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Many girls with Turner Syndrome experience puberty as a special challenge – it does not occur by itself but requires external help. For most children and adolescents, puberty is an important event and a period in their lives that they look forward to with longing, uneasiness, joy and anxiety. This process that takes several years, during which the child matures mentally, physically and socially to an adult person, is a demanding, fun but also vulnerable period in which most adolescents have many questions and thoughts.

It is a period of life in which it can be tough to be different from your peers. Those girls who start puberty early with breast development, growth of sexual hair, and menstruation are often shy, and feel it is difficult to be the first to look different. And, similarly, girls that develop late suffer feelings of being different and an outsider.

Girls with Turner syndrome often belong to the latter group. Almost 70–85% experience that puberty does not start automatically. Some experience that puberty does start, but that development then stops. Both groups require sex steroid treatment to stimulate growth of the breasts and uterus. Almost 90% need treatment with sex hormones (1). The cause of this lack of pubertal development in Turner girls lies in the ovaries. The girls do have ovaries, but whereas the ovaries in girls with normal pubertal development are filled with small follicles that produce the sex hormones, the ovaries of Turner girls are often much smaller and the follicles

have been replaced by connective tissue that cannot produce the hormones necessary for normal pubertal development. The follicles are present early in foetal development but, because Turner girls do not have two normal X-chromosomes, the follicles often die during the last half of pregnancy and early childhood. Recent studies do however indicate that follicles are present in more Turner girls than has been believed to date.

Why are sex hormones important?

The most important sex hormone in girls and women is called estrogen. Estrogen is important for many of the body's functions and it is therefore very difficult to do without it. By far the main part of the body's estrogen is formed by the ovaries, but modest amounts are also formed in the adrenals and fat tissues.

Breast development

Development of breasts in girls is dependent on the presence of estrogen in the body. The normal pubertal development (and the preferred developmental process in girls with Turner Syndrome who do not enter puberty automatically) starts with the production of quite small amounts of estrogen that stimulate

Figure 1

The pituitary is a small gland about the size of a pea in the brain that produces the hormones FSH and LH at the start of puberty.

The ovaries are affected by FSH and LH and start to grow and produce estrogen.
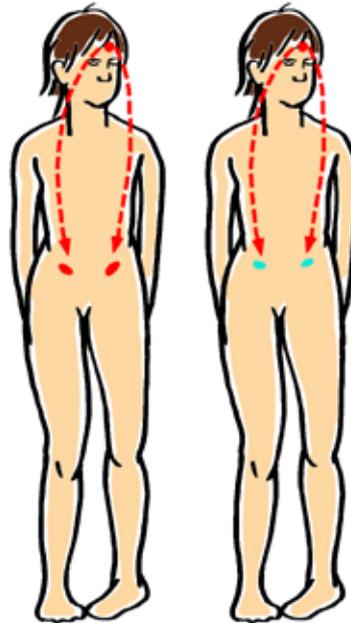
In girls with Turner syndrome, too, the pituitary produces FSH and LH.

But the ovaries do not respond to FSH and LH because they are smaller and contain connective tissue.Therefore the ovaries produce too little estrogen.

Ovaries secrete estrogen.

Estrogen affects the bones, breasts, uterus, brain, heart and blood vessels.
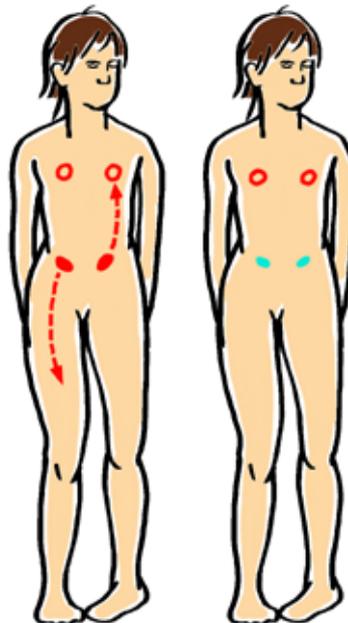
In girls with Turner syndrome, the ovaries secrete too little estrogen.

Estrogen can be taken either as tablets or as plasters. This means that the bones, breasts, uterus, brain, heart and blood vessels can develop just as in other girls.

the nipples and, later, the milk glands to grow (Figure 1). Normally, breast development starts at around 11 years of age, and it takes a few years for the breasts to attain their "adult" shape. For girls with Turner syndrome who need medical treatment to develop, it is important that this treatment is initiated using very small doses of estrogen that are gradually increased. If, at the beginning, the doses are too high, this could result in the nipple developing too quickly compared to the rest of the breast, which therefore will not develop as harmonious as it could. This may be extremely difficult to correct at a later date.

Uterus

Estrogens are responsible for the growth and shape of the uterus, and that it is later able to grow during pregnancy. The uterus is a muscle that is quite small in size prior to entering puberty. When the uterus is affected by estrogens from the ovaries, it begins to grow until it is about the size of a small pear. After the mucous membranes lining the uterus have been exposed to estrogens over a longer period of time, menstruation starts. The average age for a girl's first period is about 13 years, and it occurs about 2–2,5 years after start of breast development. At menstruation, the mucous membrane lining the uterus is expelled. Regular menstrual cycles require ovulation once a month, and many girls do not experience regular periods until several years after their first menstruation.

In girls with Turner syndrome we prefer to simulate the natural process as accurately as possible. The uterus is formed in the normal way in girls with Turner syndrome, but requires female sex hormones to develop so that later in life it can accommodate a pregnancy.

About 2–5% of girls with Turner syndrome become pregnant without medical assistance, while others need to make use of egg donations (i.e. an egg from another woman) in order to become pregnant. In recent years, there has been a major focus on how to best facilitate sex hormone therapy to ensure that the uterus grows and has the best potential for completing a future pregnancy.

Growth

As a rule of thumb, it can be said that estrogens in small quantities affect growth in a positive way, while large amounts of estrogens stimulate the bone growth zones to close thereby stopping growth. The growth spurt that occurs in normal pubertal development is among others due to the interaction between growth hormone, metabolic hormones and sex hormones.

The effects of sex hormones on growth can be an important factor when deciding when to start estrogen treatment in girls with Turner syndrome. If it appears that the girl will have a very short final growth height, it may be preferred to delay sex hormone treatment a little so that the growth hormone therapy has better and longer time to act before the sex hormones eventually close the growth zones.

Alternatively, the girl may wish to develop at the same rate as her peers, and therefore wish to start treatment at an earlier time. Often you will need to balance the various needs to finds the best solution for the girl.

Body shape

The female sex hormones are important for the development of a feminine body shape and fat distribution.

Bone density

Estrogens play an important role in the incorporation and maintenance of calcium in bone thereby preventing the occurrence of osteoporosis.

Blood vessels

Estrogens are important in the structure of blood vessel walls, and can prevent early stages of atherosclerosis. It is still not definitely known what is the best type or optimum duration of estrogen treatment for girls with Turner syndrome for preventing development of diseases of the heart and blood vessels, but studies have demonstrated that estrogens have a positive effect on blood pressure, cholesterol levels and thickness of blood vessel wall (2).

Brain

It is well-known that sex hormones affect brain development. During puberty, the structure of the brain undergoes dramatic changes. This development and maturation of the brain is important for the maturation of thought processes, emotions and social skills that are essential if the adolescent is to develop and be able to look after themself, manage their life, and to interact in social networks with other young people (3–4).

When is the best time to start sex hormone treatment in girls with Turner syndrome who do not spontaneously enter puberty?

In essence, there is no simple answer to this question. Ideally, sex hormone treatment should be started at the same time as peer puberty starts. Treatment must be given such that breast development is cosmetically satisfactory. At the same time, treatment must allow the best conditions for growth and any growth hormone treatment i.e. the bone growth zones must not close too early. The

Figure 2

Sex hormone treatment of girls with Turner syndrome who do not experience normal pubertal development. Treatment is given either as tablets or as transdermal application plasters.

Natural sex hormones are preferred to synthetic compounds.

Treatment with sex hormones does not protect against pregnancy. Preferably, do not use oral contraceptives throughout the teens, as the estrogen content is too high and could have negative effects on growth; in addition, the anti-osteoporosis effect is uncertain.

Age	Proposed treatment	Tablets	Plasters
<12	Signs of natural pubertal development. Hormone blood samples (FSH)		
12–13	Absence of spontaneous pubertal development. Elevated FSH	Human oestradiol 0,25 mg daily	Depot plasters with oestradiol 25µg/24 hours. One quarter plaster = 6,25 µg daily
12,5–15	Gradual increase of estrogen dose depending on development	Increase to adult dose (2-4 mg oestradiol daily)	Increase to adult dose 100–200 µg daily
14–16	Begin cyclic progesteron treatment after 2 years' of estrogen treatment or at breakthrough bleeding	Combined products with estrogen and gestagen e.g. Trisekvens	Transdermal treatment with estrogen is supplemented either with tablets (5–10 mg) 10 days per month or transdermal treatment with progesterone
14–30	Continued hormone treatment at full dose because normal estrogen production is maximum between 15–30 years of age	Can consider switching to oral contraceptives (see below)	
30–50	Continued estrogen treatment to counteract risk for osteoporosis and to maintain feminisation		
>50	Continued sex hormone treatment depending on risk factors similarly to women undergoing the menopause		

uterus must grow so that it can accommodate a pregnancy when this becomes necessary, and estrogen treatment must ensure development of strong bones so that osteoporosis does not occur at a young age. Estrogen treatment must also affect the brain positively so that the girl is developmentally at the same level as her peers and, finally, it is important that the treatment affects blood vessels and blood pressure favourably.

There are very many treatment outcomes to be met. Luckily many studies are ongoing so that we are continuously acquiring more knowl-

edge, but unfortunately we do not know everything, and there is still much to be learnt. Figure 3 presents an overview of the effects of the hormones.

Currently, initiation of sex hormone treatment is recommended around 12 years of age if the girl does not show signs of breast development and if blood tests reveal there are no signs of spontaneous pubertal development. As far as possible, the goal is simulation of natural pubertal development.

The principles of this sex hormone treatment are based on small doses of estrogen that are gradually increased over the following years depending on the girl's estrogen sensitivity. Figure 2 presents a proposed treatment schedule with sex hormones for girls with Turner syndrome. In particular, the effect of treatment on breast development, growth and bone maturation are measured. But also bloodsamples can be helpfull (estrogen, FSH and LH) After about 2 years, or when menstruation starts, treatment is supplemented with another hormone (progesterone) which is given for 10–14 days of the month to ensure that the endometrium lining the uterus is expelled and regular periods occur. One of the reasons for waiting a minimum of 2 years before starting progesterone treatment is to provide the best conditions for breast development and growth of the uterus.

Hormone treatment can be given either as tablets or plasters. For many years now, the practice has been to give tablets. The advantage of tablet treatment is that it is easy to take

the tablets, but the disadvantage is that the estrogens are taken up by the liver and converted to other estrogen compounds. Plaster treatment is gaining more and more favour.

As with all medicine treatments there may be side effects. Weight gain, oedema and breast tenderness, headache and depression have been observed at estrogen treatment, and weight change, breast tenderness, mood swings and irregular menstruation have been observed at gestagen treatment. It is important to be aware that girls with Turner syndrome undergoing treatment for absent pubertal development are supplemented with hormones that the body is not able to produce itself. This treatment can therefore not be compared to hormone treatment of women undergoing the menopause. That is a completely different condition with a quite different side-effect profile.

Turner girls who do not have natural pubertal development must, of course, be offered hormone treatment. The challenge lies in tailoring the treatment to each girl in order to optimise the result with the fewest side effects.

Figure 3

Importance of the sex hormones for the individual organs.

Hormon/ virkning på	Bones	Breasts	Uterus	Ovaries	Heart and blood vessels	Brain
Estrogen	Small doses: Increases the weight. High doses: Closes the bone growth zones. Prevents osteoporosis	Stimulates growth of breast mammary gland	Stimulates growth of the uterus itself. Stimulates growth of the uterine endometrium	No effects on the ovaries	Lowers blood pressure and prevents atherosclerosis	Affects cognitive, emotional and social maturation.
Gestagen			Triggers menstruation by expelling the endometrium from the uterus	No effects on the ovaries		

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Chronic disease in adolescents

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Introduction

Almost one in ten young people live with a disease or condition that requires more frequent contact with the healthcare services than other young persons. This could be asthma, eczema, diabetes, a handicap or – as in the case of Turner syndrome – a congenital chromosome change. For some people, their condition does not really affect their daily lives, and they do not feel at all ill even though they have to take medicines every day. Others may need to live all their life making allowances for their condition, and are continually dependent on help from other people. In this chapter we use the expression chronic disease, well-knowing that many people experience Turner syndrome as a condition that you can live a really good life with.

The healthcare system focuses primarily on treatment of the actual condition, e.g. hormonal imbalance, heart problems, loss of hearing and prevention of osteoporosis, while other very important areas of the young person's life are often overlooked. This can be a major problem for many during adolescence, which has many challenges anyway. The body changes dramatically, and the adolescent has to adapt to new situations in school and among friends. Many adolescents with a chronic disease are in a particularly difficult and vulnerable situation, perhaps because they look different; they have to remember to take their medicines; or perhaps because they cannot do the same things as their friends due to physical limitations. These conditions can create an increased vulnerability to op-

position, but it is also important to remember that many chronically-ill adolescents have acquired unique experiences and resources through their diseases that confer an advantage in solving problems they experience, and in generating security and protection.

This chapter provides an overview of our general knowledge on chronic diseases in adolescents, and places particular emphasis on what we know about girls with Turner syndrome. We will highlight how chronic diseases can affect the life of an adolescent, the coping strategies used by adolescents to overcome living with a chronic disease, and how parents and the healthcare system can improve their efforts to help young people with chronic diseases.

Independence and dependency

Puberty is both a difficult, demanding, and fun period for most adolescents. During puberty, identity development gets a real push and the adolescent begins to detach from their parents. For most, this is a process that stretches over several years during which they gradually become more and more independent. It is also often a period of turbulence. One day they feel on top of the world able to take on anything – "cool, calm, and collected" – and the next they are childish and small again.

A chronic disease during this time can prolong the dependence on and close ties with parents. If, for example, the child is used to the mother organising when to take the medicines and is always the one who talks to

the doctors, this may mean that the child has not taken onboard all aspects of the disease and that he/she has to take extra care of him/herself. Studies have shown that many young persons cannot explain their medical condition in their own words, and the treatment they are receiving. This may be due to doctors talking to the parents instead of directly to the child. It may also mean that the child does not assume responsibility, for example for taking medication, even though he/she can in fact manage this. However, the family's role as a support for the child with a chronic disease must most definitely not be underestimated. In a Dutch study, young women with Turner syndrome assessed their family life as better than that of the background population (1). Many young people with chronic disease manage stress factors and frustrations surprisingly well, particularly if they have the support of a well-functioning family, and many adolescents are able to mature emotionally through the experiences acquired when they manage particularly difficult periods.

Looking different

All people are, to some extent or other, concerned with how they look. Particularly during adolescence spots, the feeling of being too fat, or even a "bad hair day" can be enough to ruin everything. These "common" worries also affect young people with chronic diseases but, on top of these, they have the problems of appearance that are unique to their illness.

The body changes dramatically during puberty. In girls, puberty normally starts with breast development (at around 11 years of age), thereafter growth of sexual hair, and later the first period (at around 13 years of age). In girls with Turner syndrome, puberty is a particular problem because it often does not start or progress by itself. About 70–85% of girls with Turner syndrome do not enter puberty spontaneously. Absent pubertal development can result in low self-esteem and, consequently, withdrawal from friends and social situations, such as parties and sport activities. The girl can be perceived to be younger than she really is by people around her. This may mean that the girl could be kept at a younger developmental level, and that she is not given the same privileges and duties as her peers. The female sex hormone oestradiol is given to initiate pubertal development (see chapter 5 on Puberty). Studies have demonstrated that it is vital to start hormone treatment around the time that other girls enter puberty. It has been shown that self-confidence of girls with Turner syndrome increases when puberty starts at the same time as their friends of the same age (2).

Girls with Turner syndrome are shorter than their peers and, generally, their final height is around 21 cm lower than the average (for women). This means that while the average Danish woman is 167 cm, women with Turner syndrome are on average 147 cm. But the height of girls and women with Turner syndrome also varies a lot, just as it does for other women and children. Nevertheless, most studies reveal that in general the height is not the

greatest problem for girls with Turner syndrome. In a French study, girls and women with Turner syndrome indicated that loss of hearing, which affects around 1-in-2 girls, had the greatest impact on their social life and self-esteem (2).

In addition to short stature and delayed pubertal development, girls with Turner syndrome may have other visible signs of their chromosome change, e.g. a wide neck, swollen hands and feet, "tired" eyelids (ptosis), a low hairline, and bowed nails. Little is still known about how these physical differences affect self-esteem and quality of life, but a study in France revealed that there was no difference in how girls with and without Turner Syndrome accept their bodies. This may be because girls with Turner syndrome are used to their appearance and place emphasis on other things. As a girl who was born with a heart malformation expressed it "I have never tried what it is like to look different". It may also be due to the research methods, which do not take into account the special problems that girls with Turner syndrome have, and to the fact that almost all girls in puberty are extremely critical and often highly dissatisfied with their own bodies.

Age at diagnosis

Some children with a chronic disease have had the condition since they were quite small and perhaps do not remember a time without the illness, while others are diagnosed later. Although Turner syndrome is a congenital chromosome condition, the diagnosis is made at widely differing times of life. Half are diagnosed before the age of 15 and the other half are diagnosed after the age of 15. About 40% of all patients with Turner syndrome are first diagnosed in puberty – often because puberty does not proceed as expected.

When the diagnosis of Turner syndrome is made before the child is born or in early childhood, the parents usually accept that the child has to live with the condition. This can mean that the parents already accept the situation, and have adjusted their expectations of the child in relation to their knowledge, beliefs and ideas about the character of the condition. With time, this can affect the expectations, ambitions and goals that the young person sets for themselves.

When the diagnosis is made during puberty, many young people are thrown into an emotional crisis that can affect the entire family. For some girls with Turner syndrome it can nevertheless be a relief that there is an explanation for their absent puberty. There is a risk that the parents protect the child more than the condition and the child's abilities necessitate and the child is kept bound to the parents, perhaps limiting their endeavours for independence. Even though during puberty there is a particular risk that bodily self-perception will be primarily negative, a study of young women with Turner syndrome did not indicate that Turner syndrome negatively affects self-image (3).

There are many thoughts that go through the head of a young person when they acknowledge that they have a disease or condition that cannot be cured. There are three periods in which adolescents with a chronic disease are perceived as particularly vulnerable: The period when the diagnosis is made; during puberty; and the time when the young person leaves home. For many girls with Turner syndrome, puberty will coincide with the time of diagnosis, and this period can therefore be additionally problematic for these girls. Thoughts can be so overwhelming and the adjustment to a life with a chronic disease can demand so much energy that, for a while, they cannot cope with much else in life. There are short-term and long-term anxieties. The young girl must adjust to another identity, and develop and integrate a new self-knowledge at a time when the desire to "be like everyone else" is particularly strong.

Some of the questions girls with Turner syndrome ask are related directly to their condition here and now, but many will also wonder how it will affect their lives in general – can I still take part in sports like I used to? What about parties and drinking beer when I have to take growth hormone? Do I have to use contraceptives when I am taking hormones? Is my body normal? Can I have sexual intercourse? Who would fall in love with somebody like me? What shall I tell my friends? Who needs to know? Can you tell just by looking at me what's wrong with me? What

shall I say when people ask? Will I have boyfriends? Can I have children? Can I die from this condition?

Many of these questions can be so overwhelming and difficult to talk about that the adolescent, parent and healthcare professional may consciously or unconsciously avoid broaching them. This leaves the young person alone with her thoughts which can cause deep concerns and anxiety. In order to help the adolescent, it is important that parents, friends, doctors and nurses dare to listen and talk about the things that worry her. Some problems have simple answers and solutions while others are more complicated. Even with the complicated issues, it usually helps to share your worries with somebody who cares for you and wants the best for you. It is important to be aware that some of the feelings, thoughts and questions that occur also occur naturally in adolescents who do not have Turner syndrome.

For many young people with a chronic disease, it is more stressful to live in the uncertainty of how the condition will progress than to know the prognosis. Similarly, it is experienced as more stressful to have an "unpredictable" condition in which the symptoms vary from day-to-day than one that is stable and predictable. Unpredictability can create uncertainty and a feeling of lack of control in the young girl, and confusion in her friends. It means a lot knowing that they can go to parties, important events at school, and on trips – just like their friends. At the same time, it is important to be aware that not all existential problems are attributed to having Turner syndrome. It

is therefore very important to know the difference between issues associated with living with a chronic disease and those that are normal adolescent problems. In some ways, for young people with Turner syndrome their identity pathway is comprised of two parts: The first is normal identity development towards an adult identity, and the second is their identity as a person with Turner syndrome.

Advice for care providers

Be open and do not reproach the child

Use a language that the child understands

Involve the child in decisions and the treatment

Recognise that honesty about poor compliance is a good starting point for further cooperation

See the child without their parents present

Avoid irony and abstract language

Remember, and take into account, the resources of the family and the child

Advice for children

Look for support from other children

Find a "good adult" that you have confidence in

Know your strengths, and discover what makes you happy

Find situations in which you can use your strengths and resources

Find out about your disease and your treatment

Ask those questions that are going around in your head

Advice for parents

Let the child gradually take over responsibility for their disease

Involve the child in decisions and the treatment

Show confidence in the child

Deliberately stay in the background sometimes so that the child can put their own thoughts and questions

Be prepared for sudden and frequent changes in the child's needs

Responsibility for their treatment – or not

It can be a problem for young people to take medicine. It can be inconvenient, uncomfortable, and difficult to remember to take the medicine. Some medicines have side effects that make the disease visible to others. They are a constant reminder that you have a chronic disease. The results of many studies show that only about half of patients take medicines as instructed by their doctor, and that young people are particularly prone to "forgetting" to take theirs for shorter or longer periods. We also know that people are more inclined to take medicine for an acute, short-term illness than for a chronic disease – particularly if they are not affected by their chronic disease in their daily life. This can result in serious health problems in the short or long term, and it is therefore important to understand the underlying factors that may incline a young person with a chronic disease to not comply with the treatment.

Most girls with Turner syndrome are treated with growth hormone, and at the start of puberty take hormones in the form of tablets or plasters as well. Some girls with Turner syndrome also require tablets to regulate their metabolism. Understandably, young people prefer medicines that affect their life and lifestyle minimally. Growth hormone treatment demands injections every day, and much evidence indicates that this treatment can be very difficult to comply with – not least for young people (4). An American study showed that about 30% of women with Turner syndrome did not take their estrogen tablets as instructed (5).

Omitting to take medicine can be due to a simple slip, forgetfulness, lack of understanding of the reason for taking the medicine, discomfort at injection, side effects, denial, and many other reasons. For most people, it is not an "either-or", but a question of more or less adherence to the therapy. Very few patients want to tell their doctor that they have not taken the medicine as agreed. This means that the doctor and patient may talk over each other's heads which, in the long run, could have a negative effect on the patient's health. In order to be motivated to take her medicine properly, it is important for the young person to know why she has to take her medicine; to know how the medicine works; and to know the consequences if she does not take them (4). Openness and trust are important when talking with a young person. Information about her condition in a language she can understand, an action plan if things go wrong, and regular contact with her doctor all contribute to ensuring adherence.

Friends and social relationships

Friends are very important during adolescence, and it is essential to be a part of the community with other adolescents. Adolescents follow the example of their peers, and will often want to be different, but also to be similar to them. Adolescents are shaped and formed by each other to a far greater extent than by their parents. This also applies to adolescents with a chronic disease. For some, their condition may limit this formative social life – directly as a result of mental or physical limitations or indirectly as a result of tiredness, treatments, doc-

tor's appointments, or visits to hospital. Lack of knowledge by friends can result in misunderstandings and exclusion. Teasing and bullying have been shown to be the most important factors in depression in young girls with Turner syndrome (6). Low self-esteem is described as a problem for many adolescents with a chronic disease, and similarly among girls with Turner syndrome. Girls with Turner syndrome have several attention disorders, and they often feel alone or excluded, especially because of the hearing problems that occur in around half of the patients. Women with Turner syndrome from The Netherlands perceive themselves to be less socially-accepted, less sporty and less attractive than other girls (1).

Nobody wishes to be identified as having a disease – especially the young. Therefore many young people do not wish to talk with other young people who have the same condition. However, experiences and studies show that groups where young people meet and exchange experiences, either in meetings or via the internet, are extremely beneficial for them. In Denmark, The Danish Turner Syndrome Society has a youth group (www.turner-syndrom. dk), and many other countries also have national associations.

Education

Adolescence is also the time for choosing education and occupation. For many years, a myth has prevailed that girls with Turner syndrome were less intellectually able than others. It has now been shown that, in general, girls with Turner syndrome have normal intelligence.

Studies also reveal that more girls with Turner syndrome complete longer studies than girls from the rest of the population (7).

However, some girls with Turner syndrome can have specific problems with spatial perception and mathematics. It is important that schools and other educational institutions accommodate the special physical problems that can be associated with Turner syndrome – for example, girls with hearing problems should sit towards the front of the class, and tables and chairs should of course be adjusted for their height. It is therefore important that teachers, physiotherapists and ergonomists are acquainted with the considerations that need to be taken for each student.

Good educational advice is essential in order to live one's dream of being creative and open, and retaining self-confidence and a belief that much can be achieved. For some people, Turner syndrome can mean restrictions in physical activity, for example if they have heart problems. Consideration must be given to the specific limitations when choosing education and occupation, and the challenge is to ensure that all young people are given the opportunity to realise their full developmental potential. In Danish schools, preparations for choosing an occupation start around 7th grade, and all young people under 25 years of age are entitled to information on education and work from Ungdommens Uddannelsesvejledning (UU) (Young People's Education Guide) in the area in which they live. The Education Guide follows the young person until he/she has started their secondary

education, and for young people with special needs there is a specialist guide linked to the UU centres.

Coping strategies

There are many ways to react when you are young and chronically ill. A whole range of emotions are triggered, including anxiety and uncertainty at being different; losing control and independence; living with limitations to your abilities; and, in the long-term, thoughts of not being able to have children; and finally a fear of dying. Many people use various strategies, depending on their situation, to cope with living with their condition.

Denial is a common strategy among young people who are ill, and can provide a good protective function for a period. It can be experienced as living just as before, and nothing bad has happened. This method can provide the time needed to digest the new situation at a tempo that they need, and which their mental strength demands of them. But denial can result in forgetting to take the medicine, not attending doctor's appointments, and not looking after oneself as well as one should.

Some react by becoming more dependent on their parents than they need to be, and by behaving unexpectedly childishly. They regress to an earlier and safer stage of development. Their emotional capacity in relation to their own feelings decreases. This can mean that, for a period, the girl is not able to control emotions and situations that she previously managed and, perhaps, expresses herself in a more childish manner. Feelings of frustration, anger and guilt for being in this difficult situation can be such a burden that the anger is expressed on other people – typically parents or healthcare professionals. The same negative feelings can be expressed in external actions, by letting the anger out by throwing, destroying or vandalising objects, for example.

Compensation is another type of reaction in which normal activities are changed as compensation for the limitations imposed by the condition. For example, a dancer who can no longer dance, chooses to play music instead, or somebody with diabetes becomes an expert at preparing healthy gourmet food. Some people intellectualise – this means that they have a very rational attitude to their illness and its practical and technical details. This enables them, at least on the surface, to put their difficult emotions on hold, and experience a new control over their situation.

Living life dangerously

Many adolescents experiment with themselves and their surroundings and live life in the fast lane. Some subject themselves to risks and dangers even though they know this is not a good idea. They sleep too little, cut classes, eat too much or too little, smoke, drink, have unprotected sex, and experiment with drugs. More than 90% of Danish adolescents have tried to get drunk, more than 15% smoke cigarettes, and around half have tried smoking hash.

The latest research in this area reveals that adolescents with a chronic disease experiment and take risks just as much as other adolescents – and perhaps even more (8). It has been shown for example that adolescents with asthma and diabetes smoke more than their peers. The combination of frequent risk-taking and increased health risk puts the ill adolescent in a doubly unfortunate situation.

For adolescents, the first boyfriends and sexual experiences have a strong impact on self-confidence and, in general, adolescents with a chronic disease are just as sexually active as their peers. It has been shown that sexually transmitted infections and teenage pregnancies occur more frequently among adolescents with a chronic disease than among other adolescents. This may be because, for many years, the health services believed incorrectly that chronically ill youngsters were not as inclined to experimenting, testing and risking the dangerous, and therefore have not recognised the importance of working to promote health within this group.

Girls with Turner syndrome appear to experience the first kiss, the first boyfriend and sexual debut later than girls from the general population, and a French study indicates that these factors can affect self-confidence negatively (2). The reason is most probably a desire to be the same as others, and an idea that late sexual debut is an expression of not mastering the same as others. Furthermore, young people in general believe that others have their sexual debut earlier than they actually do. Sex in itself is of course not dangerous

– quite the contrary, it should be a pleasure and a perfectly natural part of life. But undesired sex, and unprotected sex can be both unpleasant and a health risk for everybody. Studies among healthy adolescents reveal that around 10% have experienced undesired intercourse after having drunk too much alcohol, and that between 10 and 20% did not use contraception at their sexual debut. Even though infertility is a major problem for women with Turner syndrome, it is worth remembering that between 2 and 5% can become spontaneously pregnant, and that everybody can be infected with sexually transmitted diseases. Advice and counselling on contraception is therefore just as important as for other adolescents. Some women with Turner syndrome have heart problems, and in these cases it is particularly important to avoid unplanned pregnancies, and to discuss with the doctor well in advance of any pregnancy.

Advice to parents and healthcare professionals

Although friends are very important for forming the ill adolescent's identity, for self-esteem, and for stimulation of all the senses, parents and family are highly important for adolescents with a chronic disease. At times, adolescents get tired of parental support and help, limitations on activities, their watchful eye, and reminders to look after themselves. At the same time we know that adolescents one minute can need great closeness, support and care, and a short time later need to be completely by themselves, exclude their parents, and are silent and rejecting. As a relative

or healthcare professional, it can be difficult to balance such swings. In other words, as a parent you need to keep "changing gears" to adapt to the terrain and the engine.

Adolescents with a chronic disease can often manage more than adults believe. It is therefore important that the adolescent, the parents, the doctors and nurses actively involve the adolescent in her treatment. This must take place gradually so that all parties can get used to the idea that the girl will assume more and more responsibility for her treatment, get a more mature and realistic picture of herself and her condition, and also get more influence on what is to happen. Already in early puberty it can be beneficial for the adolescent to gradually get used to having appointments with the doctor by herself. This provides her with the opportunity to talk about topics that she may not wish to bring up with her parents, and it "forces" the doctor to talk to the girl about what is wrong with her, and the goal of the treatment. If the cooperation is to be productive, the adolescent must experience that parents and healthcare professionals display confidence and trust in her as a person, and focus not only on the condition, but on her whole life as she lives it.

Parents and healthcare professionals must be aware of particularly vulnerable girls, and pay special attention during periods when things are especially difficult for her. If the girl withdraws from social situations, has low self-esteem or appears sad or depressed, extra closeness, time and care may be required, and perhaps talks with a psychologist, or other person whom the girl has contact with and trusts.

Adolescents with chronic diseases are also "normal teenagers". By inviting them to talk about normal teenage problems, you both make contact and talk about something other than the disease, even though this is important for both parents and healthcare professionals. Adolescents like honest, straightforward talk about their bodies, sexual debut, protection against sexual diseases, and how to avoid undesired pregnancies. By focusing on that which functions well and on those areas where they are similar to all other teenagers, you can contribute to enabling the adolescent to notice her own resources and discover that, in spite of her condition, she can be part of a developing community with her peers. Parents are never superfluous, but they must gradually adjust their style of parenting just as the parents of healthy teenagers need to do.

It is normal that adolescents at times do not comply with their treatment. An understanding, open and non-condemning attitude is necessary for productive communication around this. It may be necessary for the healthcare professional and the girl to define a "good enough" treatment that is not necessarily perfect from a medical point of view, but is at a level that the girl can accept. The girl must be given an explanation of how and why the medicine works, and what will happen if she does not take it – the consequences of dropping treatment. The explanation must be repeated and, as the girl matures, more detailed explanations can be given. Education, information, action plans and regular contact increases the adolescent's desire and ability to look after herself. For some, a medicine diary

is an invaluable aid. Some doctors and nurses offer home visits, and many adolescents benefit greatly from group education, even though to begin with they are often sceptical. Education, information and conversation must be given in a language that the adolescent can understand and can associate with. Give actual examples, and avoid hypothetical situations. For example, you can talk about everyday situations such as "When you are on the bus on the way home from school…" or "Is it most difficult to remember to take your medicine in the morning or in the evening?"

Summary

Young people with a chronic disease are undoubtedly in a very challenging and often difficult life situation in which they have to be able to adjust to the many changes inherent in puberty, and at the same time cope with a disease that to some degree or other affects their young lives. Parents and healthcare professionals can, to a great extent, help them through the times and processes that are particularly demanding, such as independence with regard to medicines and treatment; managing questions on sexuality and contraception; education; moving into their own home, etc. Some of the most important factors for successful interaction with adolescents are to display openness and trust, and to acknowledge their attitudes. This strengthens their independence and autonomy, and enables them to live their life fully – with the disease.

Useful links for adolescents with Turner syndrome

The Danish Turner Syndrome Society:
http://www.turner-syndrom.dk

Ungdomsmedicinsk Videnscenter på Rigshospitalet (Center of Adolescent medicine):
www.ungdomsmedcin.dk

Unge med medfødt hjertesygdom (Young people with congenital heart disease):
www.guch.dk

Unge med høreproblemer (Young people with hearing problems):
www.hoereforeningen.dk

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Typical signs of Turner syndrome

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"Typical signs" of Turner syndrome simply refers to features that are found more commonly in this population than in the general population. Recognizing them is primarily important to allow for early diagnosis by families and health care providers. Some individuals with Turner syndrome will have several signs while others will have only one or two (Figure 1). Some of the signs are present at birth, while others develop over time. Many of the signs may have absolutely no consequence, some may be of cosmetic concern, and others may point to significant health issues.

In this chapter, signs are grouped as to whether they affect stature, head and neck, trunk, limbs, skin or brain. However, it is useful to know that some of the signs are caused by decreased production of SHOX (short stature homeobox gene on the X chromosome – described in depth in chapter 8) in specific areas of the developing limbs and face; and that other signs are the result of abnormal lymphatic development.

During embryogenesis, SHOX is expressed in areas of the developing elbow, wrist, hand, knee and ankle (Figure 2). It is also expressed in the tissues that will develop into the upper jaw, lower jaw, bones of the middle ear, the tongue, the outer ear, and muscles needed to chew, equalize air pressure on the two sides of the eardrum, modulate tension of the soft palate, and make faces. Therefore, decreased production of SHOX likely explains facial features such as chronic otitis media, obstructive sleep apnea, and problems learning how to suck, blow, eat, and speak.

The mature lymphatic system is made up of a large network of thin vessels that drains fluid and proteins that have leaked out of blood vessels back into the blood as well as transporting fats and immune system cells (Figure 3).

During fetal development, the lymphatic system initially develops separately from the veins. Later, the lymphatic system develops a connection to large veins in the neck. If this connection fails to form or if flow into the venous system is obstructed, a large collection of fluid in the back of the neck may form, called a cystic hygroma (Figure 4). If severe, fluid accumu-

Figure 1

Figure 2

Figures 1–2

Figure 1.   The many faces of Turner syndrome. (1)

Figure 2.   SHOX expression (green) around developing bones in the fetal hand. (2)

Figure 3

Site of entry of lymphatic ducts

Left subclavian vein

Left internal jugular vein

Left brachiocephalic vein

Thoraic duct

Cysterna chyli

Route of drainage

Lymph nodes

Route of drainage

Figure 4

Superficial lymphatics

Jugular lymph sac

Axillary lymph sac

Thoraic duct

Cisterna chyli

Cystic hygroma
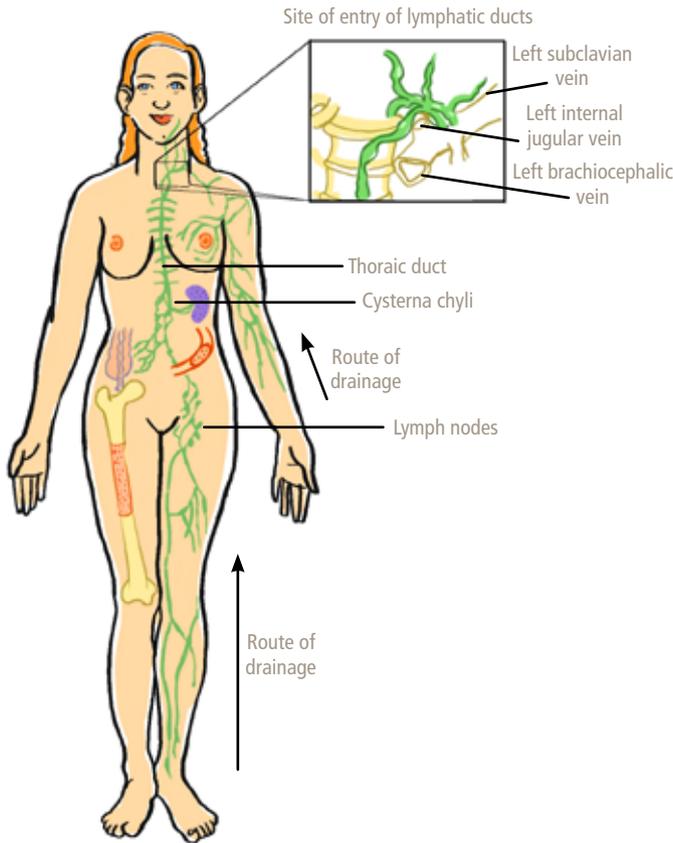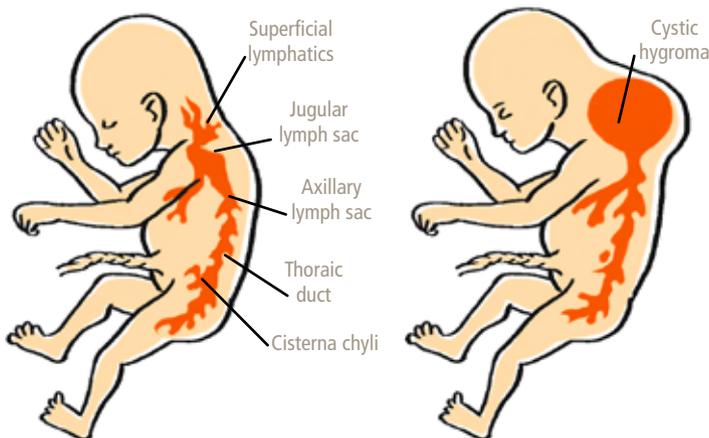
lates abnormally around the heart, lungs and abdominal organs, as well as in the skin, causing a condition called hydrops fetalis, which is often fatal. Lymphatic vessels in the limbs are usually underdeveloped as well, causing fluid to accumulate in the hands and feet.

If the cystic hygroma resolves, a baby with Turner syndrome may be left with signs such as webbed neck, low hairline, and malformed ears (Figure 5). Differences in hair placement and nail formation often occur as the result of their development in swollen tissues.

Stature

Short stature is the cardinal sign of Turner syndrome. Most girls with Turner syndrome are of normal length at birth (Figure 6) but grow more slowly during infancy and childhood (Figure 7), then fail to have a pubertal growth spurt. Growth in infancy may be slowed further because of feeding difficulties (poor suck) and growth in childhood may be slowed by the development of problems such as hypothyroidism and celiac disease. Therefore, growth should be followed on a Turner syndrome-specific growth chart. Adults with Turner syndrome who have not received growth-promoting therapies average about 20 cm (8 inches) shorter than other adult women (Figure 8).

Head and neck

Eye

The most common eye sign in an *epicanthal fold* of one or both eyes. It is a skin fold of the upper eyelid that covers the inner corner of the eye. This is very common in Turner syndrome and is of no consequence. (Figure 9) Small epicanthal folds may be present at birth and disappear as the root of the nose becomes more prominent.

Another common eye sign is *ptosis*, droopiness of the eyelid (Figure 10). Some girls need to tilt their head back to see. Occasionally, surgery is required to lift the eyelid up.

Perhaps the most significant eye sign is *strabismus*, a visual disorder in which the eyes are misaligned and point in different directions (Figure 11). The misalignment may be constantly present or it may come and go. If significant, it can lead to amblyopia, loss of vision in the eye that is not being used.

Ear

The external ear may have several different abnormalities, none of which affect hearing. Common findings include *fusion of the superior and inferior crus of the antihelix* and *enlargement of the concha*. Enlargement of the concha forces

Figure 5

Figure 8

Figure 6

Figure 7
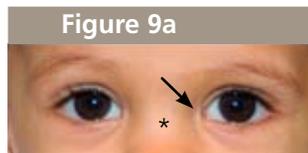
Figure 9a

Figure 9b

Figure 10

Figure 11

Figures 3–11

Figure 3. Diagram of the lymphatic system of an adult woman. Lymph is carried upward from the legs and arms toward the lymph nodes and into large lymphatic ducts such as the cysterna chyli and the thoracic duct. The lymphatic system drains into the venous system in the neck at the junction of the left subclavian vein and left internal jugular vein (insert). (1)

Figure 4. A normal fetus with open connection between the lymphatic system and the internal jugular vein (left). A fetus with a blocked connection and a resulting cystic hygroma (right).

Figure 5. Extra loose skin on the back of the neck that once covered a cystic hygroma. This will scar down to create a "webbed neck". (3)

Figure 6. Newborn with Turner syndrome of normal length.

Figure 7. 32 month old girl with Turner syndrome (on left) whose 21 month old sister (on right) is expected to surpass her in height soon. (1)

Figure 8. Nurse of average height (5'4") measuring an adult with Turner syndrome (4'10"). (1)

Figure 9. Epicanthal folds. Upper panel: Epicanthal folds of both eyes (arrow points to the left fold). The nasal bridge (asterisk) is depressed in this infant. Lower panel: Slight epicanthal fold on the right in the adolescent. (1)

Figure 10. Ptosis (droopiness) of the left eyelid. Note that she also has an epicanthal fold on the left. (3.)

Figure 11. Strabismus, misalignment of the eyes. This girl's right eye is turned in (esotropia) while the left eye looks ahead. (1)

the outer ear away from the scalp, causing the ear to protrude. The position of the ear is often <u>low</u> and the ear may be *posteriorly rotated* (Figure 12).
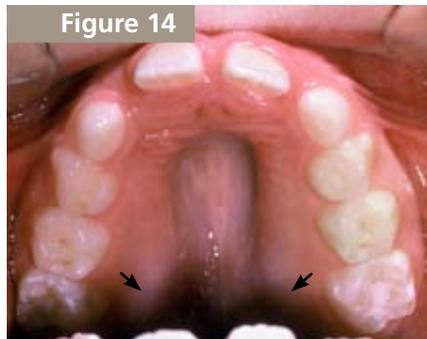
Mouth and jaws

Mouth-breathing is common. The mouth rests in an open position (Figure 13). This is often due to low tone in the muscles of facial expression and the tongue and/or obstruction of the airway by enlarged adenoids and/or tonsils. In the latter case, it is often accompanied by snoring and at times, obstructive sleep apnea.

The *roof of the mouth* may be *high and narrow.* In addition, there are often palatal bulges. These anatomic abnormalities may cause difficulties with speech and suck. Often, the palate will require expansion before braces can be applied (Figure 14).

Retrognathia (jaw is pushed backwards) is also common (Figure 15, right panel), often resulting in an overbite (Figure 15, left panel).

Neck

A common sign is a *"webbed"* or broadened *neck* (Figure 15, left panel). This is generally a cosmetic concern although on occasions it is severe enough that it limits the type of collars that can be worn as well as neck movement. The *hairline* also may be a cosmetic concern. It often extends *lower* down the neck than usual. At its base, the *hairline may sweep upwards* first (Figure 15, right panel). The *neck may be short* as the result of small and/or fused cervical vertebrae (Figure 16).

Figure 12

Figure 13

Figure 14

Figure 15

Trunk

On average, individuals with Turner syndrome have a *broad chest* with a trapezoidal appearance (wider at the shoulders than at the hips) and the *sternum often bows out*. Therefore, the chest is often described as being *"shield-like"* (Figure 17).

Pectus excavatum ("funnel chest"), a caved-in or sunken appearance of the chest, is caused by inward deviation of the lower end of the sternum (breast-plate) and inward bending of the costal cartilages (the part of the ribs that attach to the sternum) at the same level. The degree of sternal depression varies from a shallow cup to a deep funnel and may progress with growth (Figures 17–19).

The *nipples* may appear *widely-spaced* (Figure 18) and/or inverted (Figure 19). Pubertal breast development is often absent or delayed (Figures 18–19).

Scoliosis is an abnormal curvature of the spine (Figure 20). A normal spine, when viewed from behind should appear as a straight line from the base of the neck to the tailbone. The primary curve develops first. Since most children with scoliosis do not have symptoms, they can develop secondary (compensatory) curves that keep the shoulders level and give the appearance that the back is straight.

If a scoliosis curve in the upper back (thoracic area) is large enough, the spine will rotate in addition to curving from side to side. This

Figure 16

Figure 17
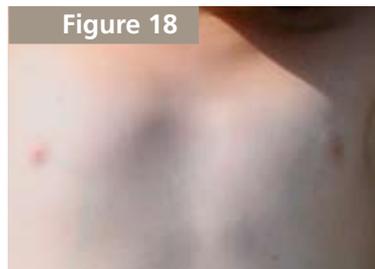
Figure 18

Figure 19

Figures 12–19

Figure 12. Left panel: External ear of normal 4-year old. The antihelix (labeled with a dotted blue line) is a folded "Y" shaped ridge of cartilage. The upper part of the "Y" is the superior crus. The lower part of the "Y" is the inferior crus. The superior portion divides into a superior crus and inferior crus. The concha is the hollow bowl-like portion of the ear between the antihelix and the opening of the ear canal. Right panel: External ear of a young girl with TS. The superior and inferior crus of the antihelix are fused. The concha is enlarged. The ear is also rotated (tipped) backwards. (Right panel: (3))

Figure 13. Mouth-breathing. The head is tipped back to promote air flow. (1)

Figure 14. High, narrow palate (roof of the mouth) with palatal bulges (arrows).

Figure 15. This delightful teenager has many signs of TS. She has a webbed neck that is best seen on the frontal view (left). On the side view (right), it can be seen that her hairline on the back of her neck is low, and sweeps upwards before falling down. Her ears are low-set and tipped backwards (posteriorly rotated). She has retrognathia (recessed jaw). (1)

Figure 16. Short neck with mild webbed neck. (3.)

Figure 17. Two views of the same chest demonstrating different aspects of a "shield" chest. Left panel: Broad chest with a trapezoidal appearance caused by relatively wide hips and even wider shoulders. Right panel: Outward bowing of the upper sternum and mild pectus excavatum (depression) of the lower sternum.

Figure 18. Pectus excavatum. Indentation at the base of the sternum (breastplate).

Figure 19. Cubitus valgus. The angle between the upper arm and lower arm is greater than 15 degrees. Note that this girl also has a rather severe pectus, inverted nipples and absence of breast development.

Figure 21

causes the ribs on one side of the body to stick out farther than on the other side (Figure 21).

Hip and limbs

Congenital hip dislocation is an important sign in Turner syndrome. If detected early, it can easily be treated over a few weeks. If not, the child's hip will develop incorrectly. Examination for congenital hip dislocation is part of the normal evaluation of every infant (Figure 22).

Cubitus valgus ("increased carrying angle"), increased elbow angulation, is caused by developmental abnormalities of the elbow joint formed by the end of the humerus (upper arm bone) and ulna (one of two bones in the forearm) (Figure 23 and Figure 19).

Madelung deformity ("bayonet deformity") is relatively rare in Turner syndrome. It is caused by developmental abnormalities of the two bones in the forearm. The end of the ulna is dislocated upwards (Figure 24).

Short fourth metacarpal is relatively common and very rarely causes problems in hand function (Figures 25–26).

A *single palmar crease* is quite common and is caused when the two horizontal creases on the palm join to form a single one in early

Figure 20

Primary curve

Secondary curve
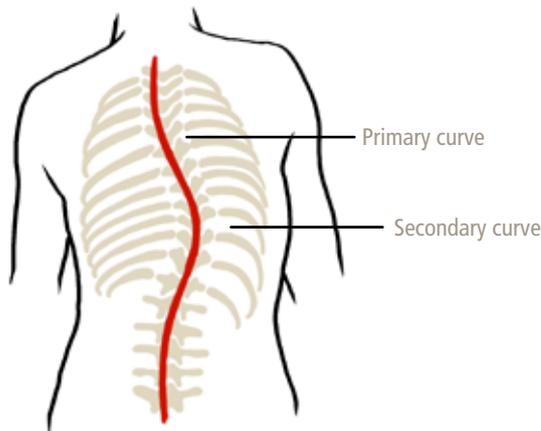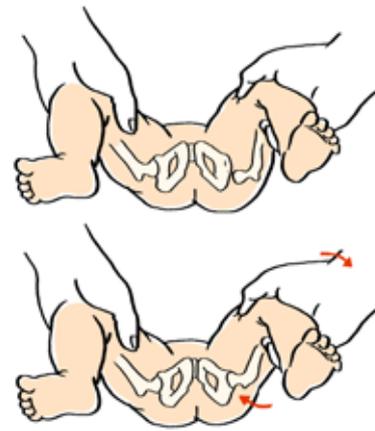
Figure 22

development (Figure 27). It can affect one or both hands and is often found in the general population.

Lymphedema, a collection of lymphatic fluid in the tissues, is most common in the hands and feet. It is generally most severe at birth and improves (Figure 28). However, it remains present in about a third of girls and resolves but reappears in another third. It may cause thickening of the skin, make wearing shoes and walking uncomfortable, and increase the risk of local infections.

Nail dysplasia, abnormal finger nail and toe nail development, usually results in nails that have a narrow diameter and are inserted into the finger or toe at a more acute angle, causing them to stick up (Figures 28–29). Ingrown toenails are common, especially if the nails are not trimmed straight across.

Figure 24
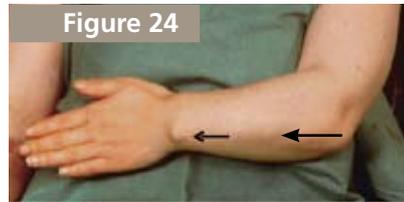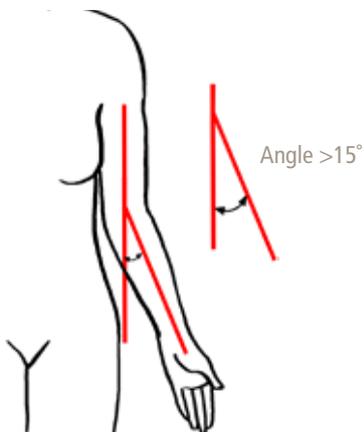
Figure 25

Figure 23

Angle >15°

Figures 20–25

Figure 20. Cartoon of scoliosis (curvature of the spine) in a person standing up as straight as possible. In this illustration, there is a primary curve in the thoracic region (containing the ribs) and a compensatory secondary curve below in the lumbar region (lower back) (3)

Figure 21. Girl with scoliosis. When she bends over, a hump can be seen on the right where the ribs are rotated out. (3)

Scoliosis is usually discovered during routine screening with the forward bend test (Adam's test), either at school or as part of a child's regular well child visits. During this exam, the child takes off her shirt (she can leave her bra on), and stands up straight, with feet together. The examiner will first check that the shoulders, scapulae (shoulder blades), and hips are level (uneven shoulders can be a sign of scoliosis) and the spine is straight. Next the child will bend forward at the hips, with the arms loosely extended and the palms held together. In children with scoliosis, bending forward will reveal an asymmetry of the back or posterior chest wall causing an elevation of one side of the back, or a rib hump.

Figure 22. Examination of a dislocated hip. Upper figure: The left hip is dislocated. Lower figure: The dislocated head of the femur has been relocated into the hip joint using the Ortoloni maneuver (3)

Figure 23. Cubitus valgus is present when the angle between the long axis of the upper arm and the axis of the forearm (with the palms facing forward) is greater than 15 degrees. (3)

Figure 24. Madelung deformity. This relatively rare deformity in Turner syndrome is caused by unusual development of the long bones in the forearm. The end of the ulna is dislocated upwards (arrow). (3)

Figure 25. X-ray of the hand showing a short fourth metacarpal. The arrow points to the 4th metacarpal in the hand. Because the 4th metacarpal is short, it falls below a line that touches the ends of the 3rd and 5th metacarpals.

Figure 26

Figure 27

Figure 28

Figure 29

Figure 30

Figure 31

Figure 32

Figure 33

Flat feet (pes planus) are common (Figure 30). Feet are relatively large compared to height, and become even more so on growth hormone therapy.

Skin

Moles (nevi) are more common in Turner syndrome and increase in number with age (Figure 31). They are no more likely to become cancerous than those of the general population. Nonetheless, it is reasonable for families to look for signs that may indicate an early melanoma (the ABCDs in English): Asymmetry (one half of the mole looks different than the other half), Border is irregular or indistinct, Color varies, and Diameter is larger than a pencil eraser (> 6 mm). Other danger signs for malignant melanoma include a sudden change in the mole's appearance, itching or tenderness of the mole, and redness or swelling around the mole.

Hypertrophic scars (Figure 32) and *keloids* may occur more commonly in Turner syndrome. Hypertrophic scars appear as thick, red scarring due to an injury to the skin and most commonly occur on the breastbone, ears and shoulders. They usually

grow only in the immediately affected area and usually decrease in size and irritability over a year or two. In contrast, keloids form within scar tissue then spread beyond the initial injury and overgrow normal skin.

Behavior

Behavioral signs may include poor feeding and delayed development in infants. In general, individuals with Turner syndrome have normal intelligence, but some may have what appears to be a nonverbal learning disability. Signs in older children and adults include problems with coordination, aligning columns of numbers, observing directionality, organizing work, and "fitting in" socially. Neurodevelopmental evaluations (Figure 33) can help to identify specific strengths and weaknesses and to formulate plans that facilitate learning.

Conclusion

There are many signs that are found more commonly in the Turner syndrome population than in the general population. Knowing these signs promotes early diagnosis of Turner syndrome and in some cases, early treatment of underlying problems.

Reference list

1. Photograph courtesy of Earl Nichols and the University of North Carolina at Chapel Hill

2. Clement-Jones M et al. Hum Mol Genet 2000. Vol 9 (5): 695-702

3. Copyright Eli Lilly and Company. All Rights Reserved. Used with Permission.

Figures 26–33

Figure 26. Short 4th metacarpal. There is a dimple where the knuckle should be. (3)

Figure 27. There is a single palmar crease on the right hand and two normal creases on the left hand. (3)

Figure 28. Lymphedema of the feet in an infant. The top of the foot is puffy. The nails are dysplastic (poorly formed). They are small and inserted at an acute angle, causing them to turn up. (1)

Figure 29. Nail dysplasia in an adult. The nails are narrow and a bit deeply inserted. (1)

Figure 30. Flat foot (also known as pes planus). Note the absence of a visible arch. (3)

Figure 31. Multiple nevi on the arm of a 12-year old.

Figure 32. Hypertrophic scar at an incision site on the thigh.

Figure 33. Child undergoing a neurodevelopmental evaluation. (3)

Turner syndrome and genetics

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Abstract

The loss of one sex chromosome in Turner syndrome affects cellular and physiological processes for which a critical level of certain sex-linked gene products is required. The role of the SHOX (short stature homeobox-containing) gene in the short stature phenotype exemplifies the importance of correct gene dosage. Divergence between the sex chromosomes was accompanied by the progressive onset of dosage mechanisms to ensure a balanced gene expression by up-regulation of genes on the active X, and X inactivation in females. Turner syndrome individuals differ from males by lack of the Y chromosome, and from females by lack of the inactive X. Thus, genes that are haplo-insufficient (meaning only present in one copy, as opposed to the normal two copies) in Turner syndrome are those with X/Y homology, including genes located in the pseudoauto-somal regions. These genes usually escape X inactivation in normal females and thus would have lower expression in Turner syndrome. In addition, the physical presence of two active X chromosomes is necessary for normal oogenesis (development of the egg cells in females). In this review, we discuss the role of genes that may be involved in Turner syndrome.

Turner syndrome individuals are females with a single X chromosome and thus can be viewed as missing one X chromosome. Males also have a single X chromosome but are protected by their Y chromosome. A change in gene activity/dosage does not necessarily bring about deficits in function of the cell or organ. For many genes, the level of expression in certain cell types can vary widely between individuals without noticeable outcomes. Either the output of these genes is above and beyond a minimum level required for normal function, or else a feedback system adjusts and coordinates activities of interacting genes. In fact, a number of autosomal (autosomes are chromosomes 1–22, as opposed to the sex chromosomes) genes are transcribed from single alleles, similar to the situation of most X-linked genes in females and of Y-linked genes in males (46). Nonetheless, the dosage of a substantial number of genes on an entire chromosome is critically involved in normal development and function of an organism. This is supported by the observation that monosomy or trisomy for most autosomes is lethal, likely due to altered dosage for particular genes, whose expression level can in turn affect genes on other chromosomes due to network interactions (41). Effects of gene dosage are specific for certain cell types and/or developmental stages, making it difficult to pinpoint critical genes without knowing where and when to search for their dysregulation.

The mammalian sex chromosomes differ significantly in their gene content. The human X chromosome contains about 1 500 genes, whereas the Y chromosome only contains 150 genes, including those whose transcripts are not translated. Many Y-linked genes have been lost due to suppression of recombination between large portions of the

sex chromosomes (24). In addition, Y-linked genes have diverged to acquire functions advantageous to males, such as those involved in male fertility (104). Loss and differentiation of Y-linked genes imply that most X-linked genes retain a single allele in males and two alleles in females. To maintain a balanced expression of the mammalian genome, two regulatory processes must have evolved: (1) X up-regulation, to double gene expression on the active X chromosome in both sexes (48; 92); and (2) X inactivation, to silence one X chromosome and avoid hyper-transcription in females (82). X inactivation takes place in early embryonic development, at which time one of the X chromosomes in each cell is randomly chosen to be silenced. The silencing state is maintained by a combination of epigenetic mechanisms including association with the non-coding RNA XIST, histone modifications, and DNA methylation at the 5'end of genes (51). The chosen inactive X, Xm (maternal X) or Xp (paternal X), is consistently silenced in all subsequent daughter cells, except in oocytes (precursors of female germ cells) where both X chromosomes are active (44).

For most human X-linked genes transcription levels are similar between 46,XX females, 46,XY males, and 45,X Turner syndrome individuals. Indeed, expression of X-linked genes is "compensated" between individuals with one or two X chromosomes owing to X inactivation. The silencing of the X, however, is not as complete and uniform as what was thought initially. A portion of X-linked genes, known as "escape genes" and representing about 15% X-linked genes, manage to be expressed from the inactive X chromosome (22). Many escape genes are found in the two terminal regions of the human X chromosome that share complete identity with the terminal regions of the Y chromosome. These two regions are called pseudoautosomal regions: PAR1, located on the short arm and PAR2, on the long arm. *SHOX*, the gene largely responsible for the short stature phenotype (a phenotype is an observable characteristic, as opposed to the genotype that represents the genetic constitution) in Turner syndrome, is one of the PAR1 genes.

Other genes that escape X inactivation are located in the non-pseudoautosomal region of the X. In females, they are transcribed from both X chromosomes, although the level of transcription from the inactive X is usually lower compared to the active X. Some of these genes have retained a paralogue (similar copy) on the Y chromosome, while others have lost it. For X/Y paralogues of similar function retention of a Y-linked copy suggests that dosage is important enough to be balanced between the sexes. These X-Y gene pairs are candidates for the etiology of Turner syndrome. In addition, escape genes that have lost or differentiated their Y-copy could be involved if they have a female-specific function dependent on their higher expression level in females. Finally, genes known to be subject to X inactivation in somatic cells must also be considered for a role in the ovarian dysgenesis phenotype of Turner syndrome since both X chromosomes become active

in normal female germ cells, implying that these genes would also be haplo-insufficient in Turner oocytes (44).

Below, we discuss in detail individual genes located inside and outside the PAR, in terms of their function and potential dysregulation and associated phenotypes. Comparisons between human and mouse are useful since mice with a single X chromosome are not affected by most Turner syndrome phenotypes, except for a slight reduction in fertility and some attention deficiencies (18; 29). Thus, X-linked genes that show significant differences in location and regulation between the species are attractive candidates (33). For most of the genes discussed below, with the exception of *SHOX*, no specific involvement in Turner syndrome has been found so far. Some genes, not discussed here, have unknown function and/or role in disease. Many of the genes discussed have important roles in development, chromatin structure, neuronal function, and immunity, suggesting a role in Turner syndrome. The dosage effects could be exerted during specific developmental stages or tissues; they could affect both the 45,X embryos and/or their placenta, and/or the surviving adults. Since most Turner syndrome fetuses do not survive it is important to keep in mind that the haplo-insufficiency is largely lethal. It will be important to measure global gene expression changes in Turner syndrome. Based on other studies of aneuploidies such as Down syndrome or trisomy 21, it is clear that dosage changes in a given chromosome may affect other genes located elsewhere in the genome (78).

1. XY gene pairs

1a. Pseudoautosomal Genes

Genes located in the pseudoautosomal regions remain identical on the sex chromosomes because of the frequent recombination (exchange of genetic material between chromosomes during pairing) between these regions at male meiosis. The frequency of exchanges in PAR1 is 20 times higher than elsewhere in the genome, suggesting that this process is essential for proper segregation of the sex chromosomes (12). PAR1 genes, which number at least 24, are transcribed from both sex chromosomes in males and in females (106). In contrast, not all five genes detected in PAR2 are transcribed from both sex chromosomes (see below). Human PAR1 genes are not conserved on the mouse sex chromosomes but are located on autosomes. We review the main functional aspects and role in disease of PAR genes in order from the end of the short arm to that of the long arm (Figure 1).

PPP2R3B

Phosphatase 2A (PP2A) is a heterotrimeric protein involved in DNA replication, cell cycle progression and tight junction. Its ß subunit, encoded by *PPP2R3B*, is responsible for substrate specificity (143). PP2A is involved in a protein complex implicated in familial cerebral cavernous malformations, a condition associated with seizures and strokes (47). *PPP2R3B*

is highly polymorphic between individuals probably due to very high recombination in PAR1 (112).

GTPBP6

GTP binding protein 6 contains several GTP-binding domains and is encoded by a ubiquitously expressed gene conserved across several species (45). Overexpression of *GTPBP6* in Klinefelter syndrome is apparently inversely correlated with verbal IQ (135), suggesting that dosage of this gene may be important.

SHOX

SHOX (short stature homeobox-containing) is the best studied PAR1 gene whose dosage deficiency is responsible, at least in part, for the short stature in Turner syndrome (12). *SHOX* is highly conserved in diverse species, including fish and chicken. The SHOX protein is a master regulator of gene transcription in chondrocytes. Upon binding of differentiation signals to precursors of these cells, SHOX migrates from the cytoplasm into the nucleus where two SHOX proteins form a dimer, bind to specific DNA sequences, and turn on transcription of genes relevant to cartilage and bone differentiation. The homeodomain structural motif of this protein is particularly important for this process and is often mutated in patients with skeletal anomalies (12). The double dosage of *SHOX* is critical for normal bone development and mutations in one copy of *SHOX* usually cause Leri-Weill dyschondrosteosis characterized by disproportionate short stature and a distinguishing curve of the radius (also known

as the "Madelung deformity"). More severe symptoms occur if both copies are deleted or defective, known as Langer mesomelic dysplasia (149).

An intricate regulatory system composed of protein factors is turned on during development to ensure appropriate levels, timing, and location of SHOX. In the chick embryo, SHOX is restricted to the central core of the early limb bud and later to the proximal two thirds of limbs. This spatial restriction is defined by inhibitory effects of proteins in surrounding tissues – FGFS and BMPS from the distal side and retinoic acids from the proximal side (128). When additional copies of *SHOX* are engineered into chick embryos, more cartilage nodules and longer skeletal elements develop (128). Thus, the phenotype is exquisitely sensitive to the dosage of *SHOX* and it is not surprising that haplo-insufficiency for this gene causes the short stature phenotype in Turner syndrome.

SHOX is among the most frequently mutated genes in humans with an incidence of one of every 1 000 newborns (84). The high frequency of deletion mutations may be attributed to repeated DNA sequences, such as Alu elements, dispersed along *SHOX* (113). In addition, DNA sequences that exert regulatory effects on *SHOX* transcription have been identified thousands of base pairs away. In a case of familial skeletal dysplasia (disproportionate dwarfism with short limbs), a large X inversion was shared by the symptomatic mother and son, with a breakpoint located more than 30kb upstream from *SHOX* (13).

Large deletions have also been detected in downstream sequences, as far as 48kb and 215kb from *SHOX* in patients with Leri-Weill dyschondrosteosis (109). A useful and frequently updated online database ([hhtp://hyg-serv-01.hyg.uni-heidelberg.de/lovd/index.php?select_db=SHOX](http://hyg-serv-01.hyg.uni-heidelberg.de/lovd/index.php?select_db=SHOX)) lists polymorphisms, small deletions and insertions identified in *SHOX,* together with a description of

phenotypes, the mode of inheritance, and ethnicity (199 entries collected in the most recent version, 12 April 2007) (93).

It is commonly thought that SHOX plays a role in determining adult height; however, it is more likely that it influences the ratio between sitting height and height (SH/H). *SHOX* mutations were detected in 3,2% of

Figure 1

Schematic of the human X chromosome indicating the position of genes with copies on the X and Y chromosomes including genes located in the PAR1 and PAR2 regions and in the 5 evolutionary strata. Genes in black escape X inactivation; genes in medium gray are subject to X inactivation and genes in pale gray have not been studied.
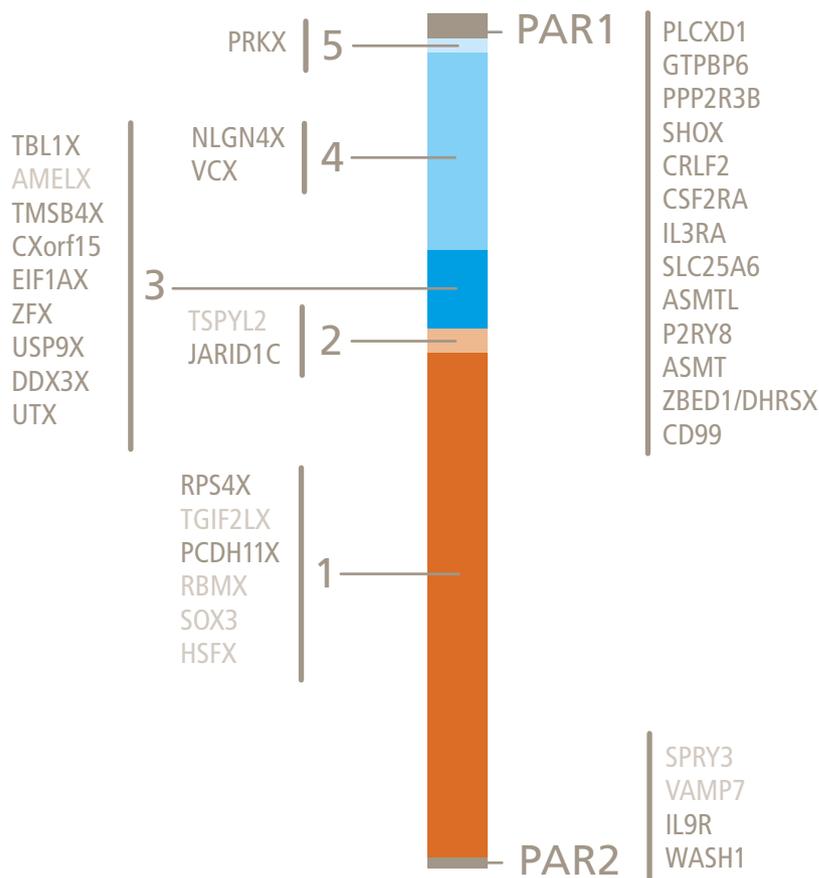
children with idiopathic short stature; but, among those with a high SH/H ratio, mutations were increased to 22% (62). A newly established phenotype scoring system is useful in deciding whether a child with a short stature should be tested for *SHOX* mutations (103). To establish this scale, 1 608 unrelated children with sporadic or familial short stature were screened, among which 68 *SHOX* mutations (4,2%) were detected. In fact, the two groups of participants, with or without *SHOX* mutations, did not differ in height. However, bone dysmorphic signs such as short forearm and lower leg, cubitus valgus, Madelung deformity, high-arched palate, and muscular hypertrophy were significantly more frequent in children with mutations. Besides short stature, anomalies associated with *SHOX* defects include coarse trabecular pattern, short metacarpals/metatarsals with metaphyseal flaring, altered osseous alignment at the wrist, radial/tibial bowing, triangularization of the radial head, abnormal tuberosity of the humerus, and an abnormal femoral neck (118).

CRLF2

CRLF2 (cytokine receptor-like factor 2) encodes an interleukin receptor. The ligand of CRLF2 is thymic stromal lymphopoietin (TSLP) (146). TSLP is produced mainly by barrier epithelial cells. By acting on myeloid dendritic cells, TSLP influences diverse processes such as regulatory T cell positive selection, peripheral T cell homeostasis, and T cell-mediated allergic

inflammation (147). Overexpression of TSLP aggravates allergic reactions such as asthma, suggesting a dosage effect.

CSF2RA and IL3RA

Receptors for interleukins often form heterodimers, consisting of a ligand-specific α-chain and a common ß-chain (68). The α-chains of the receptors for interleukin-3 (IL3) and for granulocyte-macrophage colony-stimulating factor (GMCSF) are encoded by the two adjacent PAR1 genes *IL3RA* and *CSF2RA*. Multiple cytokines such as IL3 and GMCSF compete for the limiting ß-chains on the surface of hematopoietic cells and elicit distinct cellular responses. An increased expression of *IL3RA* has been detected in acute myeloid leukemia (AML) (123). Dosage of these genes may also be important in autoimmune disorders, which are common in Turner syndrome. In a XX sex-reversed male patient diagnosed with prepubertal systemic lupus erythrematosus PAR1 genes located between *IL3RA* and *CD99* and including *IL3RA* and *CSF2RA,* were trisomic due to translocation of a portion of the Y to one X chromosome (23). This study suggests that the dosage of *IL3RA* and *CSF2RA* (and possibly of other PAR1 genes) may play a role in autoimmune disorders. However, a report of three girls with monosomy for PAR1 genes including *IL3RA* and *CSF2RA* who had relatively normal development (with the exception of short stature due to loss of *SHOX*) suggests that these genes may not be involved in Turner syndrome phenotypes that manifest

at a young age (63). Pulmonary alveolar proteinosis can be caused by deficiency in *CSF2RA* (85; 125).

SLC25A6

The solute carrier family 25, member 6 gene encodes adenine nucleotide translocase-3, a member of the ADP/ATP translocase family. Humans have four isoforms of adenine nucleotide translocase encoded by genes that are differentially expressed between cell types and developmental stages. *SLC25A6* has been translocated from an autosome to the sex chromosomes in humans and simian primates (129). SLC25A6 is imbedded in the inner membrane of the mitochondria where it catalyzes the ATP-ADP exchange and in turn contributes to energy metabolism. As a component of the permeable transition pore, it also plays a role in mitochondria-mediated apoptosis, which is affected both by overexpression and deficiency of the gene, suggesting a dosage effect (144).

P2RY8

P2RY8 (purinergic receptor P2Y, G-protein coupled, 8) is a member of the purine nucleotide G-protein coupled receptor family, which is highly expressed in lymphocytes, suggesting an important role in these cells. An activated P2RY8 receptor results in gene transcription changes mediated through various signaling pathways such as CREB and ELK-1. Patients with leukemia often express *P2RY8* at an elevated level, which likely causes mis-regulated expression of target genes (42). Disruption of *P2RY8* by an X inversion segregated with mental retardation in a family; however, the inversion also disrupted another X-linked gene located outside the PAR, which is highly expressed in brain and thus more likely to cause the phenotype (20).

ASMT

Acetylserotonin O-methyltransferase is the last enzyme involved in synthesis of melatonin, a peptide hormone released from the pineal gland, which synchronizes the biological clock (circadian rhythm) across different organ systems. A partially deleted *ASMT* gene has been linked to an increased risk for autism based on finding this variant in 2% of the general population but in 7% of individuals with autism, in particular those with mental retardation (19). The presence of a single X in Turner syndrome would place these individuals in the same risk category as males. However, the association between *ASMT* and autism is still controversial (130). An increase dosage of *ASMT* and possibly other PAR1 genes may also be deleterious: Triplication of the PAR1 from *ASMT* to *XG* was reported in a patient with schizophrenia, a disorder common in Klinefelter syndrome and triple X females (108).

ZBED1/DHRSX

ZBED1 (zinc finger, BED-type containing 1) and DHRSX [dehydrogenase/reductase (SDR family)] represent overlapping transcription units. *ZBDE1* is ubiquitously expressed and produces a DNA binding protein also known as DNA Replication-related Element-binding

Factor (DREF). DNA Replication-related Elements (DREs) are often found at promoters of genes involved in DNA replication and cell proliferation. For instance, many ribosomal protein genes contain DREs in their promoters, allowing these functionally related genes to be transcribed in a coordinated manner. RNA interference-mediated knockdown of DREF *in vivo* shows that it is needed for normal progression through the cell cycle (97).

CD99

CD99 encodes a glycoprotein on the surface of T cells, which plays an important role in the inflammatory response. Inflammation triggers leukocyte migration towards the inflamed site. Once at their destination, leukocytes align their CD99 proteins with those of endothelial cells lining the blood vessels, forming a tight junction. The homophilic attraction formed between CD99 proteins of the two cell types facilitates transmigration of leukocytes to the inflamed site (136). An elevated level of CD99 is implicated in atherosclerosis. In mice vaccinated against CD99, there were fewer CD99-expressing cells and fewer leukocytes recruited to atherosclerotic lesions, resulting in less severe atherogenic symptoms (134).

SPRY3, VAMP7

These two genes are contained in PAR2. In contrast to PAR1 genes, *VAMP7* (vesicle-associated membrane protein 7) and *SPRY3* (sprouty homolog 3) are transcribed only from the active X chromosome in males and females (37). The silenced copy of *VAMP7* becomes associated with repressive epigenetic marks that include DNA methylation and histone modifications both on the inactive X and on the Y in a mechanism similar to X inactivation (86). Klinefelter individuals silence two of the three copies of *VAMP7* (107). In contrast, the silenced copy of *SPRY3* is associated with histone changes only (30). Since both *VAMP7* and *SPRY3* are silenced on the inactive X and on the Y it is unlikely they would be involved in Turner syndrome.

IL9R

IL9R (interleukin 9 receptor precursor) is a recent addition to the sex chromosomes located in PAR2. This gene is not subject to either X inactivation or Y silencing. *IL9R* may play a role in asthma (66).

1b. Non-pseudoautosomal X-Y gene pairs

Non-pseudoautosomal gene pairs with copies on the X and Y chromosomes are mostly remnant from the ancestral proto-sex chromosomes that evolved from a pair of autosomes and progressively diverged due to lack of recombination (Figure 1). A few X/Y gene pairs including *PCDH11X/Y* (protocadherin 11) and *TGIF2LX/Y* (TGFß-induced factor homeobox 2-like) were transposed between the sex chromosomes since the divergence of human and chimpanzee lineages (106). Non-pseudoautosomal X-linked genes that have a Y-linked paralogue usually escape X inactivation, i.e. consistently generate transcripts from the inactive X, albeit at a reduced level compared to

alleles on the active X. Thus, males would have lower expression of the X paralogues, unless the Y paralogues provide some compensation. However, the Y paralogues may not always have the same function, and they are also usually expressed at a reduced rate compared to the active X alleles (Nguyen and Disteche, unpublished results). Significant differences exist between human and mouse in terms of the persistence of Y paralogues and escape from X inactivation, which are important to keep in mind since mice with a single X have a much milder phenotype than Turner syndrome individuals (33).

Escape genes (with or without a Y paralogue) represent about 15% of human X-linked genes (22). Another 10% of X-linked genes variably escape, i.e. their expression from the inactive X differs between tissues, between ages, and/or between female individuals in a population. It should be noted that escape from X inactivation has been mostly studied in cell lines, which may not represent the situation *in vivo*. Furthermore, the developmental stage at which an escape gene starts to be transcribed on the inactive X varies. *Jarid1c*, for instance, escapes X inactivation in pre-implantation mouse embryos but becomes transiently silenced when random X inactivation is established at later stages (77; 100). This silencing, however, is unstable and soon reversed, so that *Jarid1c* escapes X inactivation in adult somatic cells (77). The mechanism underlying this reversal is not fully understood but may be due to the absence of DNA methylation. Other escape genes may never be silenced on the inactive X even in early embryos;

conversely, some genes may reactivate only in certain lineages, leading to variable escape between tissues. Escape genes appear to be separated from genes subject to X inactivation by regions that bind the chromatin insulator protein CTCF, which may prevent DNA methylation and shield these genes from being stably silenced (39). The important role of regions that surround an escape gene ("domain") is emphasized by studies that showed that *Jarid1c* can still escape when inserted as a large BAC transgene within regions subject to X inactivation (75), whereas partial inserts do not result in escape (25).

The persistence of Y-paralogues of non-pseudoautosomal X/Y gene pairs is largely unexplained. These Y-linked genes may have remained intact because they provide advantages in reproduction and survival. Some Y paralogues are exclusively expressed in testis. However, a number of Y paralogues appear to have a similar function to their X paralogues based on functional studies and ubiquitous expression in multiple tissues. For such genes, dosage may be important and haplo-insufficiency may elicit abnormal phenotypes in Turner syndrome. The theory of beneficial Y paralogues that may protect males against haplo-insufficiency has been indirectly tested by calculating the ratio between non-synonymous substitutions (Ka, DNA sequence changes that alter the amino acid sequence) versus synonymous substitutions (Ks, DNA sequence changes that do not alter the amino acid sequence). If a gene is "protected" and mutations are weeded out in a population, it would have a low Ka/Ks

ratio across multiple species. The analysis of several Y-linked genes in primates suggests that these genes are under positive selection (54). Thus, for some genes, males may be protected from Turner syndrome owing to the persistence of a Y paralogue, which makes these X/Y gene pairs attractive candidates. Y-linked genes could also play an indirect role in Turner syndrome because they act as minor histocompatibilty antigens and thus could elicit autoimmune responses in mosaic individuals with a 46,XY cell line. The presence of a cell line with a Y chromosome also increases the risk of gonadoblastoma in patients with gonadal dysgenesis (132).

Below, we review selected X/Y gene pairs that may play a role in Turner syndrome. The position of the X/Y gene pairs is shown in Figure 1. The potential variability in the degree of escape from X inactivation in different tissues and developmental stages suggests that additional studies are needed to fully grasp the role of these genes in Turner syndrome.

PRKX/Y, NLGN4X/Y, VCXA/Y, TBL1X/Y, AMELX/Y

PRKX encodes protein kinase X, NLGN4X, neurologinin 4X, VCXA, variable charge protein X-A, TBL1X, transducin (beta)-like 1 protein, and AMELX, amelogenin. PRKX is a cAMP-dependent serine/threonine kinase implicated in autosomal dominant polycystic kidney disease (76). NLGN4X is a candidate for autism and mental disorders; but patients with a heterozygous deletion (some including VCX) are not impaired (56; 83), suggest-

ing that these genes, originally proposed as candidates for neurological impairment in Turner syndrome, may not be involved (148). Mutations in AMELX cause amelogenesis imperfecta (26). TBL1X has been implicated in the pathogenesis of ocular albinism with late-onset sensorineural deafness (10). In mouse, Tbl1X is subject to X inactivation, which is not the case in human (33). The functions of the Y-linked paralogues are not well defined: Heterozygous deletions of PRKY, TBL1Y and AMELY do not appear to have a phenotypic effect, suggesting that these genes do not play a role in Turner syndrome (60).

TMSB4X/Y

The TMSB4 paralogues encode the thymosin ß4 peptide and are ubiquitously and abundantly synthesized in all tissues (70). It is not known whether the X- and Y-linked genes differ in function. Thymosin ß4 is a relatively small peptide (43 amino acids) implicated in developmental and pathological processes (50). Thymosin ß4 is involved in the development of the vascular system and thus, is a candidate for the lymphedema phenotype in Turner syndrome.

Thymosin ß4 is a key player in modulating cell mobility by sequestering monomer actins. Many cellular events including migration, mitotis, and endocytosis depend on actin polymerization (50). An increased level of TMSB4X results in a greater actin reservoir and in turn a higher mobility competence of the cell. TMSB4X is clearly essential for the formation of coronary vessels (Smart et al., 2007; 14).

In the myocardium, progenitor cells are differentiated into either smooth muscle cells or endothelial cells and together assemble the vessels. When *Tmsb4x* is silenced in the mouse embryonic heart, epicardium-born progenitors fail to migrate into the myocardium and no vessel is formed (Smart et al., 2007). In adults, thymosin ß4 peptides likely contribute to the renewal of regressed vessels following cardiac injury (Smart et al., 2007).

In addition to its role in coronary vessel development thymosin ß4 promotes hair growth by promoting growth, migration, and differentiation of follicle stem cells, and it is also involved in wound healing (101; 102). Thymosin ß4 enhances the mobility of tumor cells and its expression is increased prior to metastasis (59). *TMSB4Y* is ubiquitously expressed (70) and is responsible for graft-versus-host disease (GVHD) in some patients (31).

EIF1AX/Y

EIF1AX/Y encode the eukaryotic translation initiation factor 1A proteins, which facilitate the disassembly of ribosome into 60S and 40S subunits and subsequent binding of initiator Met-tRNA to the 40S subunit (89). These universally conserved translation initiation factors are essential for protein synthesis. Both *EIF1AX* and *EIF1AY* are ubiquitously expressed (70). It is not clear whether the dosage of these important genes may have a role in Turner syndrome or whether a compensatory protein increase may occur. EIF1AY is recognized as a minor HY antigen (89).

ZFX/Y

ZFX (zinc finger, X-linked) was among the first identified gene that escapes X inactivation. The paralogues are both ubiquitously expressed in human. It has long been speculated that *ZFX/Y* may play a role in Turner syndrome stigmata, especially ovarian development (2; 8; 81; 119). Although Turner syndrome-like symptoms are present in some XY sex-reversed females with *ZFY* deletion, this is not always the case (32; 90).

The *ZFX/Y* gene pair could be involved in the high rate of embryonic lethality of Turner syndrome fetuses given the crucial role of ZFX in stem cell renewal. Both X- and Y-linked genes are actively transcribed as early as the four cell stage (127). ZFX forms a transcription regulator complex with Cnot3, Trim28, and c-Myc, which acts separately from the Nanog, Oct4, and Sox2 core complex in early mouse embryonic development, to ensure self-renewal of embryonic stem cells (43; 53). The ZFX-containing transcriptional regulator complex is also involved in the development and homeostasis of adult B cells (7). *ZFX* and *ZFY* may not be functionally interchangeable. The early onset of ZFY expression has been suggested to contribute to the male growth advantage in preimplantation embryos. ZFY acts as a minor HY antigen (31).

In mice, *Zfx* is X-inactivated in females and *Zfy* is only expressed in testes. Nevertheless, various Turner syndrome features are captured in *Zfx* mutant mice (81). Abnormalities can be detected in male and female mutants as early as embryonic day 12,5, at which time both

the number of primordial germ cells and the embryo size are smaller relative to wild-type embryos. Homozygous mutant adult females suffer from a shortage of oocytes, which leads to a significantly shortened reproductive lifespan.

USP9X/Y

The X- and Y-linked USP9 (ubiquitin specific peptidase 9) proteins are de-ubiquitinating enzymes with specific protein substrates. Mutations in Fam, the fly homologue of *USP9X*, cause defective oogenesis and eye development (40). Whether the mammalian USP9 shares similar functions is yet to be determined. Nevertheless, recent findings confirm that USP9-regulated de-ubiquitination is crucial during mammalian development as well as oogenesis, suggesting that this gene may be involved in Turner syndrome developmental and reproductive anomalies. USP9X has been implicated in a variety of cellular processes including mitosis through regulating the release of Survivin from the centromeres (137). The involvement of *USP9X* in cell proliferation is consistent with its expression pattern: Indeed, *USP9X* is highly transcribed in rapidly expanding cell populations in embryos and is a marker for stemness (61). The cleavage rate of preimplantation embryos is significantly reduced when USP9X is depleted (99). Thus, *USP9X* deficiency in Turner syndrome could impair embryonic development. In addition, *USP9X* is also a candidate for the ovarian failure in Turner syndrome based on the analysis of patients with partial X deletions (57). In mice, *Usp9x* expression is detected in early

embryonic oocytes and in adult oocytes at secondary follicle stage (94). Unlike the situation in human, *Usp9x* is apparently subject to X inactivation in mouse (33).

USP9X could also be a factor in abnormal bone growth in Turner syndrome. USP9X is an essential player in TGFß and bone morphogenetic protein (BMP) signaling pathway. Upon activation of the signaling pathway, Smad4 translocates from the plasma into the nucleus and initiates transcription of specific genes by forming a complex with other proteins including Smad2, which requires de-ubiquitination of Smad4 by USP9X (36). Otherwise, cells become unresponsive to TGFß and BMP signals and undergo tumorigenesis.

Less is known about the role of *USP9Y*. Although expressed ubiquitously, *USP9Y* may have a special role in spermatogenesis, as suggested by the finding of a *de novo* deletion, resulting in a truncated USP9Y protein, in a patient with non-obstructive azoospermia (124). However, a recent report of a complete deletion of *USP9Y* in a man with normal sperm counts casts doubt on *USP9Y's* importance in sperm development (80). USP9Y is one of the minor HY antigens (31).

DDX3X/Y

This X-Y gene pair (DEAD (Asp-Glu-Ala-Asp) box polypeptide 3) encodes for an ATP-dependent RNA helicase important in RNA metabolism and in immunity. This gene escapes X inactivation in both human and mouse (33). The reduced dosage of *DDX3X* in

Turner syndrome may result in compromised immune function, in particular during fetal development, leading to an increased risk for infection-related conditions and lymphedema. However, *DDX3Y* expression is restricted to male germ cells while *DDX3X* is ubiquitously expressed, which argues against their implication in Turner syndrome (34). Nevertheless, this gene may have a dosage sensitive role in females. Owing to its activity of unwinding specific RNAs, the helicase contributes to transcription, splicing, RNA transport, and translation. The specificity of its RNA substrates is likely defined by its subcellular locations, proteins it is associated with, as well as the RNA binding sequences.

Several studies have implicated DDX3X in immune responses against viral invasion (115). In virus infected cells, DDX3X accumulates on interferon promoters and stimulates expression. In cells with reduced levels of DDX3X, immune reactions fail to launch and interferon production is disrupted. It is noteworthy that severe phenotypes are observed even when DDX3X is only partially silenced, implying that dosage is important. Some viruses diminish the immune attack of host cells by inhibiting DDX3X, while others such as HIV-1 instead hijack DDX3X for their own benefit (145).

The role of *DDX3Y* in spermatogenesis is suggested by a severe reduction in sperm production in individuals with Y deletions that include this gene. Interestingly, DDX3X is also implicated in spermatogenesis based on its abundance in spermatids, while DDX3Y is abundant in spermatogonia, suggesting that

the proteins have different RNA substrates or enzymatic activities. The structural differences between the two proteins are certainly sufficient to elicit female rejections against male tissue grafts (31).

KDM6A/UTY (also called UTX/Y)

Methylation of histone H3 at lysine 27 is typically associated with gene silencing. KDM6A (lysine (K)-specific demethylase 6A) specifically removes tri- and di-methylation of lysine 27 of histone H3. UTX is involved in transcriptional activation of specific genes during differentiation of embryonic stem cells by removing the repressive mark. Homeobox (HOX) genes that control embryonic development are among the target genes of UTX: In embryonic stem cells, UTX is absent at silent HOX gene promoters, whereas, in primary fibroblasts, activation is associated with recruitment of UTX. UTX mutants display a disrupted anterior-posterior body pattern in zebrafish (71). The short stature phenotype in Turner syndrome characterized by a skewed sitting height/height ratio may be due in part to haplo-insufficiency of *UTX.*

UTX is frequently mutated in tumors, in agreement with altered patterns of histone H3 lysine 27 methylation (133). When reintroduced into cancer cells, *UTX* effectively reduces the rate of proliferation, thus acting as a tumor suppressor. *UTX* deficiency could potentially contribute to the increased incidence of certain cancers in Turner syndrome, including meningioma, childhood brain tumors, bladder cancer, melanoma, and corpus uteri cancer.

In contrast, the risk for breast cancer is decreased, likely owing to compromised breast development (114). Treatments with growth hormone as well as estrogens may also play a role in increased cancer risk. The involvement of various X-linked tumor suppressor genes including *UTX* remains to be tested in Turner syndrome.

Methylation of histone H3 at lysine 27 is part of the epigenetic machinery responsible for maintaining the silenced state of the inactive X (51). *UTX* may have a critical function both in escape from X inactivation by removing the repressive histone mark at specific genes and in the reactivation of the X chromosome in female germ cells. It is not clear whether escape from X inactivation is affected when one copy of *UTX* is missing in Turner syndrome patients with partial X deletions. *UTX* itself escapes X inactivation both in human and mouse (33). UTY does not have identical demethylase activity as UTX (52; 71). *UTY* is transcribed at a much lower level than its X partner in both humans (Nguyen and Disteche, unpublished results), and mice where the brain distribution of expression differs between paralogues (142). UTY has long been known to cause rejection reactions of female recipients of grafts from male donors (31).

TSPYL2/TSPY

TSPY (testis-specific protein Y) is the putative candidate gene for gonadoblastoma, as shown by deletion analyses and expression studies (132). Turner syndrome individuals who have mosaicism for a cell line that contains a Y chromosome are at risk for this gonadal tumor. Multiple copies (23–64) of *TSPY* exist on the Y chromosome. *TSPY* is normally only expressed in testis where it stimulates cell proliferation and differentiation. The X and Y paralogues have opposite functions: TSPY accelerates cell proliferation by shortening the transition between G2 and mitosis, while TSPYL2 insures a proper transition. Both proteins have SET domains and bind cyclin D, consistent with a role in cancer. *TSPY* expression in dysgenetic gonads stimulates protein synthesis, accelerates cell proliferation, and promotes tumorigenicity (72).

KDM5C/D (also called JARID1C/D)

The lysine (K)-specific demethylases 5C/D specifically target the removal of tri- and di-methylation at lysine 4 of histone H3 (55). Methylation of lysine 4 of histone H3 is associated with transcriptional activation of genes; therefore, JARID1C/D catalyzed de-methylation results in gene silencing. *JARID1C/D* are ubiquitously transcribed and the X paralogue escapes X inactivation both in human and mouse (33). The developing brain has a particularly high level of *Jardi1c* transcripts, consistent with an important role in the nervous system (140).

JARID1C is among the most frequently mutated genes in X-linked mental retardation (58). Some patients suffer from symptoms such as facial dysmorphism, short stature, and/or hypogonadism in addition to their neurological phenotypes (58; 110; 1). The deficits due to *JARID1C* mutations in males are not compensated by the presence of the Y-linked

JARID1D, indicating that the paralogues are not functionally interchangeable in spite of a high similarity in sequence and de-methylase function. We have found that *JARID1C* and *JARID1D* have similar expression levels in human brain (Nguyen and Disteche, unpublished results). However, in mouse, *Jarid1d* expression is much lower than that of its X paralogue (141). In cultured human cells, JARID1D is found in a protein complex that contains other transcriptional repressors such as the polycomb-like protein Ring6a/MBLR (73). The activities defined for JARID1D are likely shared by JARID1C, but could be especially involved in chromatin remodeling during male meiosis (3). JARID1D has been implicated as the main HY antigen (31).

JARID1C is involved in seemingly diverse processes related to neural development. It controls neuronal differentiation by suppressing transcription of specific genes (such as those involved in synaptic communication) in pluripotent stem cells prior to differentiation (126). In addition, JARID1C regulates neuronal cell death and stimulates dendritic outgrowth (55). Although JARID1C is known mainly as a chromatin regulating enzyme, it has also been identified in the cytoplasm where it is directly associated with Smad3, a critical component of the TGFß signaling pathway with a role in bone formation, whose activity it represses (67). Although the absence of severe neurological phenotypes in Turner syndrome suggests that *JARID1C/D* do not play a critical role in this syndrome, the diverse functions of these genes suggest that they still could be involved.

RPS4X/Y

The ribosomal protein S4 gene (RPS4) is conserved in all species and is an attractive candidate for features of Turner syndrome. First, both RPS4X and RPS4Y are components of the ribosome (138). Second, *RPS4X* escapes X inactivation in human but not in mouse (33). However, *RPS4X* may not be involved in Turner syndrome, as demonstrated by the finding that *RPS4X* expression is actually increased in individuals with a 46X,i(Xq) karyotype who have three copies of the gene (64).

Non-synonymous substitutions between *RPS4Y* genes from different species occur at a significantly lower rate than predicted (6). This is likely due to poor survival and/or reproductive disadvantage for individuals who carry these mutations. *RPS4Y* may render an advantage for males because of its role in muscle development. In fact, *RPS4Y* is one of two genes most highly expressed in muscle (9). RPS4Y is a minor HY antigen (31).

PCDH11X/Y

The protocadherin 11 gene has been translocated from the X to the Y chromosome in the human lineage (98). The gene pair has been proposed as a candidate for evolution of hominid-specific characteristics including the sexual dimorphism of cerebral asymmetry (139). *PCDH11X* has been implicated in late onset Alzheimer disease (21).

2. Turner syndrome symptoms and other sex-linked disorders

Turner syndrome symptoms are present in many other genetic disorders, both X- and autosome-linked. In this section, we will briefly review some of the Turner syndrome physical symptoms in relation to X-linked conditions that overlap. Any X-linked gene may be implicated because it escapes X inactivation even without the benefit of a Y paralogue to protect males. Indeed, haplo-insufficiency could still lead to Turner syndrome phenotypes if a higher expression was required for normal functions in females (e.g. ovarian). Our unpublished studies show high expression of escape genes in female-specific organs (Nguyen and Disteche, unpublished results). As discussed above, an important caveat is that escape from X inactivation, which affects about 15% X-linked genes, has been mainly assessed in cell lines (22). Differences between tissues and timing during development have largely not been addressed; yet, an interesting study has shown variable escape of *TIMP1* (TIMP metallopeptidase inhibitor 1) between tissues (4). Considering mutations in genes subject to X inactivation, Turner syndrome females would have the same risk as males, while heterozygous females are either unaffected, or variably affected due to skewing of X inactivation (88). In addition, both X chromosomes being active in germ cells of normal females, haplo-insufficiency of genes subject to X inactivation in somatic tissues should be considered for ovarian failure in Turner syndrome.

Ovarian dysgenesis

Ovarian dysgenesis can be detected in infants with Turner syndrome where primary oocytes are completely depleted, presumably due to apoptosis triggered by faulty meiotic pairing (27). In fact, oocytes in a 45,X ovary proliferate normally in early fetal development while apoptosis becomes apparent and accelerated in the second half of pregnancy (28). Premature ovarian failure (POF) may be due to both structural effects of X anomalies and to specific gene haplo-insufficiencies. Ovarian dysgenesis has secondary effects in Turner syndrome due to reduction of estrogens and overproduction of gonadotropins (LH and FSH), which may disrupt neurological, metabolic, and/or cardiovascular functions and lead to the early onset of osteoporosis (11).

Chromosome pairing is necessary for the viability of oocytes and in turn ovarian development. In contrast, monosomy X or X-linked deletions of various sizes and at different locations often result in ovarian dysgenesis. In women who are not mosaic, both Xp and Xq deletions result in ovarian dysgenesis (131). On the other hand, ovarian dysgenesis is rarely detected in girls who are 45,X/46,XX mosaic, suggesting that this condition is avoided when

oocytes containing two X chromosomes are present in the developing ovaries (28). It is certainly possible that individual X-linked genes make specific contributions to oocyte and/or ovarian development. Given that the X chromosome is enriched in genes important for reproduction, it is likely that POF can be caused by several genes.

DIAPH2, BMP15, FMR1

DIAPH2 (diaphanous homolog 2), which variably escapes X inactivation, was implicated early in ovarian failure but no mutations have been found in POF. Mutations in *BMP15* (bone morphogenetic protein 15) and in *FMR1* (fragile X mental retardation 1) both cause ovarian dysgenesis or ovarian failure (131). As discussed above, *USP9X* has also been proposed as a candidate for ovarian failure in Turner syndrome (57).

Lymphedema

Lymphedema arises due to insufficient function of lymphatic valves. In Turner syndrome, its early onset suggests the likelihood of a direct contribution of X-linked genes (111). In fact, lymphedema is often detected prenatally in fetuses with Turner syndrome. There are probably multiple genes implicated in this phenotype as shown by the lack of correlation between specific Xp deletions and the presence of lymphedema (69).

VEGFD

Vascular endothelial growth factors (VEGFs) play an important role in lymphangiogenesis, both in early development and in adults in conditions such as inflammation and cancer. Their effects are mediated through distinct receptors on the surface of lymphatic endothelial cells (65). VEGFC appears to be the master regulator of lymphangiogenesis through its binding at the receptor VEGFR3. *VEGFD,* which maps at Xp22,31 and shares high homology with *VEGFC,* encodes a protein that also binds at this receptor. Mouse knockout studies indicate that, different from VEGFC, VEGFD is not essential for embryonic lymphangiogenesis but likely participates in inflammation-associated lymphangiogenesis (49). However, there is no evidence that a single copy of *VEGFD* is responsible for insufficient lymphangiogenesis and in turn lymphedema in Turner syndrome, since males also contain one single copy of *VEGFD.*

IKBKG

Mutations in *IKBKG* (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase gamma) result in lymphedema as well as incontinentia pigmenti (35). The mutant protein disrupts signaling in response to interferons leading to an abnormal immune reaction. Mutations are lethal in male fetuses and cause variable phenotypes in female carriers who often suffer from severe lymphedema. Although *IKBKG* escapes X inactivation in cell lines, survival of carrier females is due to skewing of X inactivation in favor of the normal allele, which often occurs during the

first few years after birth (91). This suggests that *IKBKG* may not escape X inactivation in all tissues. No definite connection has been made between *IKBKG* and lymphedema in Turner syndrome.

Lymphedema has also been linked to a number of autosomal disorders. Patients with Noonan syndrome, caused by mutations in *PTPN11* (protein tyrosine phosphatase, non-receptor type 11), often have lymphedema (95). A number of other Turner syndrome symptoms are also observed in Noonan syndrome (e.g. ptosis, webbing of the neck, a deep nuchal hairline, short stature, clinodactyly, pectus carinatum, funnel chest). It is possible that a biological pathway involves both PTPN11 and certain X-linked proteins, resulting in the shared phenotypes. One candidate is the X-linked *SH2D1A* gene (SH2 domain protein 1A) mutated in a lymphoproliferative disorder associated with immunodeficiency. SH2D1A is involved in both T cell expansion and B cell differentiation at immune responses (117).

The compressive or obstructive effects of fetal lymphedema often lead to other Turner syndrome symptoms such as nuchal folds, pterygium colli, obesity, and congenital cardiovascular defects (e.g. bicuspid aortic valve and aortic coarctation) (79). Common skeletal deformities such as short metacarpals, cubitus valgus, as well as craniofacial and cervical skeletal stigmata may also result from compressive effects (96). The parent of origin of the retained X chromosome, Xm or Xp, has been repeatedly proposed to be involved in various Turner syndrome symptoms including

lymphedema. However, a large study found no evidence of parental origin on physical features of Turner syndrome (15).

Cardiovascular malformations

Many Turner syndrome patients suffer from cardiovascular abnormalities such as coarctation of the aorta, bicuspid aortic valve, aortic root dilatation, atrial, and ventricular septal defects (87). In fact, cardiovascular disease is the major cause of premature mortality and acute aortic dissection occurs at a much younger age among women with Turner syndrome than in the general female population. The compressive and/or obstructive effects of fetal lymphedema may be responsible, at least in part, for the cardiovascular anomalies (79). The association between lymphedema and cardiovascular phenotypes is consistent across various X-linked deletions in Turner syndrome.

Prenatal cardiac defects in Turner syndrome are associated with an elevated level of VEGF, with or without lymphedema (16). VEGF factors, as mentioned above, participate in endothelium growth and in the embryonic endocardial-to-mesenchymal transformation of the endocardial cushions. An abnormally high level of VEGF is often associated with fetal hydrops, abnormal endocardial cushion development and subsequent congenital heart defects, as seen in Turner syndrome. Excess VEGF in the wall of the distended jugular sacs (cervical hygroma) might contribute to other

symptoms such as short stature and gonadal dysgenesis (16). Whether the X-linked *VEGFD* is involved is unknown.

Noonan syndrome also has a cardiovascular phenotype, which often affects the right heart and is mainly associated with valvular pulmonary stenosis, in contrast to aortic stenosis and coarctation in Turner syndrome (95). Many other autosomal mutations result in calcified and stenosed aortic valve. Whether any X-linked genes interact with these candidate genes remains to be determined.

Kidney abnormality

Which X-linked genes underpin the kidney dysfunction in Turner syndrome is an open question. Several X-linked mutations are associated with kidney disorders that result in severe phenotypes in males and variable symptoms in female carriers due to either haplo-insufficiency or dominant effects. No association has been found between lymphedema and renal defects (79).

OFD1

This gene (oral-facial-digital syndrome 1) located adjacent to the PAR1 escapes X inactivation. Mutations in *OFD1* are responsible for oral-facial-digital syndrome type I (38) and for mental retardation (17). Polycystic kidney disease has been identified in a number of patients with *OFD1* mutations. The renal phenotype is recaptured in *Ofd1* knockout mice

where heterozygous females have impaired cilia formation and cystic kidneys, suggesting a dosage effect (38).

KAL1

KAL1 (Kallmann syndrome 1 sequence) is another escape gene located near the PAR1 whose mutations are associated with renal defects. Diagnostic features of Kallmann syndrome include hypogonadotropic hypogonadism and anosmia. Unilateral renal agenesis, however, has been frequently noticed (116). KAL1 is a membrane protein that yields a diffusible component upon proteolytic cleavage. *KAL1* mutations mainly affect males, but symptomatic female carriers are frequently reported, suggesting a dosage effect.

Cleft Palate

TBX22 is a gene that escapes X inactivation and whose mutations cause X-linked cleft palate in males and carrier females. Its protein product is a transcriptional repressor expressed specifically in the embryonic palatal shelves (5). Deficiency of this gene may cause the cleft lip/palate often seen in 45,X fetuses.

Mental function

Turner syndrome is associated with mild mental deficiencies related to spatial recognition (148). A large number of X-linked genes, many with XY homology and that escape X inactivation, are expressed in brain and thus attractive candidates, as discussed above (105). Visuospatial attention deficiencies have been

reported in mice with a single X chromosome (29). Potential differences in performance between Turner syndrome who inherited their X from their mother or father has lead to the hypothesis that some of these genes were imprinted (120). Comparisons between Turner individuals with Xp or Xm will help sort out this issue. Mosaic patients with lines that contain small X-derived ring chromosomes have a high risk of mental retardation, in part due to abnormalities of X inactivation of the ring chromosomes (174).

Summary

In summary, women with Turner syndrome have reduced protein levels of PAR genes and of genes that escape X inactivation (with or without a Y paralogue) compared to healthy women. Deletion analyses have shown that the short arm of the human X chromosome contains many of the genes important for Turner syndrome. Nevertheless, none of these genes, except *SHOX*, has been confirmed to be responsible for particular symptoms. The deficiency in X-linked genes in Turner syndrome is probably the major factor in bringing about phenotypes. However, the need for pairing of two active X chromosomes at meiosis is also important in understanding ovarian dysgenesis. Finally, some Turner phenotypes related to autoimmune disorders could be caused by unsuspected mosaicism for an XY cell line since most Y paralogues are known to act as HY antigens. Much remains to be studied in terms of the identification of specific genes in Turner syndrome. The advent of novel technologies to follow global gene expression will be helpful for these studies.

Acknowledgements

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part

2

Adulthood with Turner syndrome

Turner syndrome – epidemiology

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How many girls have Turner syndrome?

Turner syndrome occurs in about 50 in 100 000 *live-born* girls (1).

How many girls have Turner syndrome in Denmark?

In Denmark, about 60 000 live-born children are born every year; approximately half of these are girls. Thus, about 15 girls are born with Turner syndrome every year, and there are around 1 200–1 300 people with Turner syndrome in Denmark. It is estimated that in the EU there are about 110 000–120 000 girls/women with Turner syndrome.

How does Turner syndrome occur?

Normally, every person has 44 chromosomes and two sex chromosomes. The sex chromosomes determine the sex of the child, and the other chromosomes do not affect this in any way. The sex chromosomes can be either an X chromosome or a Y chromosome. The mother gives one X chromosome, and the father gives either an X *or* a Y chromosome. The result is either 46,XX (a girl) or 46,XY (a boy, because the presence of a Y chromosome normally triggers testicular development).

Turner syndrome can occur in several ways. The combination of the chromosomes is called the *karyotype,* and there are many different karyotypes that can result in Turner syndrome. The most well-known is 45,X, but the Y chromosome can also be present in girls with Turn-

er syndrome. It must be mentioned that the karyotype 45,Y is not normally compatible with life. This is because the X chromosome contains far more genetic material than the Y chromosome.

When is the diagnosis made?

Often, it is not immediately discovered that a newborn girl has Turner syndrome. There can be many reasons for this; the appearance of a newborn girl with Turner syndrome is not necessarily different from a newborn girl without Turner syndrome. A study of all Danish girls diagnosed with Turner syndrome reveals that the median age at diagnosis is around 15 years of age. In other words: Half of all girls with Turner syndrome were younger than 15 years of age when they were diagnosed, and the other half were *15 years or older* (Figure 1) (1).

If girls with Turner Syndrome are divided into 3 subgroups according to karyotype, it becomes apparent there is also an inter-group difference with regard to time of diagnosis. Girls who lack an X chromosome (karyotype 45,X), are diagnosed earliest at a median age of 13 years. A second subgroup, with a special chromosome combination (isochromosome Xq), are diagnosed at a median age of 14 years. The last subgroup of "other" karyotypes are diagnosed at a median age of 19 years (Figure 1). This distribution can be explained by the fact that the girls who lack most X chromosome, and thus most genetic information, often appear most different and thus are diagnosed earlier. The average age at

the time of diagnosis decreased in the period from 1970 to 1999 (1). Thus, the girls are now diagnosed at an earlier age than previously.

As is presented in Figure 1, many girls with Turner syndrome are diagnosed shortly after birth, most probably due to congenital changes in appearance. Shortness of stature is present in nearly all (untreated) girls with Turner syndrome, and can result in diagnosis during puberty. Many girls are diagnosed around or immediately after the time of the first menstruation because menstruation and normal pubertal development are generally

The number of people with Turner syndrome and their age at the time of diagnosis divided into three subgroups with differing karyotypes. CI: Confidence interval.

	Median age at diagnosis
45,X	13,3 (95% CI: 12,1–14,2) years
Isochromosome Xq	14,2 (12,4–16,2) years
Other karotypes	19,1 (17,8–21,9) years
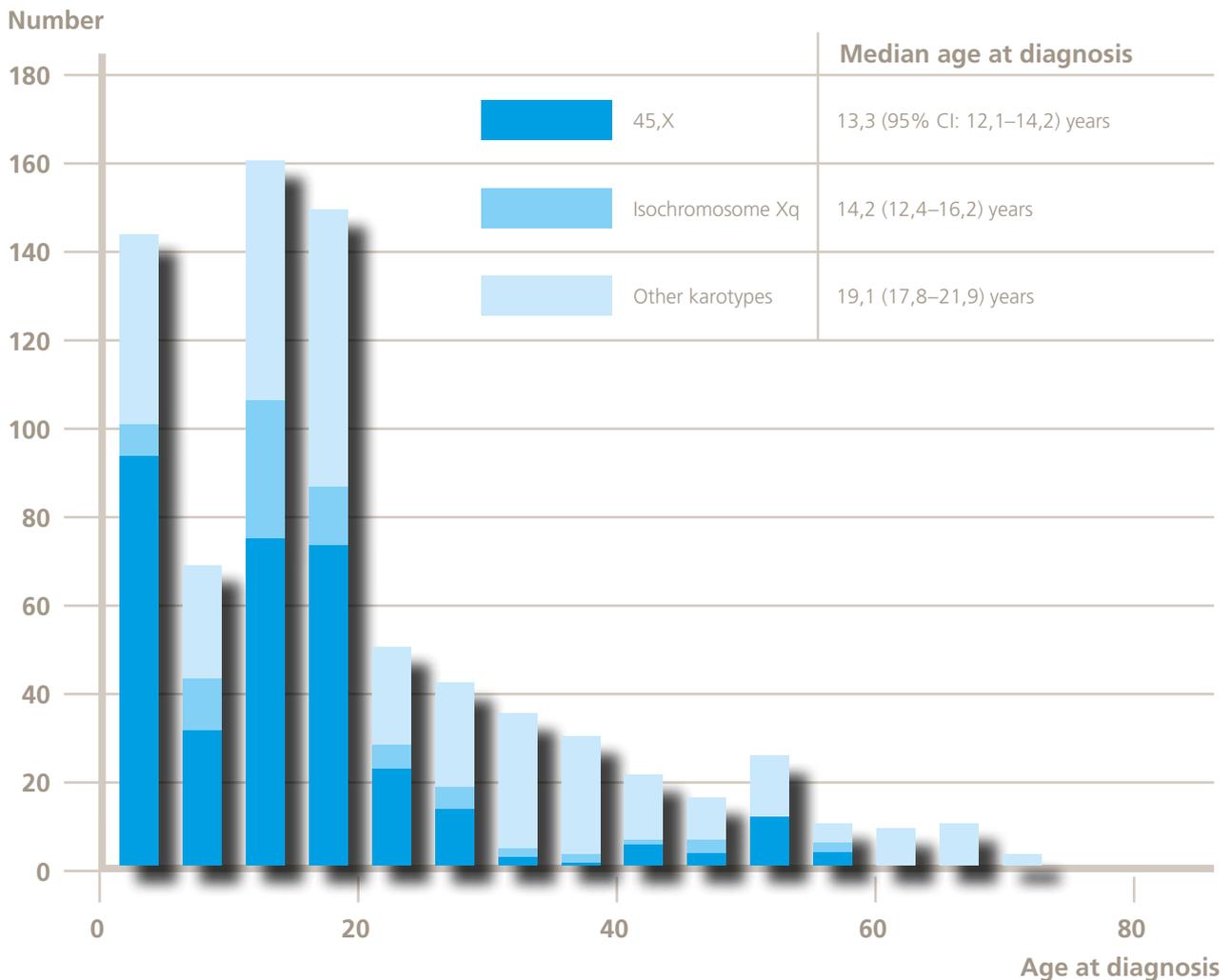
absent in girls with Turner syndrome. As can be seen from the figure, the diagnosis can also be made at quite a high age.

How many are diagnosed?

In 1970, one in 10 girls born with Turner syndrome was diagnosed; in other words 9 out of 10 were not diagnosed (Figure 2). In 1999, one in two had been given the correct diagnosis. This means that every second person was *not* diagnosed in 1999, but could hopefully be diagnosed later (1).

Which diseases?

The overall picture of the incidence of disease in Turner syndrome is identified in register surveys. In these studies, morbidity has been found to be increased in Turner syndrome assessed by the number of contacts with the healthcare services. In general, this number is increased compared to women from the general population. If the causes of contact to the healthcare services are looked at in detail, a picture emerges of increased morbidity due to congenital anomalies, metabolic diseases, diabetes and cardiovascular disease (1–2).

What about cancer – as a disease?

It is important to mention that as a disease, the incidence of cancer is the same as for the general population. Two different studies have demonstrated that there is an increased risk for colon cancer (3) and a reduced risk for developing breast cancer (4). These two findings are not confirmed elsewhere.

What are the causes of death?

Overall, mortality is increased in the group of women with Turner syndrome compared with a group of age matched women from the same country (1–2).

A Danish study of the causes of death found an increased number of deaths from cardiovascular disease, congenital anomalies and hormone diseases. These calculations are based on 69 deaths of 781 persons. The same studies indicate an improved prognosis, with decreasing mortality from 1970 to 1999. An English study has revealed an increased number of deaths due to cardiovascular disease, congenital anomalies, diabetes, epilepsy, liver disease, urinary tract disease, certain intestinal disease, and pneumonia. In this study, 296 people died of a total of 3 439.

A simple, but *rare* cause of the increased mortality is rupture of the aorta (aortic dissection). The aorta is the major artery that distributes the blood from the heart into the circulation. It is known that women with Turner syndrome have an increased risk for an inappropriate increase of the aorta resulting in damaged structure or rupture: Aortic dissection. this is potentially life-threatening, and occurs in some with Turner syndrome at a substantially lower age than in the general population. It is estimated that for each 100 000 person years for women with Turner syndrome, there will be 36 cases of ruptured aorta. In the general population, it is estimated that this occurs in 6 in 100 000 person years, of which one in three will be women. Furthermore, the average age for aortic dissection in women with Turner

syndrome is about 36 years of age. In the general population, aortic dissection typically occurs in the 50–80 year age group (5).

Finally, it can be mentioned that in women with Turner syndrome there is an increased mortality with karyotype 45,X compared to the other karyotypes.

What about cancer – as a cause of death?

In general, no increased risk for death due to cancer has been shown; in fact, one English study has shown that the risk for breast cancer is considerably lower than in the general population (2).

Figure 2

The number of people diagnosed with Turner syndrome, compared to expected number. The difference between expected and diagnosed corresponds to all people with Turner syndrome who have not yet been given a diagnosis.

Persons alive with Turner syndrome
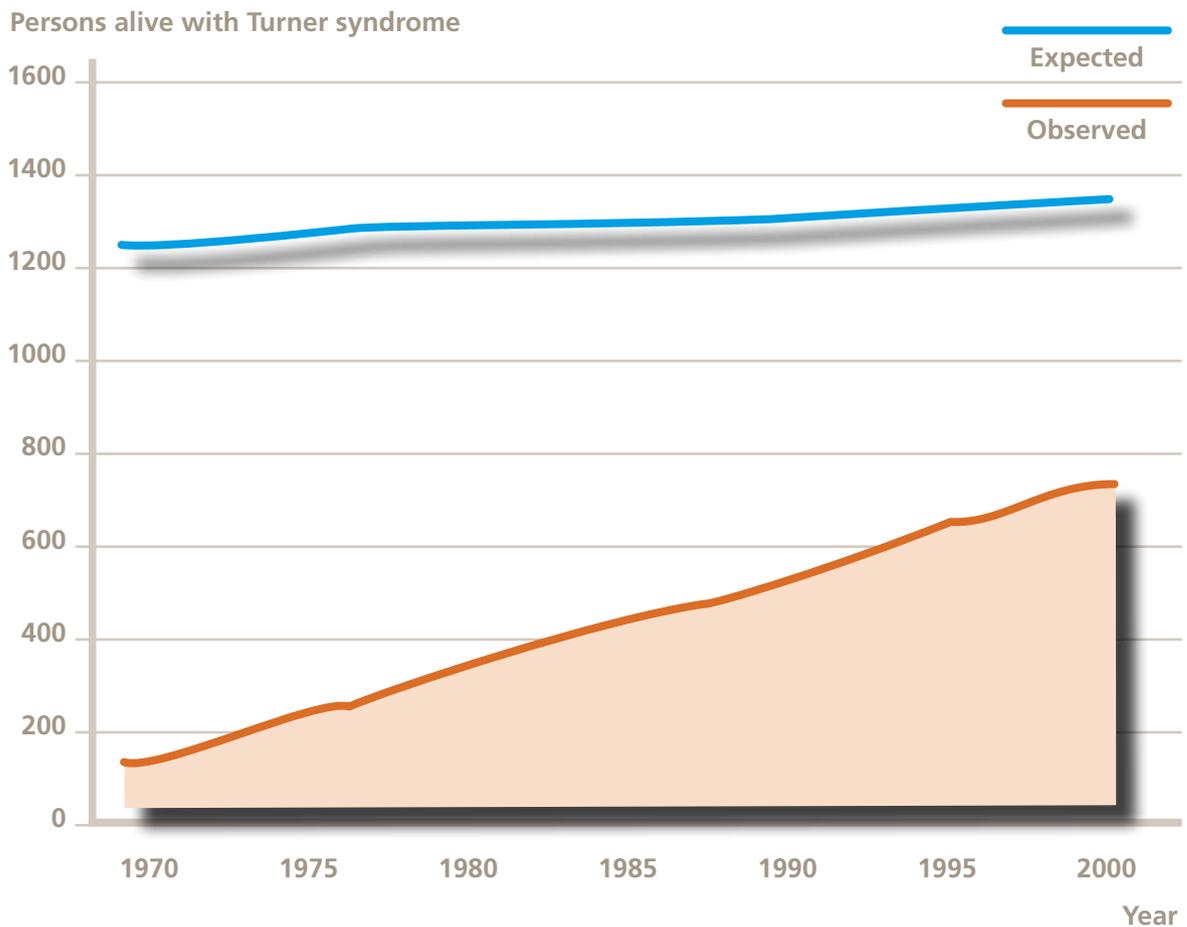
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Congenital heart disease in Turner syndrome

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Cardiovascular complications – a sizeable problem

The most concerning and life-threatening complications in girls and women with Turner syndrome relate to the cardiovascular system. As technology for diagnosis has improved, the type and range of severity of heart conditions associated with Turner syndrome has been found to be much greater than was once thought. This has emphasized the importance of cardiac screening in girls and women with Turner syndrome throughout the lifespan.

Karyotype and neck webbing

The most significant effects of congenital heart disease are often seen in the developing fetus with 45,X karyotype. These fetuses often show signs of cardiac failure accompanied by build up of lymph fluid at the neck. Such build up is called a cystic hygroma or, after birth, neck webbing. Fetuses with cystic hygroma are thus more likely to have a congenital heart disease, particularly of the left side of the heart. The most common left heart problems are bicuspid aortic valve and coarctation of the aorta. The bicuspid aortic valve is present when the aortic valve is made up of only two leaflets instead of the usual three, and coarctation is another word for narrowing of the aortic arch. We do not know entirely why cystic hygroma and cardiac anomalies tend to occur together. It may be because the build up of lymph fluid obstructs the flow of blood from the developing heart. Or, a common gene missing from the X chromosome may affect the development of the heart.

Congenital anomalies of the heart and major vessels

Often cardiac anomalies do not cause symptoms. Therefore, they may not be diagnosed until well after infancy or even in adulthood. Bicuspid aortic valve and coarctation of the aorta are the most common cardiac anomalies and present in about 16% and 11% of individuals with Turner syndrome, respectively.

Girls and women with a webbed neck are approximately four times more likely to have these two anomalies. Often bicuspid aortic valve, and sometimes coarctation, can be asymptomatic in infancy and childhood. However, they can be associated with complications. These can include narrowing of the aortic valve (stenosis), infection of the heart lining (bacterial endocarditis), and ascending aortic aneurysm, rupture, and dissection (bleeding into and through the aortic wall)

Therefore, it is important to identify these and other cardiac anomalies as early as possible, and the easiest way is by doing an echocardiogram, a sonogram of the heart. Sometimes, a magnetic resonance imaging scan (MRI) is necessary and often finds anomalies that are missed by echocardiogram.

In fact, studies using MRI screening in girls and women with Turner syndrome have shown us that they have many changes in the vascular system. Many of these are challenging to see or cannot be seen on echocardiogram. About half of women will have an unusual angle to the aortic arch or an aortic arch that is longer

Arterial hypertension

Aortic coarctation

Aortic dissection

Normal tricuspid aortic valves

Aortic dialation

Bicuspid aortic valves

Abnormal bicuspid aortic valves
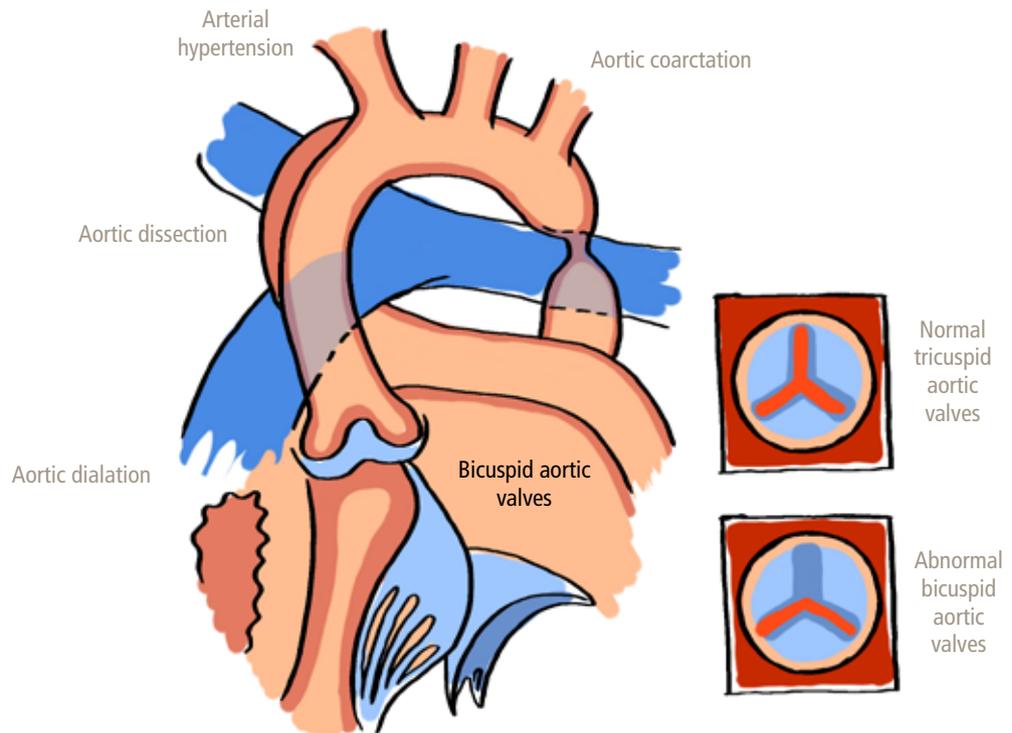
than normal (called "elongated transverse aortic arch") (figure). Elongated transverse aortic arch detected by MR

Some will have defects on the venous circulation transporting blood back to the heart. These can be partial anomalous pulmonary venous return or persistent left superior vena cava that occur more frequently than among girls and women in general. It is not clear if these changes will lead to symptoms or complications. But, the changes indicate that the vascular system in Turner syndrome is unique in many ways. Further studies may provide additional information about the significance of these vascular anomalies.

Figure 2

Aortic dissection.
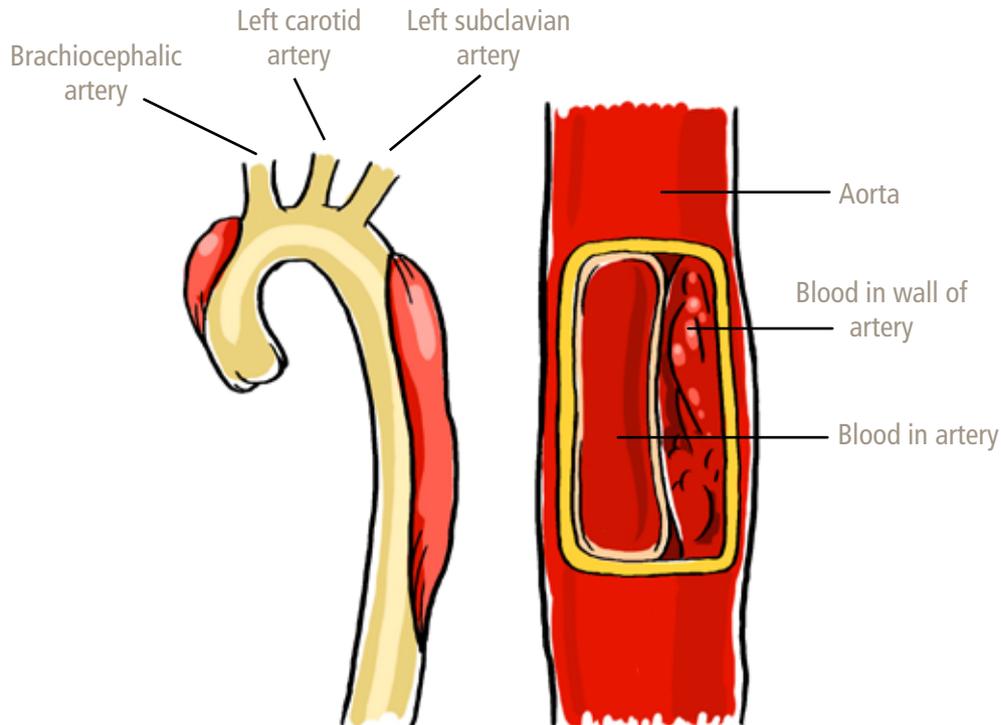
Complications to the congenital anomalies

The most devastating, though rare, cardiac complication is aortic rupture, or dissection. This can happen in any girl or woman with Turner syndrome. However, those with congenital heart disease such as bicuspid aortic valve, coarctation, or other risk factors such as high blood pressure are at increased risk for these complications. Also, approximately 40 to 50% of girls and women with Turner syndrome will have enlargement of the ascending aorta which is understood as a precursor of dissection and rupture. Similar to individuals without Turner syndrome, this enlargement happens more often when bicuspid aortic valve, coarctation, or hypertension are present. But it can also occur by itself without these predisposing factors. Pregnancy also increases the risk for dissection. It is possible

Figure 3

Elongated transverse aortic arch detected by MR.

that in Turner syndrome there is an underlying abnormality of the vasculature that increases the susceptibility to this complication.

Screening and diagnosis

Because of the variety of cardiac anomalies that can occur in Turner syndrome, it is recommended that girls and women with Turner syndrome have regular screening of the cardiac system. This begins with an initial visit with a cardiologist at the time of diagnosis. This should include an electrocardiogram (ECG) and echocardiogram in addition to a complete history and physical examination by the cardiologist. Even infants who have been diagnosed prenatally and had an echocardiogram before birth should have this repeated after birth. It is important the

entire heart and the entire aorta are well visualized. There are four important places where the cardiologist evaluates the aorta. These are the aortic valve, the aortic root at the sinuses of valsalva, the sinotubular junction (where the aorta meets the root), and about one cm above the sinotubular junction, the classic site of dilation of the aorta. If this cannot be accomplished, an MRI should be obtained even if sedation is needed. In fact, all individuals with Turner syndrome should have an MRI at some time by their early teens, or as soon as it can be performed without sedation. This MRI is best performed with the expertise of a cardiologist and radiologist skilled in evaluation of the aorta.

For those with Turner syndrome who have been found to have congenital heart anomalies, the frequency and type of follow up is guided by the cardiologist. Those who have normal cardiac imaging (echo or MRI), and normal blood pressure, should be reevaluated at transition from pediatric to adult care. A complete cardiac evaluation is also essential prior to considering pregnancy due to the risk of aortic dissection. Increased blood pressure is also a reason for prompt reevaluation by a cardiologist. Otherwise, cardiac imaging should be repeated every 5 to 10 years to monitor the size and structure of the aorta.

Although aortic dissection and rupture occur rarely, it is important that those with Turner syndrome and one or more risk factors be monitored closely for the development of this dreaded complication. The risk factors include, as mentioned earlier, hypertension, bicuspid

aortic valv, coarctation, aortic dilation, and pregnancy (Figure 4). However, dissection and rupture can happen even when none of these risk factors are present. In fact, about 10–25% of those who have experienced aortic dissection had no known risk factors aside from their underlying diagnosis of Turner syndrome. Aortic size should be followed closely. If the aorta is found to be enlarged, medical therapy such as beta-blockers is administered by the cardiologist.

Pregnancy

Cardiovascular assessments are particularly important before making the decision of whether or not to undergo pregnancy. As mentioned, pregnancy itself is a significant risk factor for aortic dissection and rupture. The chance for this to occur is further increased in those who already have other risk factors. Therefore, those with a congenital heart anomaly such as BAV or coarctation, previous cardiac surgery, known aortic dilation, or hypertension, should probably choose not to undergo pregnancy.

Physical activity and medical treatment

These risk factors should also be considered carefully when choosing physical activities. Regular moderate aerobic activity (such as bicycling or heart healthy exercise), is generally encouraged as part of an active lifestyle. However, those with Turner syndrome who have a dilated aorta may want to avoid activities such as isometric exercises (such as

weight training) and strenuous or competitive sports. This degree of activity can place excessive stress on an already stressed aortic wall causing it to enlarge further or dissect or rupture. Therefore, participation in competitive sports should only be undertaken after complete aortic imaging preferably by a recent MRI. If in doubt, the cardiologist can be consulted for advice regarding the recommended level of exercise.

Abnormal intracardiac conduction – another lifelong anomaly

Not only do women with Turner syndrome have structural heart anomalies, they can also be subject to a variety of electrocardiographic changes, heart rhythm abnormalities. These can include accelerated conduction from the upper chambers (atria) to the lower chambers (ventricles) of the heart or prolonged QTc interval (abnormal electric currents in the heart

Figure 4

Risk factors for aortic dissection

Pregnancy

Hypertension

Bicuspid aortic valv

Coarctation

Aortic dilation

musculature). Tachycardia, or accelerated heart rhythm, is also common and even seen in fetuses. This suggests that girls and women with Turner syndrome may have an underlying abnormality of the portion of the nervous system, which controls such functions as heart rate, temperature, pain, and fear response called the autonomic nervous system. We do not know whether these rhythm changes will be significant. But, it is important that individuals with Turner syndrome have periodic ECG. If the QTc is increased on ECG, it is best to avoid certain medications that will further increase this interval. These medications can cause heart rhythm abnormalities in some individuals with or without Turner syndrome with increased QTc. Your doctor can advise you what medications to avoid and how often to have ECG's repeated.

Perspective

Much remains to be learned about congenital heart problems that affect girls and women with Turner syndrome. In the years to come, it is hoped that we will have an even greater understanding of the congenital and acquired heart problems and their clinical significance and thus improve monitoring and treatment. In the meantime heightened awareness and conscientious follow up are important to avoid potentially serious complications.

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Aortic disease in Turner syndrome

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Introduction

The aorta is the major blood vessel heart carrying fresh, oxygen-rich blood to the body. The blood emerges from the heart's main pumping chamber and passes through the aortic valve into the aorta. The aorta arises in the upper chest and courses up towards the head, giving off branches that carry blood to the head and arms (Figure 1). It then curves downward, extending down along the backbone into the abdomen, where it gives off branches that supply blood to the internal organs. Finally, the aorta divides into the two main arteries to the legs. The aortic valve and aorta develop in the firstst few months of fetal life. Alterations in gene effects during fetal development may cause cardiovascular anatomic abnormalities present at birth, known as "congenital" heart disease. The chapter reviews defects of the aortic valve and aorta that are found in girls and women with Turner syndrome, based upon our experience in the evaluation of more than 400 patients with Turner syndrome over the past 5 years at the National Institute of Health (NIH) in Bethesda, MD. Each of these study participants had a comprehensive cardiac evaluation including expert consultation and examination, echocardiography, cardiac magnetic resonance scan, and other cardiac studies as indicated. More detailed information may be found in recent review articles available at our NIH website: http://turners.nichd.nih.gov/.

Aortic valve defects

Defects in aortic valve development constitute the most common form of congenital heart disease in the general population, affecting 1–2%. It is much more common in Turner syndrome, however, affecting about 30%. The aortic valve normally is formed by three separate leaflets, or cusps, that are rooted in a ring of tough connective tissue which joins the heart outflow tract to the ascending aorta. When the heart muscle contacts, blood is forced out through the open valve. When the three leaflets open separately, there is a wide triangular orifice for blood outflow. However, sometimes during fetal development, two of

Figure 1

Ascending thoracic aorta

Aortic arch

Aortic valve

Descending thoracic aorta

Abdominal aorta
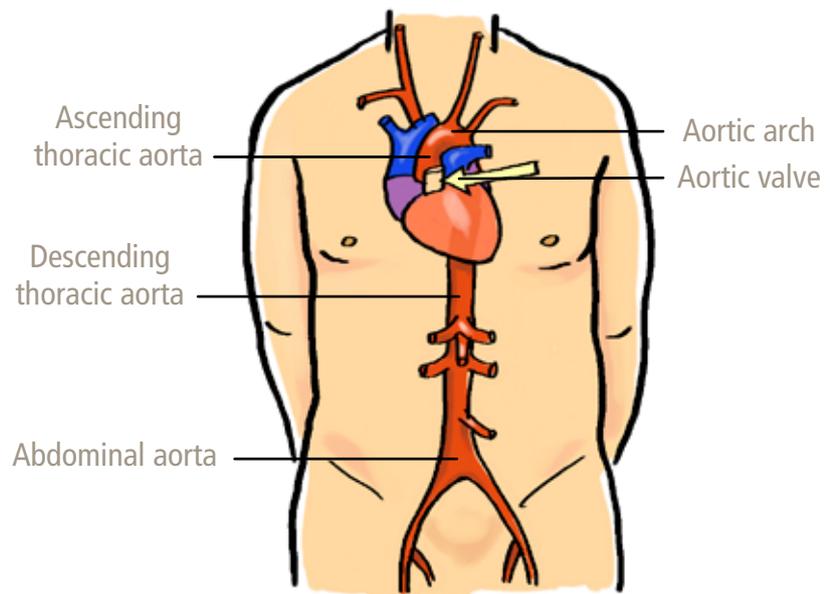
the three leaflets remain fused together, either partially just from the valve base, maybe half way to the tip, or totally (FIG. 2). This causes the two leaflets to remain tethered together and function as a single leaflet, so the opening is more slit-like than triangular. In the case of partial fusion, the abnormality may be called a "functional" bicuspid aortic valve. With complete fusion of two cusps, it is known simply as bicuspid aortic valve. This defect is usually without symptoms in children and young adults and is easily missed on routine transthoracic echocardiography. To be sure you or your child has had an adequate evaluation for abnormalities of the aortic valve, the cardiologist must have clearly visualized all three aortic valve leaflets and seen that they function independently. If the aortic valve is not well visualized on echo, cardiac magnetic resonance will usually provide the answer (see more on cardiac magnetic resonance below).

It is important to know about the structure of the aortic valve in Turner individuals because there is a risk for deterioration of bicuspid aortic valve function over time. If not detected early and properly treated, this could cause irreparable heart damage. This seems to be true for both the full bicuspid aortic valve and the partial, or functional bicuspid aortic valve. The blood flow through the irregular bicuspid aortic valve is often turbulent and may cause a sound or murmur heard by a stethoscope. Over time, the turbulence may damage the valve so it becomes leaky, and allows blood to spill back into the heart (aortic regurgitation or insufficiency). If a substantial amount of

blood goes backward into the heart instead of forward into the body's circulation, heart failure will result. Aging, infection or inflammation may cause the valve to become sticky or stiff, so it can no longer open adequately to let enough blood pass through to supply the body. This is called aortic stenosis, and may cause symptoms of shortness of breath with mild exertion, chest pain, palpitations or syncope. Knowledge of the presence of an abnormal aortic valve structure allows the patient to be followed by a cardiologist familiar

Figure 2

Normal and Bicuspid Aortic Valves. It is also vitally important to know the status of the aortic valve in girls and women with Turner syndrome because the presence of a bicuspid aortic valve is closely associated with an abnormal aorta and risk for aortic complications such as aortic aneurysm or dissection. See section below "Aortic Aneurysm or Dilation".

From http://www.med.yale.edu/intmed/cardio/echo_atlas/entities/aortic_stenosis_bicuspid.html. For additional discussion of issues related to bicuspid aortic valveBAV with excellent illustrations, see: http://www.teamt.us/Bicuspid_Aortic_Valve.htm

Normal aortic valve

Bicuspid aortic valve
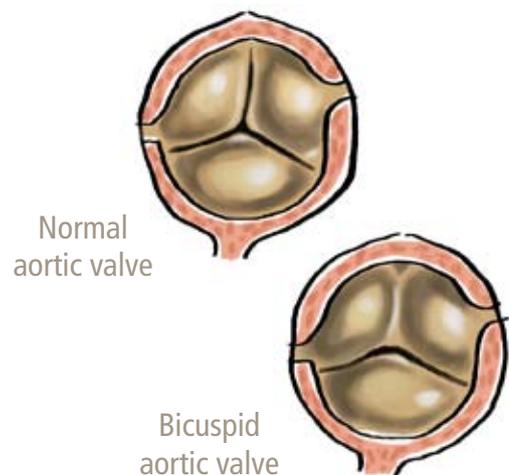
with valve disease with regular evaluation of valve function and early intervention to correct problems before permanent harm is done. The medical technology for correcting valve defects is advancing rapidly, and it is likely that more and more cases may be treated without the need for open heart surgery as time goes by. (Figure 2)

Aortic coarctation

This defect involves a constriction, or narrowing of the aorta that impedes the forward blood flow (Figure 3a). A very severe constriction usually becomes apparent early in life due to high blood pressure in the upper body and low blood pressure and poor blood circulation in the lower body. If not corrected, severe aortic coarctation causes enlargement, and eventually failure of the heart. The treatment usually is a surgical resection of the constricted portion and end to end reconnection of the normal aortic segments. Sometimes a graft (a tube made of Dacron or similar material) is used to reconnect the two ends of the aorta or to bypass the coarctation.

If an aortic coarctation is very severe it may have to be repaired in infancy and then revised one or more times as the child grows. In isolated cases not associated with Turner syndrome, endovascular dilation of the constricted aortic region by balloon angioplasty has been used, but this approach has not been established for girls with Turner syndrome. A surgically repaired coarctation should be monitored with imaging such as magnetic resonance angiography in later years because

aneurysm formation may occasionally occur at anastomosis sites. Furthermore, coarctation is often associated with other abnormalities such as bicuspid aortic valve, which need ongoing monitoring by cardiology.

Aortic aneurysm or dilation

An aneurysm is a balloon-like dilation or bulge in an artery (Figure 3b). Aneurysms may be present from birth or may develop during postnatal life. Some appear to form due to an intrinsic weakness in the artery or aortic wall structure, for example, in Marfan syndrome (a syndrome often complicated by aortic dilation as well as muscle, skeletal and eye related problems). This disorder is caused by mutation or deletion of one of several genes important for arterial wall integrity. The aorta appears normal at birth but as the Marfan child ages, the ascending aorta progressively stretches or dilates, and the wall becomes progressively thinner and weaker. Specific medications including beta-adrenergic blockers (e.g., metoprolol) and more recently angiotensin system blockers (e.g., losartan) are moderately effective in slowing or even arresting the dilation in some cases. However, many individuals with Marfan syndrome un-

Figure 3

Aortic coarctation and aneurysm.

Coarctation   Aneurysm
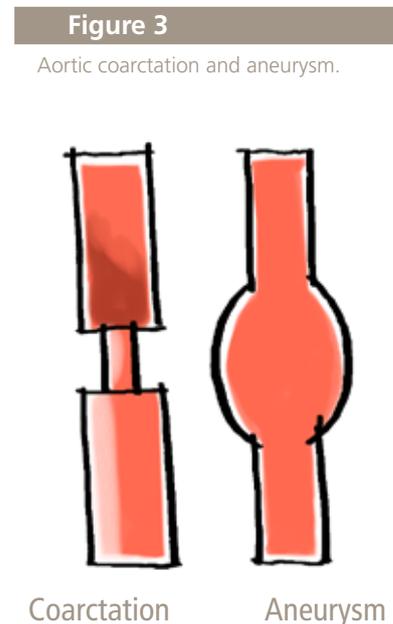
dergo surgery to correct the aortic aneurysm and prevent dissection (tear in the aortic wall) or rupture.

Aortic aneurysm also occurs in some patients associated with the presence of a bicuspid aortic valve, and this seems to be particularly true in Turner syndrome. Thus it is very important to know the status of the aortic valve; if it is abnormal, then the diameter of the ascending aorta needs to be assessed carefully. Routine transthoracic echocardiography often has difficulty in imaging thoracic aorta, and it is not adequate to assess only the diameter of the "aortic root" which is the lowest portion of the aorta. The region that dilates in patients with bicuspid aortic valve is the "ascending aorta" (Figure 1) which is several centimeters higher in the chest and is easily assessed on cardiac magnetic resonance. Pediatric cardiologists have the expertise to interpret the size of the aorta in relation to a child's body size. Most adult cardiologists do not consider this issue but it is highly relevant in the case of exceptionally small adults, i.e., adult women with Turner syndrome less than 5 ft tall. The aorta is proportional to body size, and small statured individuals normally have small aortas. The "normal range" for aortic diameters was derived from the study of average men and women, with combined average height of 170 cm (5'8") or so. What is considered normal aortic diameter for that size group may actually represent an aneurysm for someone 140 cm (~4'8"). To take into account differences in body size among adult patients, we devised the aortic size index, which takes the aortic diameter in cm (at the level of the pul-

monary artery determined on cardiac MR) and divide by the person's body surface area. No control women had aortic size index greater than 2,4 cm/m^2; about 10% of the Turner syndrome adult group did, and several of these individuals had major complications related to dissection. Thus we consider an aortic size index >2,4 to identify patients at very high risk of complications and in need of close monitoring, medical treatment and possible surgical intervention if the diameter increases further. Individuals with aortic size index >2 cm/m^2 also deserve close monitoring and possible medical treatment with angiotensin system blockers 1.

Treatment for aortic dilation in Turner syndrome

The best treatment for individuals with aortic dilation or aneurysm in Turner syndrome is unknown at present. Current studies are examining if medications such as metopropol or losartan may be helpful in this condition, but the outcomes are not yet known. Patients with Marfan syndrome generally do quite well with prophylactic surgery to replace their aortic aneurysm with a synthetic graft to prevent dissection or rupture. This has not been tried in Turner syndrome because it is not known what degree of dilation should prompt intervention, or whether the graft repair will be as successful. This is the best advice we can offer at present for patients with Turner syndrome and apparent aortic abnormalities. For those with:

- Bicuspid aortic valve but normal aortic diameters – follow bicuspid aortic valve function and aortic diameters every 1–2 years per your cardiologist. Adults should be followed at an "Adult Congenital Heart Disease Clinic" where staffs are experts in congenital heart defects and where ample patient education and support are also available (a list of U.S. clinics is at http://www.achaheart.org/for_members/clinicdirectory/index.php).
- Aortic valve is normal but ascending aorta is dilated, i.e., aortic size index >2 cm/m². You need aggressive control of blood pressure with target 110/70 mmHg. I strongly favor angiotensin receptor blockers as a first line of treatment with addition of calcium channel blocker if needed. I recommend follow-up by cardiology every 6–12 months to assess stability of aortic dimensions. If stable over a period of years then adjust frequency per your cardiologist suggestion.
- Bicuspid aortic valve and dilated ascending aorta- this seems to be the highest risk situation for potential aortic complications. Recommendations include:

a)   Patient & family education about signs/symptoms of aortic dissection (chest or back pain, feeling like you are having a "stroke", cold sweat) and the need to seek immediate care at a major medical center (aortic dissections are usually able to be surgically repaired if diagnosed within ~ 24 h after onset).

b)   Wear a medic alert medallion/bracelet "aortic aneurysm" – this will help emergency room staff to immediately order the correct test (MR or CT of the aorta) to get the right diagnosis.

c)   Regular cardiology follow-up every 6–12 months or more frequently as needed with specialist in Congenital Heart Disease.

d)   Medical treatment using angiotensin system blocker to potentially protect aorta and maintain blood pressure ~110/70.

If biscuspid aortic valve function deteriorates to the point where surgical intervention is contemplated, consider repairing the aortic aneurysm at the same time

Cardiac magnetic resonance

Cardiac magnetic resonance imaging has many advantages over echocardiography. Firstly, it clearly visualizes the entire thoracic aorta and all the great vessels. Frequently it is perfectly obvious in viewing the entire aortic arch that the ascending portion is dilated relative to the rest of the structure, and this overview is never seen by echocardiography. Secondly, unsuspected abnormalities of the aortic arch and descending aorta may be detected (as in the coarctation noted in Figure 4). Thirdly, about 15% of individuals with Turner syndrome have abnormal pulmonary vessels that may require surgical intervention and these are rarely detected by echocardiography. Last but not least, the aortic valve may be clearly viewed in most cases, and its opening

examined for signs of abnormal blood flow. The disadvantages are that it is more expensive and is slower to acquire the images. However, it is absolutely essential to get a good cardiac magnetic resonance evaluation to know what you are dealing with. Subsequent follow-up, e.g., bicuspid aortic valve function or aortic diameter, can usually be accomplished by cardiac echo. Cardiac computer tomography provides anatomical resolution and detail similar to MRI or magnetic resonance, but also delivers a substantial amount of radiation, so is reserved for emergencies or for patients that cannot do magnetic resonance.

Figure 4

A moderate coarctation (white arrow) was detected by cardiac magnetic resonanceMR imaging using gadolinium as a contrast agent (MR angiography or MRA). This woman had severe hypertension for many years, but the coarctation was not detected on echocardiogram, and the blood pressure in her legs was never checked until her evaluation at the NIH.

Prevalence of CHD in Turner syndrome

In the NIH study population, 30% of about 400 participants have an abnormal aortic valve. Only about half of those with bicuspid aortic valve also have a dilated ascending aorta. Of those with a normal aortic valve, about 10% have a dilated aorta. Of the whole group, about 50% have some cardiovascular anomaly that makes us think the cardiovascular system is "affected" by the Turner genetic deficiency. For the other 50%, even after the most comprehensive imaging and examination, we are able to find no evidence of cardiovascular abnormality. We are following the whole group longitudinally, so in 5–10 years will have a better idea if the non-affected continue their apparently normal course. Some of the case reports of aortic dissection in women with Turner syndrome have mentioned that the patient was "not known" to have congenital heart disease, and thus some reviewers conclude that aortic dissection may occur in an individual with no congenital heart disease. This is not a correct conclusion, since routine evaluation for congenital heart disease in many of the historic published cases involved only physical examination, and more recent cases only transthoracic echocardiography done in a community setting (i.e., not in a center specializing in congenital heart disease). This is in our experience frequently very uninformative and certainly does not rule out the presence of significant congenital heart disease. It seems likely that the risk for serious aortic complications affects those women with underlying abnormal aortic anatomy. All

of seven recent, well-documented cases about which I have extensive knowledge had clear, pre-existing aortic defects.

Activity limitations

For Turner syndrome individuals that have congenital heart disease, we advise activity restrictions similar to those for Marfan syndrome. Heart healthy exercise involves aerobic activities that get the heart pumping faster and work many of the body's muscles in a balanced way. At the same time, healthy exercise should not over-stress skeletal structures to avoid promoting injuries and accelerated development of degenerative joint disease and arthritis that puts an end to healthy exercise prematurely. Thus parents should encourage free play activities that promote physical activity, hobbies that promote structured & supervised exercise and team sports that are for fun rather than highly competitive. All types of dance provide exercise and may help with social skills and self esteem as well. Swimming, brisk walking, hiking, cycling, golf and tennis are also generally quite safe and beneficial.

Strenuous activities that produce high intrathoracic pressure are to be avoided: Weight-lifting, gymnastics, skiing, sky-diving and some martial arts. Hi-impact, collision prone, intensely competitive sports should be discouraged as well.

Pregnancy

Pregnancy imposes a major strain on the cardiovascular system which may be very dangerous for women with Turner syndrome. The incidence of aortic dilation definitely increases during pregnancy, and a high rate of catastrophic aortic dissections has been reported in recent years. In my view, women with a known cardiovascular defect should not attempt pregnancy because the risk of a fatal or crippling complication that would prevent mothering the ensuing baby is too high. For those women that have no apparent congenital defects after a comprehensive evaluation including cardiac magnetic resonance, there still seems to be higher than usual risk for hypertension, diabetes and eclampsia indicating that pregnancy should be under-taken only after the most careful consideration and discussion with family members.

Acknowl-edgements

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High blood pressure

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High blood pressure in Turner syndrome

High blood pressure is seen more frequently in Turner syndrome than in other girls and women. About 1-in-3 young girls and 1-in-2 adults with Turner syndrome have high blood pressure that requires treatment (*hypertension*).

Limits for high blood pressure

High blood pressure is defined as an elevation of the highest blood pressure measurement (*systolic blood pressure*), of the lowest blood pressure measurement (*diastolic blood pressure*), or of both blood pressure measurements (Figure 1). A high blood pressure can be present during the whole day or it can be limited to the wake hours or nights. In order to eliminate the risk for incorrect treatment, the classification of high blood pressure will often require repeated measurements to ensure that the increase observed is a true, persistent increase.

The limit for high blood pressure is 140/90 mm Hg, which is derived from general population studies. If the blood pressure is higher than this, medical treatment is recommended in order to prevent any harmful consequences of the elevated blood pressure. If cardiovascular disease (including dilation of the aorta), diabetes, or kidney disease, then starting blood-pressure reducing measures at blood pressures below 140/90 mm Hg is recommended. The presence of cardiovascular risk factors such as smoking, high cholesterol levels, or a history of cardiovascular disease can also warrant treatment at levels below 140/90 mm Hg.

The cause of high blood pressure

The cause of high blood pressure in Turner syndrome is unknown. However, this high blood pressure is thought to be triggered by the same factors as those causing high blood pressure in the general population where no specific triggering factor is known (*essential or primary hypertension*). If we look at everybody, regardless of whether they have Turner syndrome or not, then this type is present in nine out of ten people with high blood pressure.

The rarer type, in which the high blood pressure is due to other diseases (*secondary hypertension*), is not common in Turner syndrome. The specific causes in this case could be kidney disease, hormonal disturbances, or tumours. Nevertheless, there is one possible triggering disease that is seen more frequently in Turner syndrome and that is constriction of the aorta (*coarctation*). This aortic disease increases the risk for high blood pressure but the causative mechanism is currently unknown.

Exact knowledge of the triggering mechanism in high blood pressure is lacking in Turner syndrome. Even though a triggering factor for the high blood pressure seen in Turner syndrome is not known at present, it is distinctively different from similar disease in other girls and women. This is because high blood pressure not only occurs more frequently but also in a significantly younger age group than in the

general population. Furthermore, the elevated blood pressure occurs more frequently in the lowest blood pressure (*diastolic hypertension*) in Turner syndrome. In addition, the ability to vary the blood pressure at transition from night to day is reduced in Turner syndrome. This could be due to a changed function of the autonomous nervous system that regulates unconscious processes in the body such as heart rhythm and digestion. The disturbance in the function of this nervous system is similarly presumed to cause the higher average pulse in Turner syndrome. The higher average pulse and the impaired ability to spontaneously reduce the night blood pressure indicate a high risk for cardiovascular disease.

Types of high blood pressure

There are two distinct forms of high blood pressure:

- *Benign hypertension.* The most common form, also seen most frequently in Turner syndrome, with a moderate elevation of blood pressure. It normally develops slowly. This blood pressure disease is associated with a risk for complications that stretches over months to years. The blood pressure should be reduced to a normal level within a few weeks in order to avoid harmful effects. This type of high blood pressure is mostly not noticeable but, at times, non-specific symptoms such as tiredness or dizziness can be present. In cases of long-term, untreated high blood pressure, symptoms may occur as a result of harmful effects on the heart and circulation.

Figure 1

About blood presure

Blood pressure

When the left half of the heart contracts, oxygenated blood is pumped out into the circulation. This generates a pressure that forces the blood through the artries to the tissues of the body. This pressure varies during the cardiac cycle. The pressure is highest just after the heart has pumped the blood out into the circulation (felt over an arteries as a pulse beat) and lowest when the heart is refilling with blood, where the blood flows into the left chamber of the heart from the pulmonary circulation.

Everybody has a blood pressure. It is determined using the highest pressure *(systolic pressure)* and the lowest pressure *(diastolic pressure)*. The highest pressure is the peak of pressure development when the blood is forced out into the body, and the lowest pressure is the lowest pressure when the heart fills with blood. Blood pressure is written as the highest pressure over the lowest pressure and is given in mm Hg, for example 120/80 mm Hg.

The most important factors contributing to the blood pressure are the force with which the heart muscle contract, and the resistance given by the blood vessels to transporting the blood from the heart and around the body to the organs.

Measurement of blood pressure

Blood pressure is measured on the upper arm using an inflatable blood pressure cuff. This enables measurement of both the high pressure *(systolic blood pressure)* and the low pressure *(diastolic blood pressure)*. Sometimes the blood pressure is different in the two arms, but this is quite normal. If the difference is large, constriction of the aorta *(coarctation)* should, however, be considered. Because of the natural, small differences, the initial blood pressure measurement is made on both arms. After this, the arm that initially gave the highest measurement is always used.

Some situations can affect the blood pressure (stress, caffeine, body position, measuring device, etc.). It is therefore important the measurement is made in the correct situation and, in cases of doubt, several times. It can be difficult to measure blood pressure correctly, so is recommended that qualified health personnel take measurements at regular intervals.

Blood pressure measurements can be performed with different methods:

• Office blood pressure, where the doctor or nurse performs repeat measurements in the upright sitting position after a short resting period. These measurements can indicate the blood pressure level but they will not always be able to definitively confirm a suspected high blood pressure. The diagnosis of high blood pressure will therefore often require repeat elevated blood pressure measurements at different consultations. In some cases, the blood pressure will, however, be elevated to an extent where repeat measurements are unnecessary.

• Home blood pressure measurement, where the patient herself measures the blood pressure during the day. This method is widely used to investigate the presence of high blood pressure. However, it has not been used in any of the studies that have investigated the effects of blood pressure lowering treatment. This makes it more difficult to use to monitor the effect of treatment. The method also faces the drawbacks that the precise levels for elevation of the blood pressure have not been established for this method and it only informs of the daytime blood pressures.

• Ambulatory blood pressure measurement, where the blood pressure is automatically measured and recorded by a transportable, small computer carried in a belt or in a small bag around the neck. It measures both day and night blood pressures. This method is generally considered optimal in terms of diagnostics and monitoring of the effect of blood pressure lowering treatment. Also, most studies on the effect of blood pressure lowering therapy use this method nowadays making it easy to link daily clinical practice to results seem in research. It is therefore widely implemented as the first-choice-method for blood pressure measurement.

- *Malignant hypertension.* This is a rarer form. It is more progressive and manifests as an extremely high blood pressure. The blood pressure should be lowered while the patient is hospitalised, because the elevation in the short term can result in permanent damage. This highly serious hypertension can manifest as headache, sleepiness, confusion, tingling in the hands or feet, nosebleeds, headache or severe shortness of breath.

Risks at high blood pressure

The blood pressure should be checked regularly, because a normal blood pressure can become elevated over time. If high blood pressure is diagnosed, it is necessary to focus on effectively reducing the blood pressure to a normal level, as untreated blood pressure overloads the circulatory system and the heart. And in Turner syndrome it is particularly important to prevent development of cardiovascular diseases because these often occur in a younger than normal age group.

High blood pressure plays a major role to the increased risk in Turner syndrome for:
- Dilataion of the aorta with a risk of rupture
- Blood clots or haemorrhage in the brain
- Blood clots in the heart
- Stress on the heart pumping action.

At the same time, high blood pressure increases the risk for:
- Kidney disease

- Atherosclerosis of the circulatory system (hardening of the arteries)
- Eye disease.

The timeline for development of these complications often extends over years. It is however important to start preventive measures before the high blood pressure results in damage from many years of harmful effects on the heart and circulation (Figure 2). Damage to the eyes, kidneys, blood vessels, and heart is often irreversible. Late treatment can limit further progression, but the damaging effects of long-term untreated high blood pressure often do not disappear and therefore comprise a future risk for symptom-producing disease. Even though this high blood pressure frequently does not produce symptoms, the damaging effects can be critical for the quality of life and life expectancy. It is therefore important to measure blood pressure regularly so that treatment can be started before complications arise.

Actions to combat high blood pressure

Certain factors increase the risk for high blood pressure. These include a familial tendency to high blood pressure, overweight, smoking, alcohol abuse, a diet high in fat and salt, lack of exercise, diabetes, kidney disease, and certain medicines. The individual can therefore help to bring down their blood pressure through:
- Not smoking
- Losing weight
- Exercise
- A reduction of alcohol consumption

- A healthy diet (low in salt and fat).

In most cases, it will be necessary to supplement the personal efforts with blood pressure reducing treatment. There are several types of blood pressure reducing medicines. These are: 1) ACE inhibitors and angiotensin receptor blockers, 2) beta-blockers, 3) diuretics, 4) calcium channel blockers, and, 5) others, less commonly used. Overall, these groups have a comparable efficacy with regard to lowering blood pressure but the mechanisms of action are different. Therefore, the side effects are different, as are effects other than the direct, blood pressure lowering effects. Individual treatment must be chosen taking age, any other diseases, or other medicines taken into account.

Often, more than one preparation is necessary to lower the blood pressure sufficiently in order to effectively reduce the risk for complications of high blood pressure. Blood pressure disease is frequently a life-long phenomenon. Therefore a high blood pressure that is treated and lowered to an optimal level is interpreted as a sign of an effective treatment rather than

Figure 2

Changes in the retina

Stroke as a result of bleeding or blood clot

Dilatation of the aorta and rupture

Atherosclerosis with a risk of stroke

Coronary sclerosis with a risk of blood clot in the heart and heart failure

Kidney disease

Atherosclerosis with hardening of the arteries
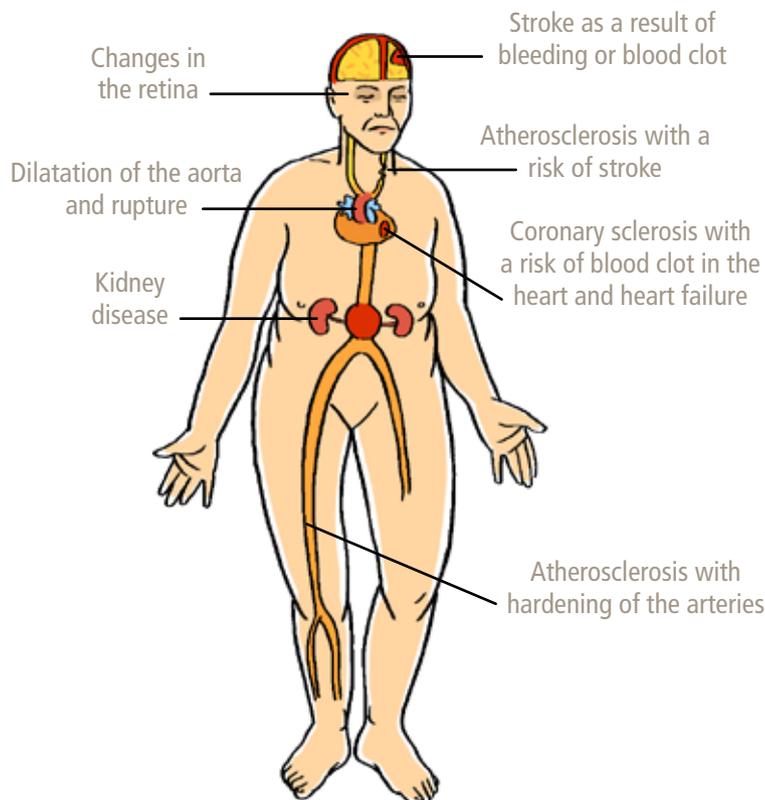
a sign that the disease is about to disappear. The level to which the blood pressure should be reduced is individual, and will involve an assessment of any damage caused by the high blood pressure and other factors such as aortic dilation, heart disease, or kidney disease. Thus, there are no precise limits to which the blood pressure should be reduced, but too abrupt a reduction will most frequently manifest as dizziness and tiredness. The treatment can be given less intensively by reducing the dose or the number of preparations.

There have been no studies in Turner syndrome on the optimal blood pressure reducing treatment. Therefore, the four types of treatment can be considered to be equally good. But one study indicates that a medicine belonging to the beta-blocker group is particularly effective in preventing aortic dilation. Recent research has, however, indicated that angiotensin receptor blockers may be better in the prevention of rupture of the aorta. Either of these medications is therefore often recommended when treating hypertension in Turner syndrome, and particularly if there is a state of aortic dilation. It is hoped that new knowledge will become available in the near future on the optimal treatment of Turner syndrome.

Blood pressure check-ups

The risk for developing high blood pressure means that blood pressure must be checked not only when Turner syndrome is diagnosed but also afterwards at regular intervals. This will prevent the occurrence of harmful effects from unnoticed and untreated high blood pressure.

It is important to continue with regular follow-ups even when the blood pressure is well-controlled. It can increase over time in spite of treatment. In addition to checking blood pressure, these follow-ups should also assess the presence of any damage caused by a high blood pressure (Figure 2). This should be planned in collaboration with the treating doctor and may involve blood tests, electrocardiograms, urine tests, heart scans, eye examinations and other tests. The follow-ups will furthermore focus on other risk factors for cardiovascular disease such as cholesterol levels and smoking.

Supplementary reading

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Thyroid disease in Turner syndrome

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Thyroid gland

Basics about the thyroid gland

The thyroid gland is situated on the front of the neck (Figure 1) and the gland produces hormones which regulate the body metabolism. All cells are influenced by these hormones. One could compare the thyroid with a thermostat regarding temperature, motility of the gut, cardiac, renal, liver and nervous function. The action of thyroid hormones are in layman terms called "metabolism". The names of the hormones are thyroxine (T4), and triiodothyronine (T3). The thyroid gland is under influence of the thyroid stimulating hormone (TSH) coming from the pituitary gland The pituitary gland is positioned under the brain and produces several different hormones (Figure 2).

The regulation of thyroid hormones is based on a feed back system, so when the concentration of T4 becomes elevated, TSH decreases in order again to suppress both the production and the release of more of the T4 from the thyroid gland. This is called a negative feed-back system, and such systems regulate most of the other hormones in the body (Figure 3).

When the thyroid gland does not produce enough T4, TSH increases in order to orchestrate the production of T4. Eventually, if the thyroid gland cannot produce enough T4, primary hypothyroidism develops. This is also called myxedema or hypothyroidism or "low metabolism" (Figure 4). On the contrary, when T4 increases, TSH decreases to almost undetectable levels and the stimulation of TSH from the pituitary is completely gone. However, often the thyroid gland becomes autonomous and produces increasingly high levels of T4 and T3. This is called hyperthyroidism or in layman terms "elevated metabolism".

T4 and T3 are transported in the blood bound to proteins and exert their effects after binding to receptors in the target cells in the body. Sometimes the thyroid gland begins to grow

Figure 1

The location of the thyroid gland (in red) below the larynx on the front of the neck and surrounded by the great vessels.

A Carotis communis

A Tyreoida superior

A Tyreoida inferior

A Subclavia

V Jugularis interno
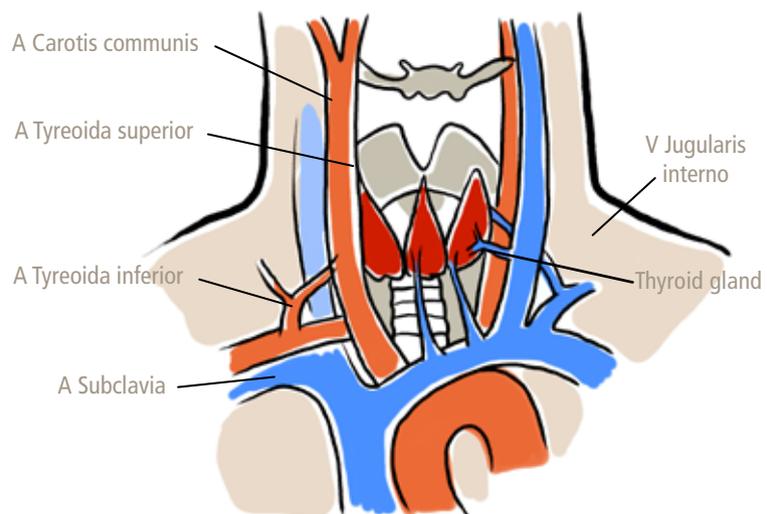
Thyroid gland

Figure 2

The location of the pituitary gland and its regulating hormones. From Acromegaly, Editor A Harris, Sandoz Pharma Ltd, Basle 1991.
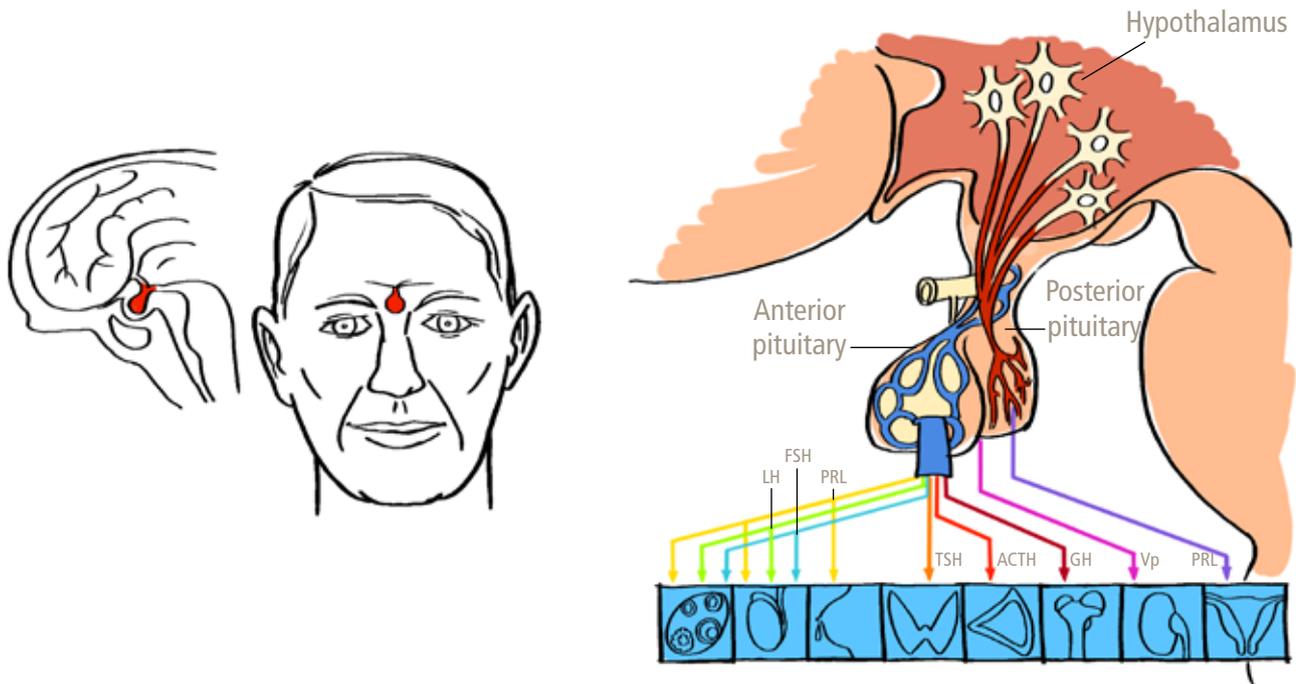
when TSH tries to increase the T4 hormone production (hypothyroidism) or if the T4 is autonomically increased (hyperthyroidism) and goiter (thyroid enlargement) develops. It is important to emphasize that goiter can be present with both hypo- and hyperthyroidism, as well as completely normal thyroid function.

Primary hypothyroidism/ myxedema/"low metabolism"

Primary hypothyroidism is the most common thyroid disease in the general population afflicting about 2–5%, with a female prepon-derance (4/1 Female/Male) (1). The disease is frequently found in several members of the same family due to an autosomal genetic form (2). The pathogenesis can be congenital or due to severe iodine deficiency, autoimmune disease, surgical excision, radioactive iodine treatment, external radiation, drugs like lithium (used for depression) and amiodarone (used for heart diseases) as well as other diseases. Thyroid peroxidase (TPO) on the cell surface catalyses the production of T4 and T3, (Figure 5). Iodine is important in

Figure 3

The feedback regulation of the thyroid hormones from the pituitary to the thyroid gland. TSH: Thyroid stimulating hormone, TRH: Thyroid releasing hormone.
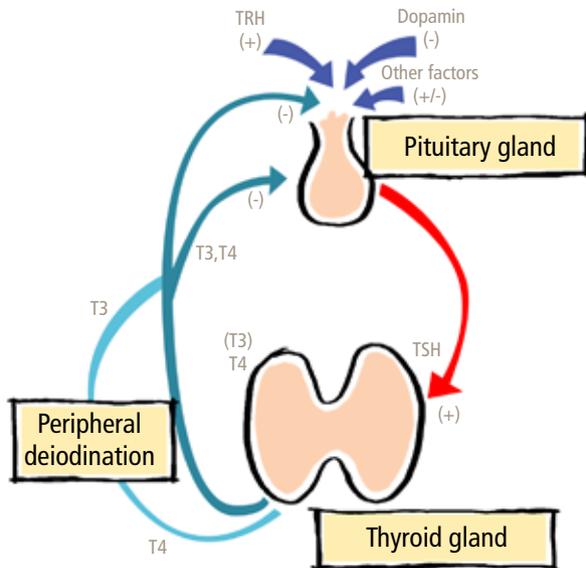
## Figure 4

Illustration of a woman developing hypothyroidism. Caption from the publication: Ord, WM. On myxoedema, a term proposed to be applied to an essential condition in the "cretinoid" affections occasionally observed in middle-aged women. Medico-Chirurgical Trans 1878. 57-61

Figure 5

The regulation of thyroid hormones in the thyroid cell. Tg: Thyreoglobulin, TPO: Thyroid peroxidase.
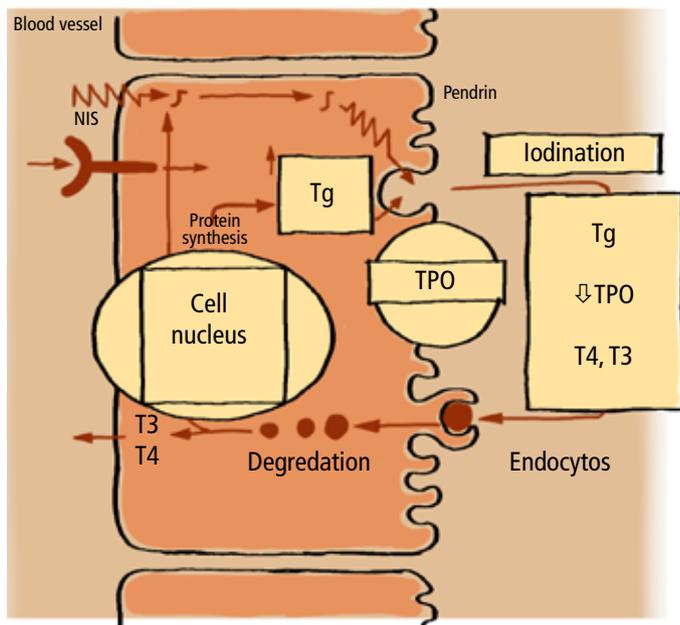
the production of T4 and T3, however too high doses of iodine can cause problems as well – see more details later.

The most common form of hypothyroidism is autoimmune thyreoditis (Hashimotos thyroiditis). It starts with an often silent inflammation of the thyroid gland, completely unnoticed by the patient. By the time the T4 producing cells have been destroyed, autoantibodies against TPO have developed. The level of TPO antibodies (reference <100 kU/l) is used in the diagnosis of hypothyroidism and strengthens the indication for starting substitution with thyroxine at a fairly early level of decreased free T4 and slightly elevated TSH, often named subclinical hypothyroidism. When the level of TPO antibodies is elevated, thyroxine substitution is usually required life long.

The carrier proteins for T4 and T3, thyroid-binding globulins (TBG), can be influenced by other diseases or drugs. Liver and kidney diseases can lead to decreased protein levels and hence, to low levels of thyroid hormones. Antiepileptic drugs lead to decreased free T4 levels in this way. During pregnancy the TBG increases. The same phenomenon is seen with estrogen hormone substitution (HRT) and contraceptive pills. The substitution dose of thyroxine has usually to be increased during pregnancy and HRT. Thyroid hormones and TSH can also be affected by "non-thyroid illness" with an initial lowering of all hormones and then an increase depending on the severity of the illness.

Hyperthyroidism

An autonomic increase in thyroid function due to a localized area called toxic adenoma, or hyperfunction of the whole thyroid gland leads to abnormally high T4 and T3 concentrations. This is called hyperthyroidism, thyreotoxicosis or Graves´ disease. The disease often produces immunoglobulins antibodies against the TSH receptor are commonly found in the circulation, so called thyroid receptor antibodies (TRAb) (hyperthyroidism can also occur after too high thyroxine substitution and iodine containing drugs as amiodarone (used for different heart diseases). Conditions called subacute or acute thyroiditis can occur after giving birth, here hypothyroidism can develop after some months. TRAb and TPO antibodies can be elevated simultaneously. Hyperthyroidism can occur in both young and elderly people. The prevalence is 1% in the population and more common in women (10/1 Female/Male).

Symptoms of hypothyroidism

Hypothyroidism during fetal life can lead to kretinism which is an irreversible mental and physical retardation. This is due to lack of iodine or thyroxine during the fetal stage. In young and adults hypothyroidism has often diffuse symptoms with unexplainable tiredness that may bring the person to the doctor, if ever (Figure 4). Usually, the history of symptoms spans gradually over many years and therefore hypothyroidism is often diagnosed when thyroid hormones are checked routinely and not always aiming at that diagnosis. Somehow, many patients get used to a state with

reduced thyroid function, probably because the function very slowly decreases. Some patients experience dry skin, dry hair, constipation, feeling chilly, increase in body weight, decreased initiative and mood, depression etc., all in variable degree; the symptoms reverse on proper treatment (Figure 6). Untreated hypothyroidism can lead to elevation of serum cholesterol, which decreases when thyroxine substitution is adequate. A more rapid progress of hypothyroidism can develop after a subacute thyroiditis, mainly after giving birth. The thyroiditis patient can have symptoms like a swollen and painful thyroid gland and difficulties to swallow during some weeks, as well as flu-like symptoms.

Symptoms of hyperthyroidism

The diagnosis of increased thyroid metabolism is often easier to detect. Patients are feeling warm, can have palpitations, tachycardia, loss of body weight, sleep

disturbances, increased activity in general, resulting in tiredness. Goiter and eye symptoms can develop. These are signs of Graves´ disease with ophtalmopathy like extruding, red and irritating eyes, see figure 6 below.

Figure 6

Some examples of symptoms of hypo- and hyperthyroidism without frequency order.

Hypothyroidism	Hyperthyroidism
Tiredness	Increased activity
Feeling chilly	Feeling warm
Weight gain	Weight loss
Obstipation	Diarrhea
Depression, low mood, memory and concentration disturbances	Irritation, aggression, concentration disturbances
Muscular weakness, stiffness	Muscular weakness, osteoporosis
Bradycardia, low pulse rate	Tachycardia, palpitations
Dry hair and skin	Hair loss, thin nails
Swollen around the eyes	Exophtalmus, red and irritating eyes
Goiter	Goiter
Increased serum cholesterol	Decreased serum cholesterol
Decreased blood glucose	Increased blood glucose

Turner syndrome

Thyroid disease in Turner syndrome

Hypothyroidism of autoimmune origin is the most common endocrine disease, except ovarian insufficiency, in Turner syndrome women. Among all females with Turner syndrome 20–50% have the disease, and it occurs also during childhood (3–9). Diagnosis of hypothyroidism started at age 7 in one study (8) and 50% were younger than 18 years in another (5) while the number of new cases with hypothyroidism increased throughout the entire adult life in the adult Turner syndrome cohort with an annual increase of 3% (9–10) (Figure 7). Probably, HRT has no influence on the development of hypothyroidism as estrogen was not given to the small children (8) and HRT was stable and unchanged in the adult life of the Turner syndrome women (10). The hypothyroidism is usually of autoimmune origin and 40–50% of hypothyreotic Turner syndrome women have elevated TPO levels (4; 9–11) (Figure 7). However, as in all other persons, not all Turner syndrome girls and women develop TPO elevation in spite of a fully developed hypothyroidism (8–10).

A karyotype should be checked and Turner syndrome suspected in children with hypothyroidism if short stature, hearing impairment and/or cardiac anomalies are present. In adults, Turner syndrome should be suspected if hypothyroidism develops in women with secondary amennorrhoea or premature ovarian failure and especially if more Turner syndrome stigmata are present (12–13).

Hypothyroidism is also one of the most common hormonal dysfunctions in women of the general population, affecting 2–5% of the grown up population, indicating a link with the X-chromosome itself (1). A positive family history increases the risk for hypothyroidism in women (2). Wilson et al. found elevated TPO in both Turner syndrom patients and their mothers

Figure 7

Prevalence of hypothyroidism in women with Turner syndrome <31 years, 31-49 years and >49 years (n=171). The percentage of Turner syndrome women with elevated thyroid peroxidase antibody titer (TPO) is given in each bar (10).
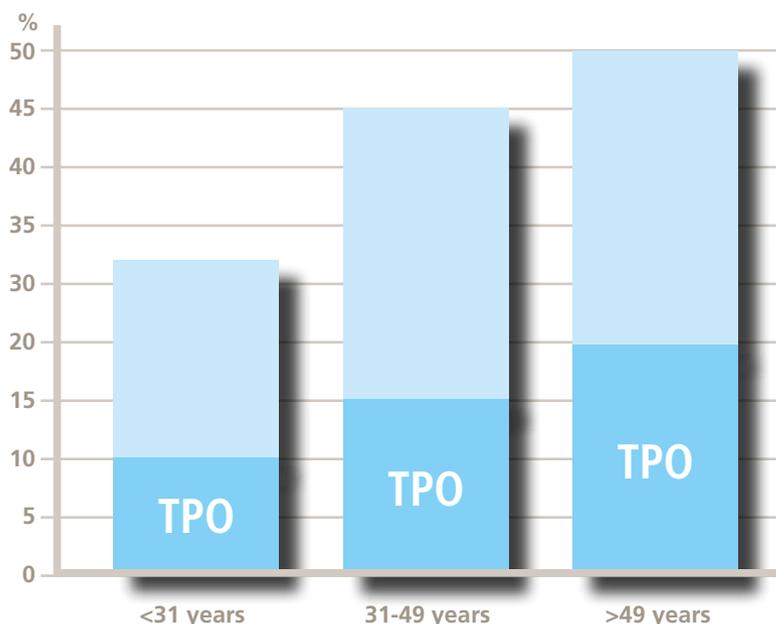
(11). However, a positive family history was not found in a Swedish study in adult Turner syndrome (9).

It has been suggested that there is a casual relationship between aberrations of the X-chromosome, and especially in women with isochromosome X, and the risk of autoimmune hypothyroidism (4; 7; 11; 14). The 45,X/46,XX mosaic Turner syndrome girls did not differ from control girls (4). Other authors found no difference between the prevalence of hypothyroidism in Turner syndrome women with 45,X and 45,X/46,XX mosaicism, respectively, analysed with conventional chromosome analysis and by Fluorescence In Situ Hybridization (FISH), which is a more advanced method of examining the chromosomes, respectively (5; 7; 9). Neither growth hormone nor HRT did affect the incidence of hypothyroidism (4–5).

Elevated TPO was present in 30% of all females with Turner syndrome, compared with 7% in the female population (15) and in 37% of Turner syndrome with hypothyroidism in one study (9). After 5 years follow-up, another 15% developed hypothyroidism giving an annual incidence of 3%. Altogether, 45% had hypothyroidism at mean age of 38 years. In females with Turner syndrome above 50 years of age 50% had hypothyroidism (10) (Figure 7). Hence, almost every other Turner syndrome woman will probably develop hypothyroidism and those with elevated TPO levels are at highest risk.

Hypothyroidism and other autoimmune and metabolic diseases in Turner syndrome

Autoimmune diseases in general, are more common in women than in men. Autoimmune hypothyroidism is usually connected with other autoimmune states like vitamin B12 deficiency due to pernicious anemia, celiac disease (allergy to gluten), type I diabetes, primary adrenal deficiency (called Addisons disease which is the inability to produce cortisol) and alopecia (balding, which can be partial or complete). Almost all of these states have autoantibodies for their cell receptors or enzymes. Some of the most common links of hormonal and metabolic aberrations in Turner syndrome are listed in figure 8. Fine motor function was lower in females with Turner syndrome with, than in those without hypothyroidism (16). Diabetes mellitus in Turner syndrome is mainly type II, and

Figure 8

Metabolske og andre hormonale afvigelser, der kan kobles til hypothyroidisme i Turner syndrom.

Hypothyroidism linked to other aberrations in Turner syndrome

Obesity

Abdominal fat distribution

Impaired fine motor function

Vitamin B12 deficiency

Coeliac disease

Diabetes mellitus

Elevated liver enzymes

Elevated blood lipis
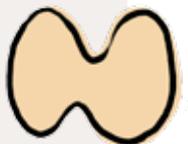
possibly hypothyroidism could lead to increased body weight and thereby precipitating diabetes.

In the Swedish cohort of adult Turner syndrome there was a positive correlation between TSH and liver enzymes, which in turn, were positively and independently correlated with serum cholesterol. Almost half of the adult Swedish Turner syndrome population developed pathological liver enzymes as well as hypothyroidism during a five-year follow-up (17) (Figure 9).

Care and treatment of hypothyroidism in Turner syndrome

In the Swedish Turner syndrome academy we have stated national guidelines for care and treatment of children and adults with Turner syndrome since 1993. A special schedule is followed regarding the most common examinations in Turner syndrome (Figure 10). These recommendations are similar to the international guidelines decided by The Turner Syndrome Consensus Study Group, at the Turner Consensus meeting 2006 (10; 18). As seen in figure 10, thyroid hormones are checked yearly after transition from the children clinic. Many of the cases with hypothyroidism are subclinical, with TSH 2–4 mU/l, but substitu-

Figure 9

Prevalence, in frequency order, of different hormonal and methabolic abberations in women with Turner syndrome in Sweden during 5 years follow-up.

	Start	After 5 years
Elevated liver enzymes	36	53
Hyperthyroidism	22	31
Vitiman B12 deficiency	15	10
Obesity	11	16
Diabetes mellitus type II	3	3,5
Celiac disease	2	2

%
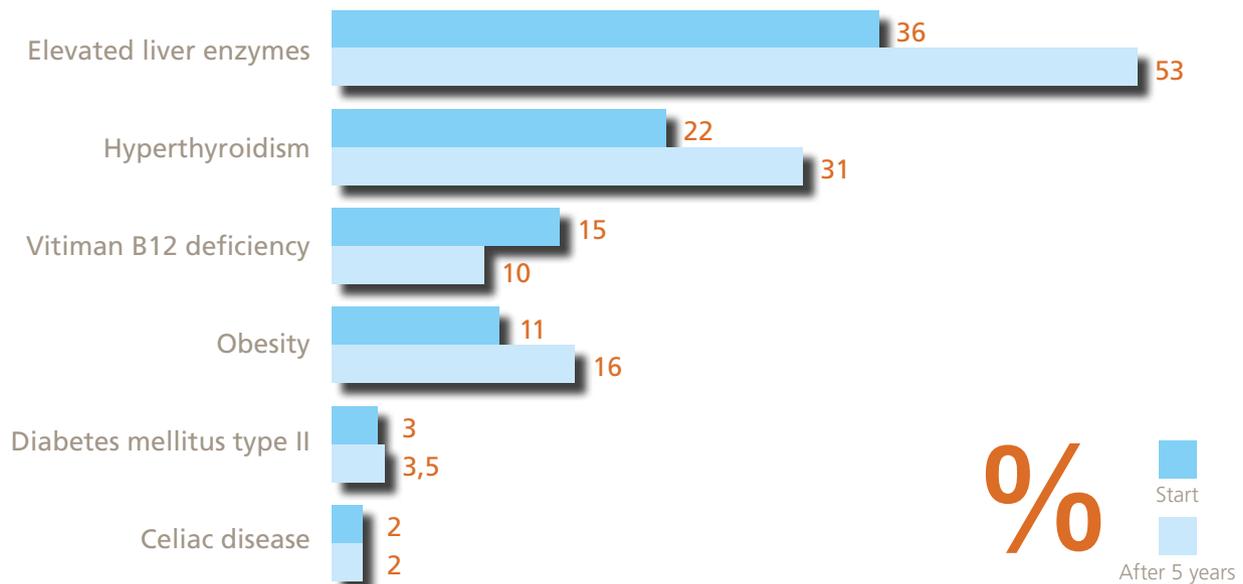
tion is started early to avoid further weight gain and hopefully diminish the risk for development of factors included in the metabolic syndrome (Figure 8). It is not clear whether elevated liver enzymes will develop due to untreated hypothyroidism but it cannot be excluded, as the correlation between liver enzymes and TSH was positive (17). Furthermore, elevated liver enzymes correlated with serum cholesterol independently of other factors. The pathogenesis could be a non-alcoholic liver steatosis, which is also called "fatty liver infiltration".

HRT is nowadays used in >90% of Turner syndrome women from puberty induction and onwards. Estrogen and oral contraceptives increase the TBG and the amount of detectable free T4. This might explain why many Turner syndrome women have increased TSH but fairly often maintained, normal free T4 concentrations.

Treatment of hypothyroidism in Turner syndrome

The doses of thyroxine substitution are similar to those recommended in the non-Turner syndrome subjects with an initial dose of 25–50 ug daily and an increase during the first year. The final dose is often 100–150 ug/day. Some females with Turner syndrome do need doses up to 200 ug/day. The TSH concentration should be around 0,1–1 mU/l and the free T4 levels around 20 pmol/l.

Figure 10

Guidelines for the transition from the paediatric to the adult clinic and follow-up of girls and women with Turner syndrome in the Swedish Turner Academy at all University Hospitals in Sweden.

Specialist ⬍ Year ⇨	1	2	3	4	5	6	7	8	9	10
Gynaecol	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Audiogram	✓				✓					✓
Blood pressure	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Echocardiogram	✓				✓					✓
Thyroid function	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bone mineral density	✓				✓					✓

Hypothyroidism and pregnancy in Turner syndrome

Hypothyroidism in pregnant Turner syndrome women should be treated in the same way as in non-Turner syndorme women. The thyroxine dose is adjusted so the TSH levels is <2,5 mU/l. It is recommended to check blood samples every 6th to 8th week of the pregnancy. As most of the Turner syndrome pregnancies are planned and assisted, thyroxine substitution should be considered generously in subclinical cases 6–12 months before pregnancy induction in order to avoid a negative influence on the fetus. An increase with 25 ug thyroxine before induction of pregnancy is recommended in Turner syndrome with already treated hypothyroidism. There is an increased need for thyroxine during the fetal period (Figure 11), and especially during the first trimester of the pregnancy when all fetal organs develop.

Figure 11

The fetal circulation during pregnancy influences the thyroid gland via the human chorion gonadothropin (hCG). A higher amount of thyroxine is needed from the maternal blood. Reproduced by courtesy from Professor Ernst Nyström Editor, Nycomed AB and Media center TVB AB in Tyroideasjukdomar hos vuxna 2007.
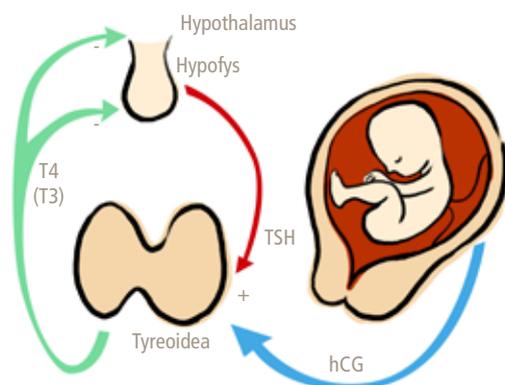
Hyperthyroidism and goiter in Turner syndrome

Hyperthyroidism, mainly Graves´ disease, is less common in Turner syndrome than hypothyroidism: 2–3% vs 1–2% in the female population irrespective of a positive family history (2; 7–9). Goiter due to Graves´ or hypothyroidism is also uncommon (9). However, Radetti et al noticed goiter in 39% of young females with Turner syndrome by ultrasound (5) and mainly due to hypothyroidism. Treatment for Graves´ disease should follow the same guidelines as in the non-Turner syndrome population with thyreostatics (drugs to reduce the excessive levels of T3 and T4), surgery or radioactive iodine and symptomatic treatment with beta-blocking agents. Radioiodine is contraindicated at pregnancy and should be avoided if pregnancy is planned. Goiter is treated by surgery if subjective problems are present and if not reduced after thyroxine substitution in hypothyroid patients. In case of goiter a biopsy for cytogenetic test is performed (Figure 12).

Figure 12

Biopsy of the enlarged thyroid gland, goiter. Reproduced by courtesy from Professor Ernst Nyström Editor, Nycomed AB and Media center TVB AB in Tyroideasjukdomar hos vuxna 2007.
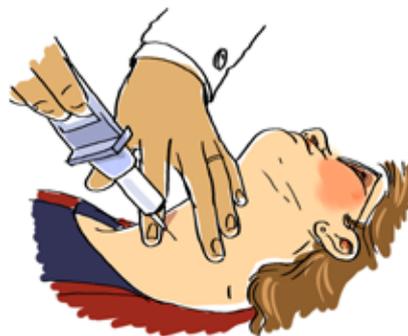
Conclusion

Hypothyroidism is common in Turner syndrome and independent of karyotype. Almost every 2nd Turner syndrome woman will probably develop hypothyroidism and those with elevated TPO are at the highest risk. It is recommended to check the thyroid function annually in women with Turner syndrome.

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Osteoporosis in Turner syndrome

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Background and definitions

Bone is made up from a combination of calcium and minerals together with a protein matrix which is mainly made up of collagen. Osteoporosis describes the situation where the amount of both calcium and collagen in the bone is reduced causing an increase in the risk of fracture.

Two main cells contribute to the strength of bone. Osteoblasts make the collagen matrix and the enzyme alkaline phosphatase that drives the laying down of calcium. Osteoclasts dissolve bone and this "resorption" allows for bone to be remodelled. The strength of bone over time will depend on the balance between the laying down of new bone and the resorption of old bone. The skeleton reaches a peak of "bone mass" between the ages of 25 and 35. As bone is lost with age, the amount of calcium in a given volume of bone decreases. The amount of calcium in bone is measured as the density of bone usually by X-ray called DEXA or DXA scanning.

Figure 1 shows a bone density DEXA scan for a woman with Turner syndrome with individual measurement of the spine and the hip plotted against a reference range for women without Turner syndrome.

Bone fractures in Turner syndrome

The main reason why osteoporosis is so important is because it is one of the major risks for breaking a bone. The second major risk factor for bone fracture is the tendency to fall. Falls can be more common in women with low muscle strength or who are taking some medication such as sedatives or tablets to lower blood pressure.

A fracture of a hip can be a major acute event in an elderly person and may result in the need for a hip replacement. A fracture of the vertebrae can lead to curvature of the spine, loss of height and acute pain from nerve entrapment.

Women with Turner syndrome have an increased risk of fracture of a bone (1) although some studies have reported that with adequate estrogen replacement, the fracture rate is not increased (2). On average the risk of breaking a bone for a woman with Turner syndrome is about twice that expected with the wrist being a particularly vulnerable site.

Measuring bone density in Turner syndrome

The World Health Organization definition of osteoporosis is based on bone mineral density measurements. Bone density measurements are usually made in two or three sites although it is possible to measure the density of the entire skeleton. The spine is chosen as an example of trabecular or spongy type bone. The hip is an example of cortical bone with outer layer of dense compact bone. Bone density is also often measured at the wrist as this is such common place to fracture in a fall on an out stretched hand.

Figure 1

An example of a bone mineral density scan from a woman with Turner Syndrome. On the right the X ray shows the computerised outline of the area in which the density of calcium content is estimated. On the left, the graphs show measurement plotted against the reference range distributed by age. The t-score of the spine was -2,7 and for the hip -1,5.
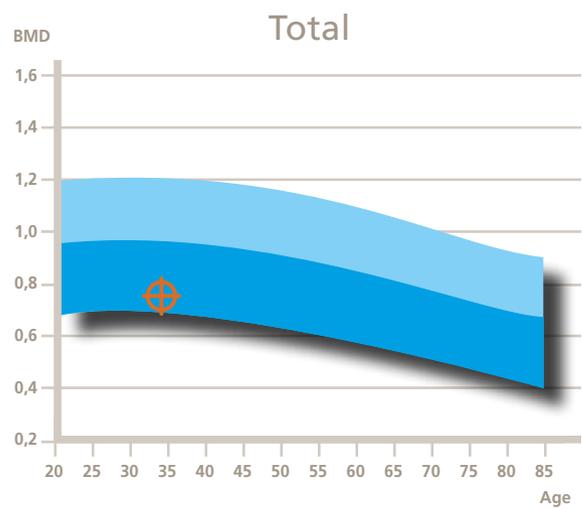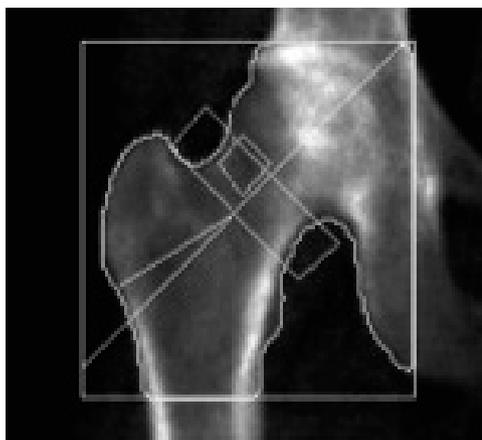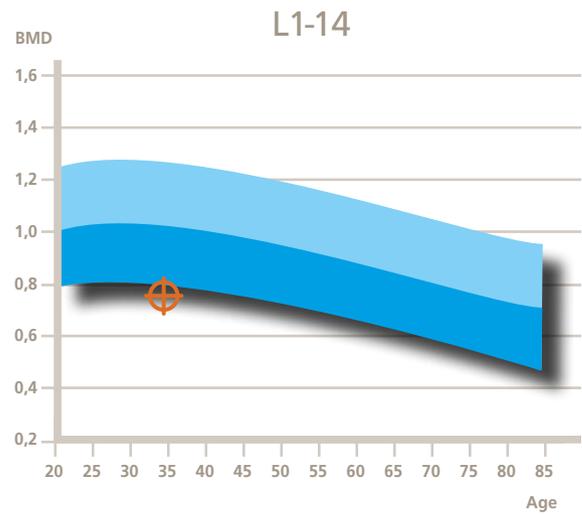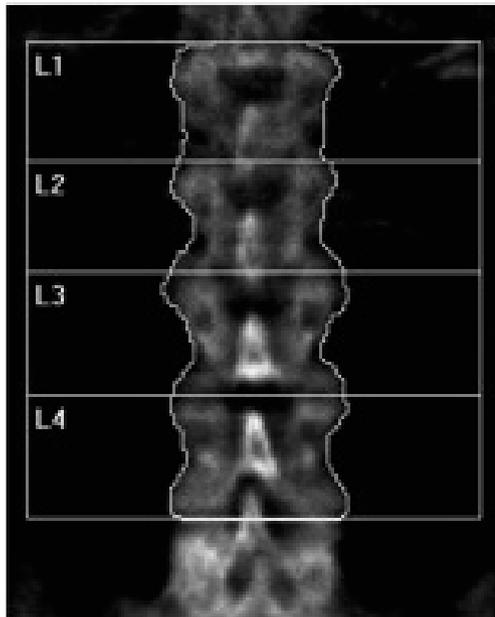
A bone density measurement is converted to a "t-score" which is the degree to which an individual's bone density differs from the average peak bone mass for subjects in their 20s. A BMD t-score of less than -2,5 qualifies for "osteoporosis" where as a t-score between -1,0 and -2,5 is classified as "osteopenia". A BMD t-score greater than -1,0 is considered normal. Very roughly, a woman with a t-score of -2,5 has a 4 fold increase risk in fracture compared to a woman with a t-score of 0,0.

Many studies have shown reduced bone density in women with Turner syndrome (3–4). Figure 2 show a graph of bone density measurements in a population of women with Turner syndrome attending a clinic for adults in London. In common with many studies this graph shows that the bone density for most women with Turner syndrome are in the lower half of the normal range when compared to a reference population. Bone density measurements however, are confusing as they tend to read low in women with short stature. This is because BMD actually measures an area of bone rather than a true volume. The shorter people the vertebrae are also less deep when measures front to back and compares to taller people. Therefore, short women with small bones tend to have low BMD measurements (5). Studies that have taken the trouble to measure a true volumetric bone density in women with Turner syndrome, report values that are very similar to those in normal women (1). Other studies have noted that the risk of fracture persists even with normal bone density in Turner syndrome. (6) Nevertheless, bone density in women with Turner syndrome does correlate with the risk of bone fracture. (7)

Causes of low bone density

There are probably several factors that contribute to low bone density in women with Turner's syndrome. It may be that the missing material on the X chromosome causes bone to form abnormally. Also, girls with Turner syndrome may be resistant to the effects of growth hormone to promote normal bone strength during development. Treatment with growth hormone for increased final height may also improve bone density in girls with Turner syndrome (8). Recent studies, however, report that the effect of GH on bone density in adolescence is minimal (9–10).

The most important factor contributing to low bone density in women with Turner syndrome is the lack of estrogen (11–12). In normal development, the ovary begins to make estrogen from about the age of 10 and then periods start at about the age of 13 as a result of estrogen levels rising in a cyclical manner every month. In the majority of girls with Turner syndrome, the ovary makes no estrogen and spontaneous period never occur – called "primary amenorrhoea". Estrogen acts to decrease bone remodelling by reducing the life span of osteoclasts which break down bone and possibly by increasing the activity of osteoblasts to build new bone resulting in an overall increase in bone density (13). Estrogen also acts to close the end plates of the long bones in adolescence so low doses of

Figure 2

Bone density measurements (g/cm²) in a population of women with Turner Syndrome measured by DEXA scanning. Lines indicate the median and 95th centiles for a reference population of women without Turner syndrome.
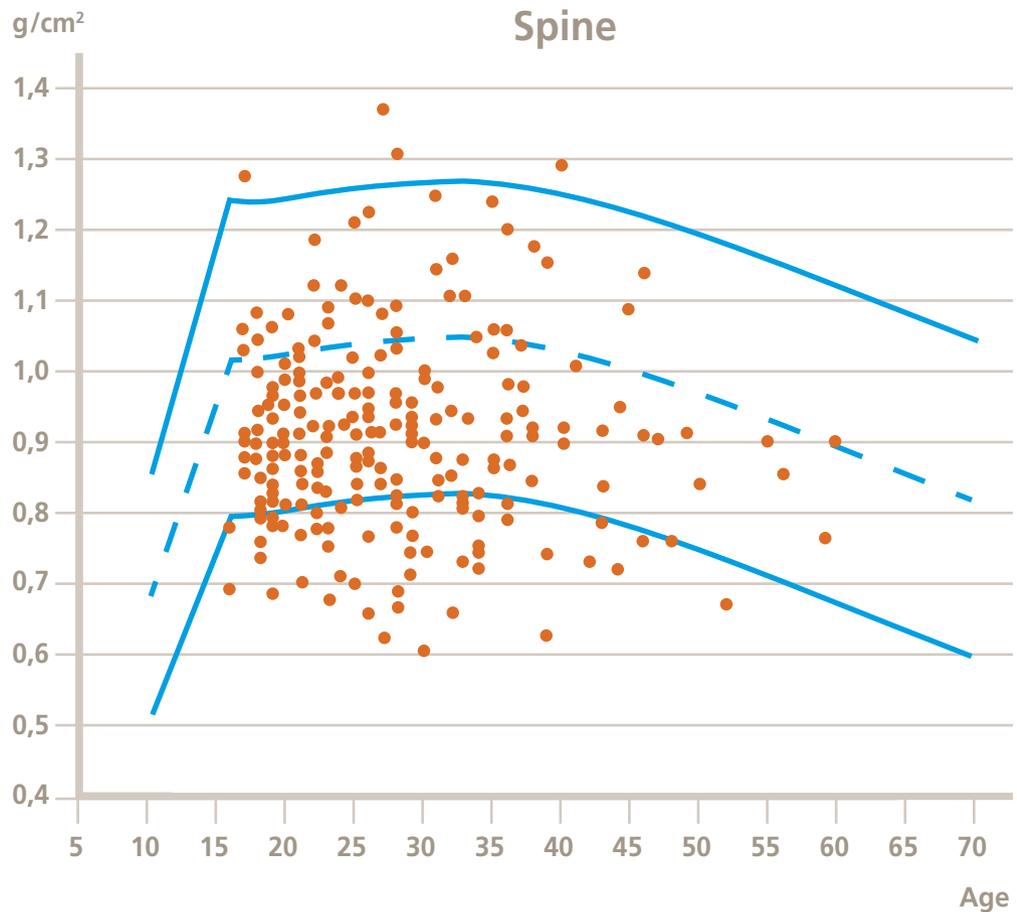
this hormone have to be used in childhood in order to avoid reducing final height. Women with Turner syndrome who keep taking estrogen throughout life and until the age of 50 can expect to prevent the development of osteoporosis as long as vitamin D levels are adequate and enough exercise is taken.

Vitamin D is important for healthy bones acting in various ways. This vitamin promotes the absorption of calcium for the intestine and acts on bone to enable better calcification. It also suppresses the hormone for the parathyroid glands – PTH – which is responsible for releasing calcium from bone. Vitamin D is present in the diet in fish, eggs and for-

Hip
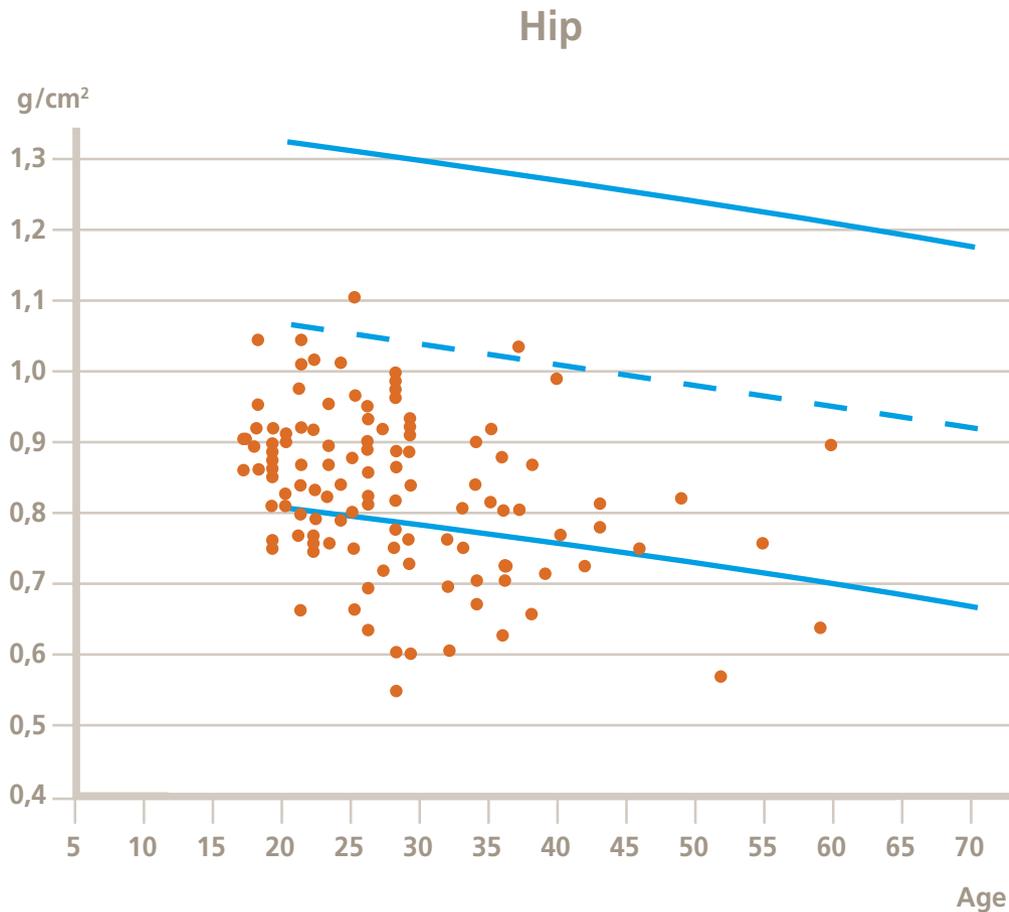
tified milk and is also made in the skin in response to exposure to sunlight. Women with Turner syndrome often tend to run low levels of circulating vitamin D and benefit from supplements (14).

Exercise alone can increase bone density by stimulating the production of osteoblasts so that bone formation is more efficient. Both weight bearing exercise and resistance exercise have positive effects. It is reported that women with Turner syndrome often take less exercise than average and this is clearly a simple discipline that can reduce fracture risk

not only by increasing bone density but also by improving muscle strength and therefore lowering the tendency to fall. Defects in balance and hearing may also contribute to the propensity to fall (15–16).

Treatment of low bone density

In the absence of evidence of intervention in women with Turner syndrome, the basis of treatment of low bone density is borrowed from existing guidelines in postmenopausal women. For instance, the National Osteoporosis Foundation in the USA and National Institute for Clinical Excellence provide guidance on both primary prevention of fractures in women with low bone density and on secondary prevention in women who have sustained a fracture. While information sources such as these are important, women with Turner syndrome have condition specific risk factors such as life long estrogen deficiency and low exercise participation that require particular attention.

At all ages, life style measures are important to optimise bone health and help prevent osteoporosis. These include keep up a good exercise regime aiming for sessions of 30 minutes 2 or 3 times per week particularly including weight bearing exercise. Food intake should be reviewed to make sure that sufficient calcium is consumed. For those who have little calcium in the diet, supplements of 1–1,5 g of calcium per day should be taken. In order to absorb this calcium, vitamin D levels should be maintained. Vitamin D supplements may be required if exposure to sunlight is limited particularly during the winter in temperate climates. The usual recommendation is to supplement vitamin D 800 units per day if circulating vitamin D3 levels are below 50 nmol/L.

In young women with Turner syndrome the focus on bone health is to promote optimal bone development to achieve a normal peak bone mass by the age of 35. In adolescence, attention should be paid to making an early start to the induction of puberty and preventing delay pubertal development. Estrogen replacement should continue through life until about the age of 50 – the time of the natural menopause. Compliance can be improved with individualised treatment using the full range of estrogen preparations. In women with Turner syndrome who have missed several years of estrogen replacement, extended use of estrogen beyond the age of 50 may be considered as it is the cumulative years of estrogen exposure that dictates breast cancer risk rather than the maximum age of exposure. In some instances, bone density measurements decline with age at a faster rate than average despite normal dose estrogen replacement. The beneficial effect of estrogen on bone is dose dependent so an increase in dose may be indicated.

For women who are intolerant to estrogen or in whom estrogen is contraindicated, then raloxifene or tibolone are possible alternatives. In those women, in whom all of the above measures have not prevented bone loss or who have sustained a fracture then bisphosphonates may be used. In general,

bisphosponantes are reserved for the older age groups and used as they would be for women without Turner syndrome. Alendronate, Residronate and Ibandronate are all popular options. The place of more unusual treatments such as Strontium or parathyroid hormone is the same as for osteoporosis in women without Turner syndrome.

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Diabetes

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Diabetes is a chronic disease that is increasing in frequency with the rise in living standards. Diabetes is often caused by eating too much and exercising too little. Seven percent of the world's population has diabetes, with the highest incidence in North America and Europe.

In diabetes, the body's ability to metabolise sugar (glucose) is impaired. Insulin, which is produced and secreted from beta cells in the pancreas, is the primary factor in the regulation of blood sugar levels. Not only does an increase in the glucose level in the blood result in immediate release of the insulin stored in the beta cells (primary insulin response), it also stimulates the beta cells to produce and secrete more insulin (secondary insulin response). The ability to secrete insulin depends not only on the number of beta cells but also on the individual cell's ability to produce and secrete insulin. This ability is reduced in people with an increased risk for developing diabetes such as persons who are overweight, or who have reduced glucose tolerance, or who have family members with diabetes (1). Several hormones and proteins stimulate insulin production, for example when eating, the mucous membranes of the stomach release proteins that have this effect (2). After release, insulin binds in particular to the surface of muscle, liver and fat cells, thereby stimulating the tissue's uptake of glucose which is then converted to energy that can be used or stored.

Diabetes occurs if the relationship between the ability to secrete insulin and insulin sensitivity is disturbed. This disparity can occur as a result of reduced insulin production (type 1 diabetes), or as a reduced sensitivity to insulin in those organs to which insulin binds, primarily muscle and liver (type 2 diabetes), or as the result of a combination of the two. Many factors have an effect on insulin sensitivity (Figure 1).

The diagnosis of diabetes can be confirmed by the result of a blood sugar test taken in the morning after 8–12 hours fasting. If this is elevated (above 6,1 mmol/l) at two measurements on two different days, the patient has diabetes. If the fasting blood sugar is elevated, but is not above 6,1mmol/l, an oral glucose tolerance test is recommended. This test investigates in more detail the body's ability to metabolise sugar, because the patient drinks a carefully measured amount of sugar water (75 g). If, 2 hours after drinking, the blood glucose is moderately elevated, the patient does not have diabetes but has reduced glucose tolerance, and an increased risk of developing diabetes later in life. If the blood sugar level is above 11.1 mmol/l (capillary blood/finger blood) after 2 hours, the diagnosis of diabetes is confirmed.

The symptoms of diabetes can be sparse or completely absent. In type 2 diabetes in particular, the blood sugar level can be moderately elevated without giving symptoms. If the blood glucose level is high, the typical symptoms are increased thirst, frequent urination, and weight loss.

Complications of diabetes include cardio-vascular disease, impaired kidney function and impaired vision. This contributes to a decreased quality of life and life expectancy. The risk for these complications is reduced by good regulation of blood sugar levels, and this is why it is important to diagnose and treat diabetes as early as possible.

The type of treatment for diabetes depends on the blood sugar levels, and will often be life-long. For Type 2 diabetes, the primary treatment can be dietary changes, exercise and weight loss. If this is not sufficient, it may be supplemented with tablets, or insulin treatment. Type 1 diabetes is always treated with insulin. For all patients with diabetes, it is important that blood pressure and fat content of the blood (cholesterol and triglycerides) are checked and treated if elevated. In addition, it is important to monitor kidney function and vision.

Turner syndrome and diabetes

Diabetes is seen more frequently in women with Turner syndrome than in other women. Scientific records of morbidity and mortality have revealed that women with Turner syndrome develop both Type 1 and Type 2 diabetes more frequently than other women (3–4).

In scientific studies the fasting blood sugar levels in women with Turner syndrome are not higher than in women of comparative age (5–6). On the other hand, in some studies the insulin levels have been demonstrated to be higher (6), and this has been interpreted as due to reduced insulin sensitivity. Reduced insulin sensitivity suggests that larger amounts of insulin must be secreted in order to attain normal blood sugar levels after a meal.

Insulin sensitivity has been investigated in a number of older studies which found that insulin sensitivity in women with Turner syndrome was lower (6–7) but, in some of these studies, the women with Turner syndrome had a higher body mass index (BMI) than the control women. The difference in insulin sen-

Factors that reduce insulin sensitivity

Genetic factors

Obesity

High blood glucose levels

High fat content of blood (cholesterol, triglycerides)

Fatty diet

Lack of muscular work/exercise

Smoking

sitivity can probably be partially or completely explained by the fact that insulin sensitivity drops with increasing BMI.

In a study in which the participating women with Turner syndrome have a BMI that is comparable to that of the control women, no difference is found in insulin sensitivity (unpublished data). The same study found only marginally reduced insulin secretion from the beta cells in the age range 20–40 years. However, several studies have found that the glucose level after an oral glucose tolerance test is higher in women with Turner syndrome, and that around 50% of the women have reduced glucose tolerance. This is significantly more than in the women in the control group (5; 8–9).

The incidence of reduced glucose tolerance is also higher among women with Turner syndrome compared to a group of women who lack estrogen due to other reasons (9). Thus, lack of estrogen does not itself explain the changes in sugar metabolism. In the same study, estrogen replacement therapy resulted in lower fasting glucose and insulin levels, and an improvement in control of glucose levels. A possible explanation is that treatment results in an improvement of the fitness rating, and a positive change in body composition with an increase in muscle mass (5), because all of these factors have a desirable effect on control of glucose.

Figure 2
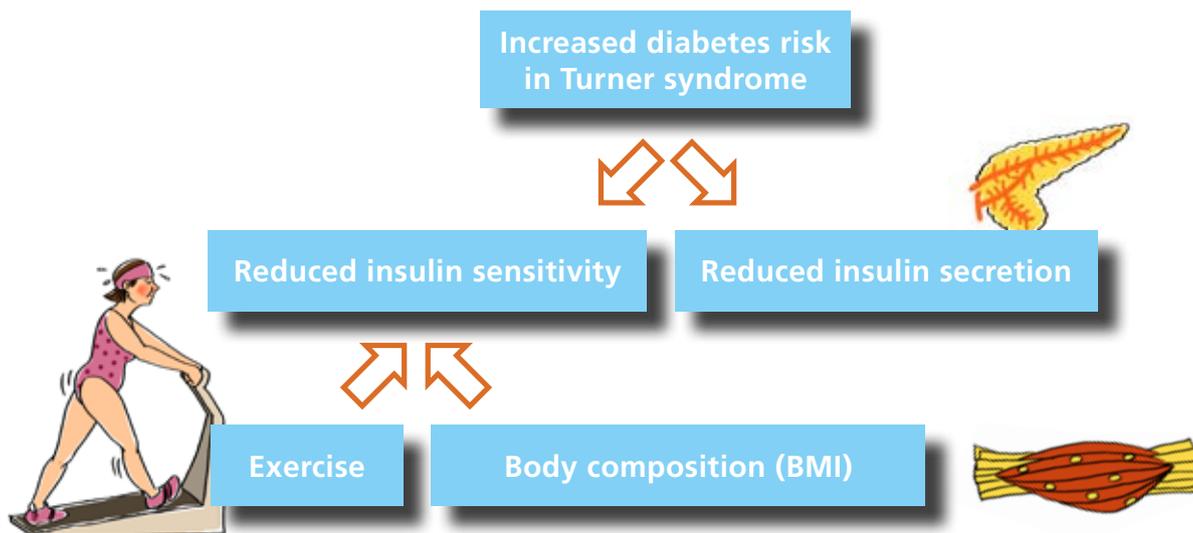
Scientific studies have found that women with Turner syndrome have a higher BMI (10–11) and are less physically active than the control women in the studies. Because insulin sensitivity is higher at lower BMI and in individuals who are physically active, it may be well-advised to focus on promotion of physical activity and avoidance of overweight in girls and women with Turner syndrome as prophylactic measures against diabetes. A BMI of less than 25 is recommended. This is beneficial not only with regard to sugar metabolism, but also for the increased risk for osteoporosis and for elevated blood pressure, for which exercise and normal weight have similar prophylactic effects.

Growth hormone has an effect on glucose metabolism, and can increase blood glucose, increase the insulin level, and reduce insulin sensitivity. It is therefore important to monitor fasting blood sugar levels during growth hormone treatment of girls with Turner syndrome. Growth hormone treatment however also changes the body composition, with a reduction in the fat mass and an increase in the muscle mass. This is believed to be the explanation for the reduction in insulin sensitivity in the first months of treatment (an effect of growth hormone), while after 6–12 months of treatment, stabilisation of insulin sensitivity is observed (an effect of changes in body composition). When treatment with growth hormone stops, both glucose and insulin levels return to the pre-treatment levels.

In conclusion, there appears to be a reduced ability to manage glucose loads in women with Turner syndrome. The reason for this has not been clarified but, even though estrogen replacement therapy has a positive effect on glucose metabolism, neither lack of estrogen nor BMI alone can explain this reduced glucose tolerance.

The criteria used for confirming a diagnosis of diabetes in women with Turner syndrome, are the same as those for the general population. However, due to the increased risk for diabetes, it is recommended that women with Turner syndrome should be followed with a prophylactic fasting blood sugar test every 1–2 years. Cholesterol and triglycerides should also be measured because a changed glucose metabolism can affect fat metabolism, and diabetes and elevated cholesterol/triglycerides are risk factors for development of cardiovascular disease. The recommended treatment of diabetes is identical to that for others with diabetes, and could include weight loss, dietary considerations, tablets, and/or insulin treatment.

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Gastro-intestinal diseases in Turner syndrome

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Turner syndrome girls and women show a high prevalence of autoimmunity, therefore they are at increased risk of developing several autoimmune conditions, in particular with advancing age: Autoimmune thyroiditis, celiac disease, pernicious anemia with anti-parietal cell antibodies, autoimmune hepatitis, primary biliary cirrhosis, lichen planus, idiopatic rheumatoid arthritis, acquired von Willebrand disease and inflammatory bowel disease . Some of these conditions can occur simultaneously in a person with Turner syndrome. Many studies have reported an increased prevalence of chronic intestinal diseases: Celiac disease and inflammatory bowel disease such as ulcerative colitis and Crohn's disease.

Celiac disease

Celiac disease is a gluten-sensitive enteropathy of autoimmune nature, characterized by villous damage of small intestinal mucosa, interfering with absorption of nutrients from food (Figure 1a). It is a long-life problem.

Figure 1a

Intestinal villi in Celiac Disease.

Normal intestinal villi

Shortened villi
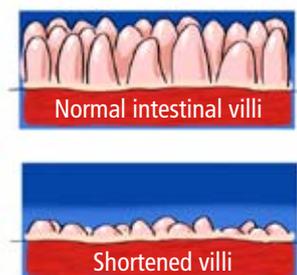
Cause

Celiac disease is a multifactorial disease:

Environment

Gluten is the critical environmental component. Gliadin fraction of wheat gluten and similar alcohol-soluble proteins of barley and rye in genetically susceptible subjects cause the damage.

Genetics

A genetic component is involved in the development of the disease: Inherited genetic factors have been known to affect disease susceptibility. Abnormalities in genomic regions containing genes with immunological function have been identified in association with celiac disease.

In celiac disease patients there is an abnormal T-cell response to gluten. The inflammatory response leads to architectural changes in the small intestine, including villous atrophy, crypt hyperplasia and an increase in the number of intra-epithelial cells. If gluten is removed from the diet, in many cases architecture returns to normal over several months.

Incidence

In Turner syndrome individuals celiac disease is significantly more frequent than in the general population (4,2–6,4% in Turner syndrome vs 0,35–0,5% in the general population). Celiac screening studies, previously performed in the paediatric population, confirmed the

Figure 1b

The Celiac iceberg.

Symptomatic celiac disease

Manifest muscosal lesion

Silent Celiac Disease

Latent Celiac Disease

Normal muscosa

Genetic Suspectibillity: DQ2, DQ8 positive serology
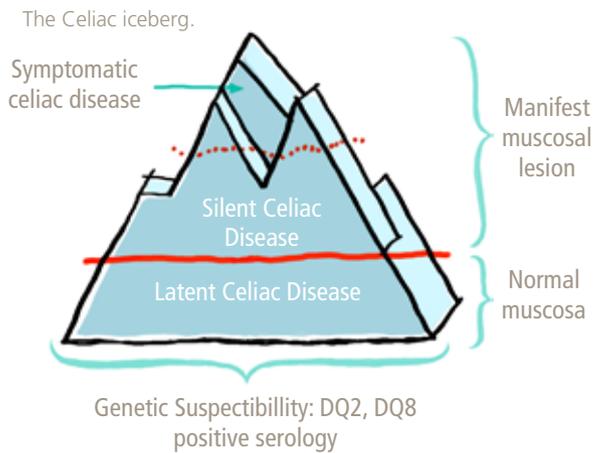
increased prevalence also in women with Turner syndrome. The high prevalence found in these subjects indicates that the connection between celiac disease and Turner syndrome cannot be coincidental.

Clinical signs

Celiac disease is frequently unrecognized. (Figure 1b) Celiac disease occurs in symptomatic individuals with gastrointestinal and non-gastrointestinal symptoms (classic and atypical form) and in some asymptomatic individuals who have conditions that are associated with celiac disease: Autoimmune diseases (insulin-dependent diabetes mellitus, thyroiditis) and some genetic diseases (Down syndrome, Turner syndrome, Williams syndrome).

Some studies reported that about 40% of the individuals with Turner syndrome and celiac disease show typical clinical signs of celiac disease, 30% atypical signs (anaemia, anorexia,

delayed growth for Turner syndrome-growth curves, hypertransaminasemia) and the remaining ones have silent forms. In the general population we observe the opposite situation, in fact most of the individuals have silent forms of celiac disease. Typical signs include diarrhea, weight loss and fatigue (Figure 1d).

Short stature can be the primary manifestation of mono-symptomatic celiac disease. When a Turner syndrome girl shows a growth velocity slower than expected for Turner syndrome curves, first she has to be evaluated for celiac disease. Otherwise only few subjects with Turner syndrome and celiac disease show a height lower than the 3° percentile for Turner syndrome growth charts.

Celiac disease can also have a role in the insufficient effect of growth hormone therapy. In fact, some studies have demonstrated that unrecognized autoimmune pathologies may interfere with growth hormone therapy and thus compromise final height.

Diagnosis

The screening for celiac disease is performed with the determination of celiac disease-associated antibodies. Testing for immunoglobulin A against endomysium and human tissue transglutaminase is highly specific and sensitive for disease detection. In particular, transglutaminase determination is a low-cost screening method, alternative to endomysium determination.

Subjects with immunoglobulin A deficiency have to be tested for immunoglobulin G antibodies, to transglutaminase and endomysium.

Celiac disease must be confirmed by finding certain changes to the villi of the small intestine. Small bowel endoscopy with biopsy is recommended in positive cases.

Intestinal biopsy

A flexible tube-like instrument is placed through the mouth, down the throat, past the stomach and into the small intestine to obtain small tissue samples to examine.

Therapy

At present the only therapy is gluten-free diet. (Figure 1c) When a person with celiac disease eats food containing gluten, the immune system responds by damaging the small intestine.

Anti transglutaminase and anti endomysial antibodies can be used to monitor compliance to a gluten free diet; antibodies will disappear with diet.

The importance of a strict gluten-free diet for life has to be strongly emphasized to reduce the risk of further complications and improve quality of life. New research suggests that serum celiac disease-antibodies may have a role in the development of thyroid dysfunction, in fact

in celiac disease subjects gluten exposure seems a predisposing factor for autoimmune thyroiditis.

It is essential that newly diagnosed subjects be referred to a dietitian with expertise in celiac disease, be educated about the disease and

Figure 1c

Grains allowed in the gluten free diet.

The gluten free diet

GRAINS ALLOWED

Amaranth

Arrowroot

Bean Flours

Buckwheat

Corn

Horniny

Millet

Nut Fluors

Potato

Quinoa

Rice

Soy

Sorghurn

Tapioca

Leff

Wild Rice
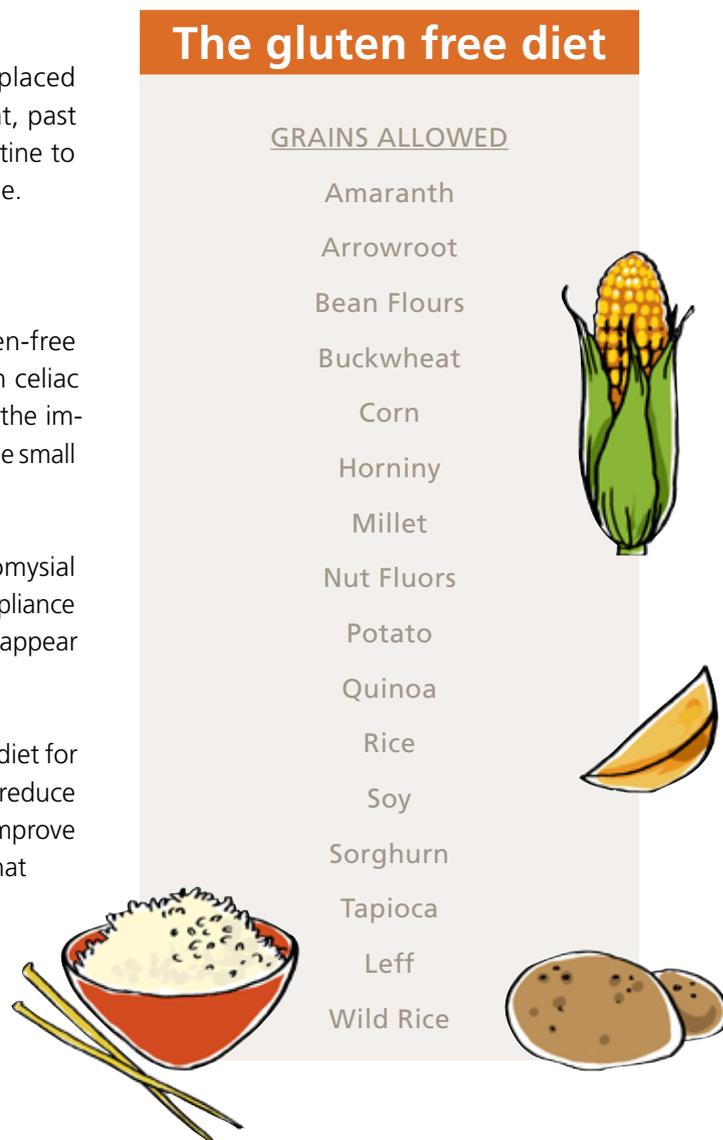
informed that celiac disease needs a lifelong adherence to a gluten-free diet. Nutritional deficiencies during the diet have to be identified and treated. Successful management of celiac disease, requires a long-term follow-up by a multidisciplinary team including: The subject, the family, the physician, the dietitian and an *individualized dietitian plan.*

Recommendations

As a high risk population Turner syndrome girls and women should be screened for celiac disease:

- A screening based on anti-tissue tranglutaminase autoantibodies.
- The screening for celiac disease could be proposed as soon as possible after the diagnosis and periodic screening should begin at age 6 and repeated every 2–5 years.
- Celiac disease screening should be performed in presence of short stature or growth velocity lower than expected for Turner syndrome charts.
- Celiac disease screening should be performed before the beginning of growth hormone-therapy: To avoid a bad response to treatment, to improve growth and optimize bone mineral density.
- Alternatively, HLA-typing with regard to DQ2/DQ8 status can be performed, as individuals without DQ2 or DQ8 need no further screening.
- No gluten-free diet should be started before investigations for celiac disease, have been completed, because it can interfere with making a correct diagnosis.

In Italy a collaborative study is in progress to evaluate in a long-term follow-up the effect of gluten free-diet on final height of Turner syndrome subjects and to better define the immunological consequences of the association celiac disease and Turner syndrome.

Inflammatory bowel disease (Crohn's disease and ulcerative rectocolitis)

Inflammatory bowel disease is a disorder characterized by chronic relapsing inflammation of the gastrointestinal tract and it is characterized by a dysregulated mucosa immune response. Two distinct forms of inflammatory bowel disease have been recognized: *Crohn's disease* and *ulcerative colitis*. Recent studies suggest an increasing frequency in paediatric and adult Turner syndrome.

Incidence

The incidence of inflammatory bowel disease is increasing. Crohn's disease and ulcerative colitis are most prevalent in North America, northwestern Europe, especially Scandinavia, and the United Kingdom. Countries in southern Europe, South Africa, and Australia

Figure 1d

Clinical symptoms in the different forms of celiac disease.

Clinical symptoms in the different forms of celiac disease

CLASSIC FORM

Abdomen pain

Low weight

Meteorism

Anemia

ATYPICAL FORM

Growth failure, pubertal delay

Anemia

Rickets, osteoporosis

Enamel dysplasia

Recurrent Abdominal pain

Seizures

increased levels of liver enzymes

SILENT FORM

Only one or two symptoms suggestive of celiac disease

Figure 2

Ulcerative Colitis.
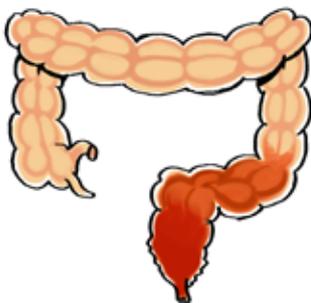
Rectocolitis
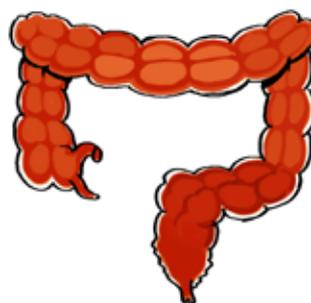
Pancolitis

have lower incidence rates. Peak occurrence of Crohn's disease is observed in late adolescence or young adulthood. A second smaller peak is observed in the sixth decade.

Prevalence in Turner syndrome

Turner syndrome has a higher prevalence of inflammatory bowel disease. Gravholt et al. calculated a twofold increase in risk of developing Crohn's disease and ulcerative colitis. Other studies found an even greater risk estimated at about 2,6–3% of these individuals. In Turner syndrome Crohn's disease is at least twice as common as ulcerative colitis. The highest risk has been found in subjects with abnormal structural abnormalities of X chromosomes, accounting for 52% of the reported cases of inflammatory bowel disease in Turner syndrome.

Cause

The precise cause is unknown and the mechanisms of inflammation appear complex. Genetic factors seem to play a significant role in determining inflammatory bowel disease susceptibility. Crohn's disease and ulcerative colitis have different causes and specific mechanisms of tissue damage, but they share several factors in particular that arise from an interaction between an intrinsic genetic predisposition and environmental factors.

Age of onset

Gastrointestinal symptoms often develop at a young age, between 9 and 40 years with a mean of 16 years.

Ulcerative colitis

Ulcerative colitis is a chronic inflammatory condition involving primarily the large intestine, small intestine is never involved (Figure 2).

Ulcerative colitis, primarily presents in late adolescence and early adulthood, although the diagnosis may be made at any age. The distribution of age at onset of ulcerative colitis, is bimodal, with peaks occurring in the second and third decades and again in the fifth and sixth decades.

Clinical symptoms

Symptoms of ulcerative colitis, are dependent upon extent and severity of disease.

Gastrointestinal signs

Most commonly, ulcerative colitis, presents with the insidious onset of diarrhoea, but usually without systemic signs of fever, weight loss or hypoalbuminemia. In contrast, severe colitis is characterized by five or more bloody stools per day, significant anemia, hypoalbuminemia, fever, tachycardia, and weight loss. Nocturnal defaecation is also often reported.

Intestinal complications

Complications such as toxic megacolon, perforation of the colon and massive haemorrhage may occur with a severe exacerbation

at any point of time, while stricture and colon cancer typically happen in the setting of long-standing disease. (Figure 3)

Extra-intestinal complications

Extra-intestinal manifestation can be present and involve the skin (5–20%), the joints (2–20%), the eye (1–3%), the liver (5–50%) and the kidney (1–10%). They may accompany the presentation in about 10% of cases and rarely precede intestinal symptoms. (Figure 3)

Diagnosis

A gold standard for the diagnosis of ulcerative colitis, is not available. The diagnosis should be established by a combination of medical history, clinical examination and typical endoscopic and histological findings. An infective cause should be excluded.

Flexible sigmoidoscopic or colonoscopic inspection of the colon and ileum, in conjunction with mucosal biopsies, provide the most sensitive and specific evaluation of intestinal inflammation: Continuous and confluent colonic involvement and rectal involvement.

Therapy

The goals of medical therapy of ulcerative colitis in children are the induction of remission with control of symptoms, the prevention of relapse, the avoidance of complications, and the provision of optimal quality of life.

Figure 3

Intestinal and extra intestinal complications in Ulcerative Colitis.
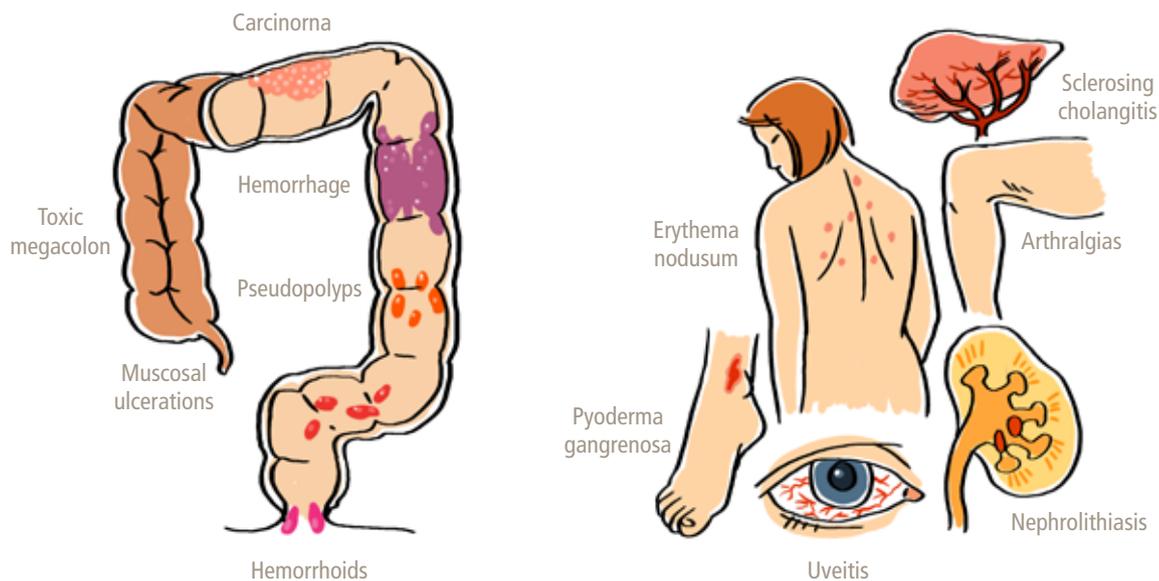
The extent of ulcerative colitis influences the patient's management. The choice of therapy depends on the severity of the inflammation, the distribution of inflammation in the colon and the pattern of the disease (relapse frequency, response to previous medications, side-effect profile of medications, extra-intestinal manifestations).

Severe active colitis should be treated in hospital.

Crohn's disease

Crohn's disease is a lifelong disease and, differently from ulcerative colitis, can affect the entire gastrointestinal tract. (Figure 4)

28%
42%
30%
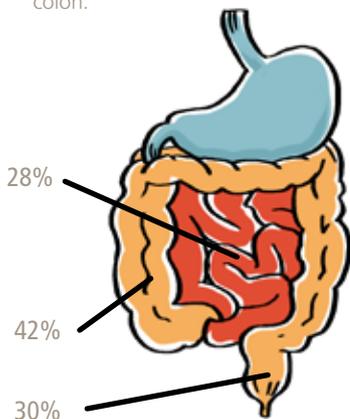
Crohn's disease most frequently presents in late adolescence or early adulthood. At the presentation the symptoms vary according to the location and the severity of disease.

Clinical symptoms

Intestinal signs – The symptoms are heterogeneous, but the classical presentation commonly include diarrhoea for more than six week, poor appetite, abdominal pain (most frequent in children) and/or weight loss in any age group. These symptoms should raise suspicion especially in subjects at young age. Chronic diarrhoea is the most common sign. Blood and/or mucus in the stool may be seen in 40–50% of subjects with Crohn's disease. Crohn's disease may present as short stature and delay in sexual maturation.

Systemic signs

They include malaise, anorexia and fever.

Intestinal complications

Intestinal stenosis, obstruction, fistulas, intra abdominal abscess are the most common complications. Free perforation and refractory massive haemorrhage are clear unequivocal indications for surgery, yet rarely occur.

Extraintestinal complications

Other systems are frequently involved: Skeleton, eye, liver and skin. Osteoporosis and osteopenia are common in subjects with Crohn's disease and in Turner syndrome individuals the risk of fractures is higher than in the general population.

Diagnosis

An accurate and complete medical history and physical examination is the first step for the diagnosis. The presence of short stature or growth velocity lower than expected for Turner syndrome-charts may induce us to exclude other pathologies such as chronic intestinal diseases.

The diagnosis is based on a compatible clinical presentation, radiologic assessment of the small bowel, endoscopy of the ileocolon and of the upper gastrointestinal tract in children with pathologic examination of mucosal biopsies, and exclusion of other causes of chronic intestinal inflammation.

At the biopsy the features of Crohn's disease are those of a chronic inflammatory process and in contrast with ulcerative colitis, is a more focal process. The presence of granuloma is specific for Crohn's disease.

Therapy

The therapy is based on pharmacologic, nutritional, and, where appropriate, surgical interventions, not only to alleviate symptoms but also to optimize growth, facilitate normal social development, and avoid long-term disease-related complications.

The general principle for treating active Crohn's disease are established on the activity, site (ileal, ileocolic, colonic) and behaviour of the disease. The severity of Crohn's disease is more difficult to assess than ulcerative colitis. The choice of therapy may be individualized. No treatment is an option for some patients with mild symptoms.

The care of Crohn's disease is now primarily managed by the medical gastroenterologists. Drugs are evolving rapidly and symptomatic relief may be achieved by medical therapy. Surgery may be considered only in selected cases.

General principles of therapy of inflammatory bowel disease

Considerable progress has been made in the earlier diagnosis and more aggressive therapy of inflammatory bowel disease over the recent years.

Several drugs are used for the therapy of inflammatory bowel disease: Aminosalycilates corticosteroids and budesonide, immunosuppressive agents (azathioprine, 6-mercaptopurine, methotrexate, tacrolimus, cyclosporin), and anti-TNF agents (infliximab, adalimumab, certolizumab).

Nutritional interventions and surgery (i.e. resections, surgery for perianal disease and conservative interventions such as strictur-oplasties) need to be properly managed in these patients.

Intestinal telangiectasia

It has been estimated that the incidence of gastrointestinal haemorrhage in Turner syndrome is about 7%. Patients with Turner syndrome showed an increased incidence of gastro-intestinal bleeding due to intestinal telangiectasias, infiammatory bowel disease and portal hypertension. Intestinal telangectasia is one of the clinical manifestations of Turner syndrome and may result in gastro-intestinal bleeding. In the literature different cases are reported. Gastrointestinal vascular anomalies have to be considered as diagnostic hypothesis in cause of abdominal pain in Turner syndrome.

Intestinal telangiectasia are vascular lesion of gastrointestinal tract that may be a source of upper and lower gastrointestinal bleeding. It is a multifocal disease potentially involving the whole digestive tract. Subjects with duodenal telangiectasia show a higher risk of jejunal or ileal lesions.

Clinical symptoms

The clinical presentation is variable ranging from asymptomatic cases and iron deficiency anaemia to acute or recurrent bleeding.

Diagnosis

Endoscopy should be performed in patients with Turner syndrome and anaemia even if there are not signs of active gastrointestinal bleeding.

Wireless capsule endoscopy is a useful diagnostic tool for the detection of such small-bowel vascular lesions, indicating a more specific prognosis and treatment strategy. Capsule endoscopy has high sensitivity and specificity to detect a bleeding source in patients with obscure gastrointestinal bleeding.

Therapy

The intermittent bleeding caused by telangectasia can be responsive to progesterone and an adjustment of hormonal replacement therapy can limit the need for surgery.

Spontaneous regression of the intestinal telangiectasia observed in subjects with Turner syndrome may occur and account for the improved prognosis with age.

Having established the diagnosis, subsequent haemorrhages, which are likely to occur, can generally be managed conservatively.

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vascular anomalies have to be considered as diagnostic hypothesis in cause of abdominal pain in Turner syndrome.

Recommendations

As a high risk population Turner syndrome girls and women should be screened for inflammatory bowel disease:

- An inflammatory bowel disease should be considered in subjects with intestinal signs such as chronic diarrhoea, abdominal pain, blood and/or mucus in the stool. Chronic diarrhoea is the most common sign in adults, whereas abdominal pain is the most frequent symptom in children.
- General signs of suspicion of inflammatory bowel disease may be poor appetite and/or weight loss in any age group. These symptoms should rise the suspicion especially in subjects at young age.
- Inflammatory bowel disease screening should be performed in presence of short stature or growth velocity lower than expected for Turner syndrome charts.
- Subjects with Turner syndrome and with inflammatory bowel disease should be encouraged to participate actively in therapeutic decisions.
- Subjects with ulcerative colitis are best cared for jointly by a gastroenterologist and colorectal surgeon.

Acknowledgements

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Liver involvement in Turner syndrome

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Abstract

Liver test abnormalities are frequent in subjects with Turner syndrome. The changes found in the cells from the liver in Turner syndrome patients may be explained by one or more distinct mechanisms. Steatosis, steatofibrosis and steatohepatitis (see glossary) are frequent, caused by metabolic disorders, which are commonly associated with overweight. Marked architectural changes, including two specific, but rare diseases, called nodular regenerative hyperplasia and cirrhosis, may be associated with severe complications. Architectural changes are frequently associated with vascular disorders of the liver and of other organs. Finally, bile duct alterations, resembling small duct sclerosing cholangitis (a disease of bile ducts), are relatively common. Estrogen replacement therapy does not cause liver toxicity and is not contraindicated in patients with elevated liver enzymes. In Turner syndrome patients, the regular screening of liver enzymes (performed by a blood test) is recommended for early detection of potential liver involvement.

Keywords

Steatohepatitis, nodular regenerative hyperplasia; vascular liver disease, biliary lesions

Introduction

Liver involvement is frequent in adult patients with Turner syndrome. The prevalence of liver test abnormalities (especially the elevation of aminotransferases, gamma glutamyl transferase and alkaline phosphatase) ranges from 20 to 80%, depending on the patient's age, with the highest values in the oldest patients (1; 4–5).

Multiple causes may lead to liver test abnormalities in Turner syndrome patients. All common causes of liver involvement such as viral hepatitis or chronic alcoholism must be ruled out at first; their prevalence is not raised in Turner syndrome, compared to the general population. Excess weight and estrogen replacement therapy have both been suggested to cause elevation of liver enzymes (2–3). Although estrogen therapy is definitely not a cause of liver toxicity in Turner syndrome individuals, excess weight is one of the most frequent causes of liver tests abnormalities in women with Turner syndrome.

For a long time, comprehensive studies of liver involvement in Turner syndrome patients have been missing, contrasting with a relatively high number of case reports or epidemiological studies (6–10). More recently, a cohort study with systematic histopathological examination analyzed the histological features, causes and prognosis of liver involvement in Turner syndrome patients (11). The take-home message of this study was that severe liver complications, such as portal hypertension,

are rare but possible in Turner syndrome patients. Consequently, screening for liver involvement should be systematically included in the follow-up of women with Turner syndrome, leading to specific investigation in case of detected liver test changes.

Hepatic lesions and mechanisms of liver involvement

Liver involvement in Turner syndrome patients is asymptomatic in most cases, discovered during systematic blood testing. In general, the diagnosis of Turner syndrome precedes that of liver involvement but, sometimes, abnormal liver tests can lead to the diagnosis of Turner syndrome.

The hepatic histological changes reported in Turner syndrome patients are variable including minimal abnormalities (12), steatosis (13), steatohepatitis (3), biliary involvement (13–16), cirrhosis (6–8) and nodular regenerative hyperplasia (9–10, 17–18). In most initial studies, the mechanisms and prognosis of liver disease had not been investigated, but it appeared that the consequences of the hepatic involvement may sometimes be severe (12). Accordingly, a five-fold increased risk of "cirrhosis" was reported in Turner syndrome patients, compared to control patients (19). In the cohort study mentioned above, where liver biopsy was performed in most patients, three principal types of lesions were identified (Figure 1). Steatosis was the most common and the mechanism of its development is becoming clear. For the two others lesions, the architectural changes with nodular formation and the biliary lesions, the pathophysiological mechanisms remain hypothetic.

Liver steatosis or fatty liver

Steatosis is part of the group of non-alcoholic fatty liver disease, which includes a spectrum of liver injuries that mimic alcohol-induced liver disease in patients who are not heavy drinkers. Non-alcoholic fatty liver disease includes the steatosis itself, which has a benign course, and steatohepatitis, which may eventually be associated with fibrosis (scar tissue in the liver) and progression to cirrhosis. Histopathological (examining a liver biopsy under a microscope) features of non-alcoholic fatty liver disease have been found in several Turner syndrome patients. Overweight and insulin resistance syndrome have been recently recognized as a common cause of non-alcoholic fatty liver disease (20–21). Since overweight, defined by a body mass index (BMI) value above 25kg/m^2, and diabetes are frequent in Turner syndrome patients (19; 22–23), it is likely that these hepatic lesions reflect the same pathophysiological mechanisms as in overweight patients without Turner syndrome (24).

Figure 1

The three main hepatic lesions observed in Turner syndrome
   a) Steatosis (the arrow indicates a fatty vacuole).
   b) Architectural changes, here a nodular regenerative hyperplasia (arrows delimitate two nodules).
   c) Biliary lesions (arrows point a concentric fibrosis surrounding a bile duct).
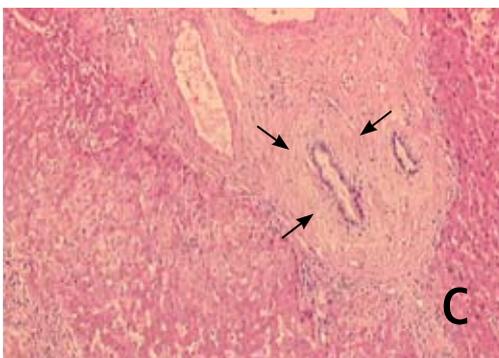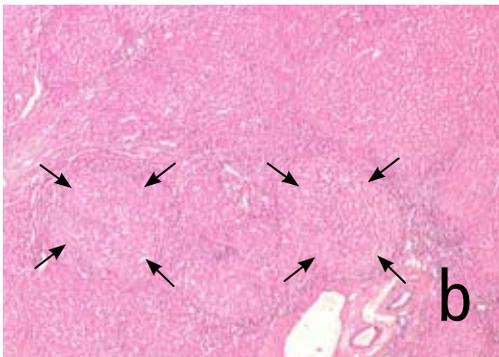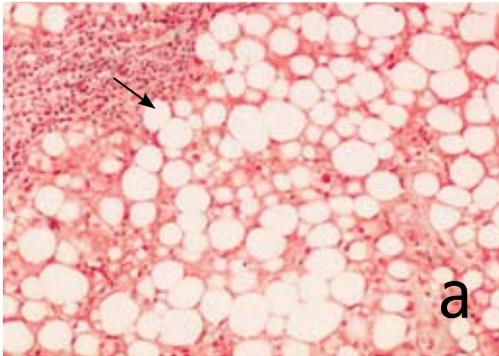
Liver architectural changes and nodular formation

Normally the liver looks very characteristic on a liver biopsy – in other words the architecture of the tissue looks similar in different people. However, marked liver architectural changes can be observed in some Turner syndrome patients. They include cirrhosis, defined as multiple small parenchymal nodules with annular fibrosis (seen in a liver biopsy), and nodular regenerative hyperplasia. The latter is defined as the presence of multiple small parenchymal nodules without annular fibrosis. More specifically, changes in the intrahepatic portal veins, including thrombosis, intimal thickening, or complete obstruction and replacement by a fibrous scar containing numerous vessels, are frequently associated to liver architectural changes; they are considered as features of obliterative portal venopathy (25). Several findings suggest that a primary vascular involvement is the cause of the architectural changes described above. Finally, cirrhosis with no evidence for a known cause of chronic liver disease in Turner syndrome patients may correspond to the final stage of a vascular disorder. Vascular abnormalities (including aortic coarctation, aortic bicuspidia, cerebral vessel aneurysm, and gastrointestinal telangiectasia) are common in Turner syndrome (26–28) and were found more frequently in patients with marked architectural changes of the liver (11). Therefore, some hepatic changes in Turner syndrome patients could be part of a general disorder involving vessels of different sizes, types and locations. A congenital origin would be a likely hypothesis to explain this vascular disorder.

Biliary lesions

Whereas biliary atresia (a condition where there is no possibility to excrete the bile) has been reported in only one child with Turner syndrome (15), non-inflammatory, concentric fibrosis of small intra-hepatic bile ducts, resembling primary sclerosing cholangitis, has frequently been found in Turner syndrome adult patients. Turner syndrome patients have a higher than expected incidence of inflammatory bowel disease (29), a condition that is frequently associated with primary sclerosing cholangitis. However, sclerosing cholangitis mostly involves extra-hepatic bile ducts, whereas only intra-hepatic bile ducts are involved in Turner syndrome patients. In addition, associated inflammatory bowel disease is generally not reported in Turner syndrome patients with biliary lesions. These findings indicate that the changes (called ductal fibrosis) in Turner syndrome patients are caused by a different (pathophysiological) mechanism than primary sclerosing cholangitis. Bile duct fibrosis frequently occurs in patients with damaged arterioles near bile ducts (30). Thus, the concentric biliary fibrosis might be related to an altered blood supply.

Cholangitis and ductopenia (decreased number of liver bile ducts), which have also been described in patients with Turner syndrome (11), are common features in patients with primary biliary cirrhosis. The frequency or prevalence of primary biliary cirrhosis in Turner syndrome has never been studied, despite the fact that the Turner syndrome biliary involvement and primary biliary cirrhosis share some similarities (31). In both diseases, cholestasis is age-related and both diseases are strongly associated with autoimmune disorders. Moreover, a recent study reported significantly more frequent X chromosome monosomy in patients with primary biliary cirrhosis than in controls (32).

Role of estrogen therapy

Estrogen-induced hepatotoxicity (liver toxicity) has been proposed as the main cause of liver test abnormalities in Turner syndrome patients receiving hormone replacement therapy (33–34). However, the causative role of estrogens has never clearly been established. Both alterations in liver tests and liver architectural changes have been reported whether Turner syndrome patients were treated with estrogens or not (11). In addition, these alterations were not improved by cessation of replacement therapy (1; 10). Therefore, the discontinuation of replacement therapy is not necessary. Moreover, several studies demonstrated a beneficial effect of natural estrogens on liver function of Turner syndrome patients (4; 35–37).

Figure 2

Management Chart of liver involvement in Turner patients. Abbreviations used in the figure: PHT: Portal hypertension, UDC: Ursodeoxy-cholic acid.
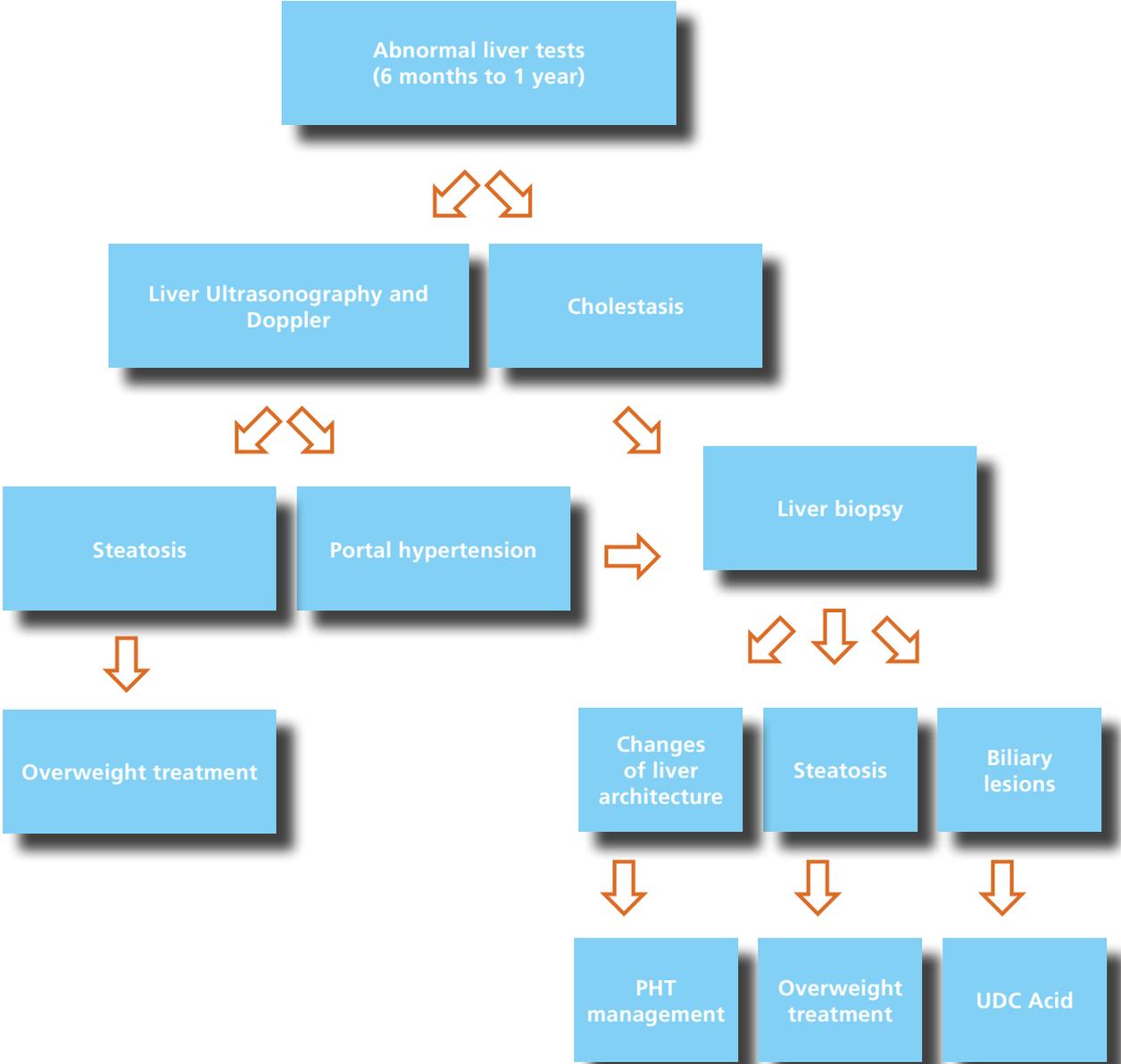
Liver involvement outcome

Natural history of liver involvement in Turner syndrome patients

To date, only one study reported long term follow-up of Turner syndrome patients with liver involvement. In this cohort study, patients referred to liver departments for abnormal liver tests were followed for an average of nine years (11). In most cases, liver involvement did not progress to overt liver disease. Major complications were observed in three patients who all displayed liver architectural changes. One patient died of uncontrolled refractory ascites. The second patient experienced uncontrolled venous bleeding from the esophagus, which required liver transplantation six years after the diagnosis of liver involvement. The third patient underwent surgery (portocaval shunting) for recurrent venous bleeding from the esophagus. In conclusion, major liver complications are uncommon in Turner syndrome patients and are only observed in case of marked architectural changes.

Outcome under ursodeoxycholic acid treatment

Ursodeoxycholic acid is commonly recommended in biliary disease, mainly in patients with primary biliary cirrhosis (38). As biliary involvement may occur in about two third of Turner syndrome patients with elevated liver enzymes, particularly in case of a cholestatic profile, ursodeoxycholic acid treatment has often been prescribed. This treatment proved to be effective at least on biological tests. In one study, serum aminotransferase and alkaline phosphatase levels returned to normal after a few weeks of treatment in most patients receiving ursodeoxycholic acid, although the liver enzyme, gamma glutamyl transferase, remained slightly increased (11). Ursodeoxycholic acid treatment had no beneficial effect on biological tests in patients with liver architectural changes. Although a positive effect of ursodeoxycholic acid on anatomical lesions has not been documented so far, in the absence of a case-control study it cannot be ruled out that the progression of liver lesions may be delayed by the ursodeoxycholic acid treatment. In conclusion, ursodeoxycholic acid therapy may have some beneficial effect in Turner syndrome patients with biliary lesions and no alteration of liver architecture.

Managing of Turner syndrome patients with persistent elevated liver enzymes

Initial evaluation

The initial evaluation of Turner syndrome patient with abnormal liver tests (for more than six months) should include abdominal ultrasound with assessment of blood flow by Doppler to detect hepatic nodules, portal hypertension and/or liver steatosis. In case of isolated cholestatic syndrome with normal ultrasound examination, ursodeoxycholic acid should be tried. In case of ultrasonographic signs of hepatic steatosis, the treatment of the metabolic syndrome is required, to avoid complications seen in non-alcoholic fatty liver disease. This includes primarily loss of weight. (Figure 2)

When ultrasonographic signs of portal hypertension (high blood pressure in the liver) are present (again, this occurs rarely), the histological examination of the liver should be performed (liver biopsy). If liver architectural changes are present, upper gastrointestinal endoscopy will establish the presence or absence of esophageal varices, which require ei-ther long-term ß-blocker treatment or variceal ligation. The treatment of steatohepatitis and of biliary lesions is based on the correction of the metabolic syndrome and on long-term prescription of ursodeoxycholic acid.

Subsequent monitoring

Liver blood tests and blood cell counts are recommended twice a year for all patients with Turner syndrome and abnormal liver enzymes. For patients who did not undergo liver biopsy at the initial evaluation, persistently elevated liver enzymes for more than 6–12 months despite the correction of the metabolic syndrome and or ursodeoxycholic acid treatment, a liver biopsy should be considered. In case of liver architectural changes, abdominal ultrasound must be performed once a year and upper gastrointestinal endoscopy every three years to detect portal hypertension signs.

Glossary

Ascites: Is an excess of fluid in the space between the tissues lining the abdomen and abdominal organs

Biopsy: A piece of tissue removed from an organ – for example a liver biopsy.

Biliary atresia: A condition in which the liver bile ducts are blocked or absent.

Cholestasis: Is a condition where bile cannot flow normally inside the liver or from the liver to the gut.

Cirrhosis: Is a consequence of chronic liver disease characterized by replacement of normal liver tissue by scars (fibrosis) surrounding nodular areas of liver tissue.

Esophageal varices are extremely dilated veins in the mucosa of the esophagus. They are most often a consequence of portal hypertension, such as may be seen with cirrhosis; patients with esophageal varices have a strong tendency to develop bleeding.

Nodular regenerative hyperplasia: Is defined as the presence of multiple small nodules of liver tissue not surrounded by fibrosis

Portal hypertension: Is abnormally high blood pressure in the portal vein, the large vein that brings blood from the intestine to the liver

Primary biliary cirrhosis: Is an autoimmune disease of the liver marked by the slow progressive destruction of the small bile ducts

Sclerosing cholangitis: Chronic liver disease caused by progressive inflammation and scarring of liver bile ducts

Steatosis: Also called fatty change, is the process describing the abnormal retention of lipids within a liver cell. It reflects an impairment of the normal processes of synthesis and elimination of triglyceride fat. Excess lipid accumulates in vesicles that displace the cytoplasm.

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# Hearing and disease of the middle ear in Turner syndrome

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The ear and hearing

I n persons who genetically loose one X chromosome, no or very low levels of estrogen, the female sex steroid hormone, is produced due to the loss of function of the ovaries. This is found in Turner Syndrome where also hearing problems have been found to be frequent and have been added to the other occurring symptoms. A Swedish team provided in 1969 an initial description of hearing loss connected to the syndrome (1). Several studies have since then confirmed this finding. Because estrogen is missing there are indications that estrogens may have an effect on the ear and hearing, but the relationship is not fully investigated. Estrogens work through two receptors, estrogen receptor alfa (ERα) and beta (ERß). The expression of these receptors varies in different tissues and also in between species. They are shown to be present in the inner ear of both rodents and humans, which is a must for estrogen to have any effect on hearing at all (2–3). No other sex hormone has so far been proven to have a direct effect on the ear and hearing. Since the early eighties Turner syndrome girls have been offered growth hormone treatment to increase height velocity and estrogens to promote the appearance of secondary sexual female characteristics. How this hormone therapy affects hearing later in life, has not yet been possible to investigate, since these girls are just reaching the age when hearing loss starts.

Vestibular part
(the area dedicated to hearing)

Cochlea

Outer ear   Middle ear
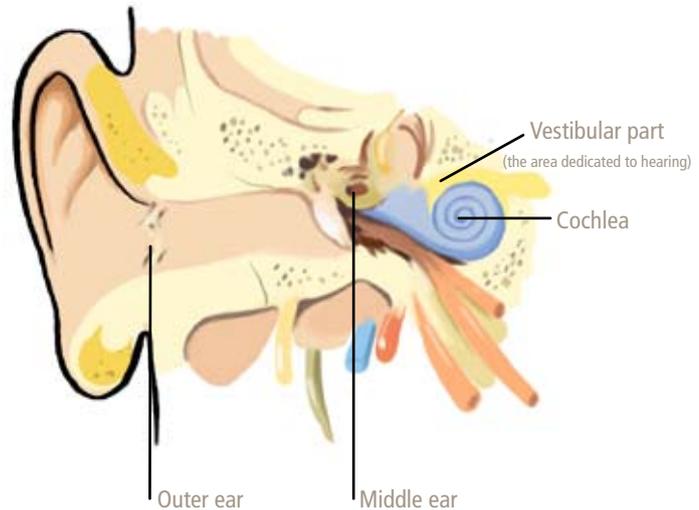
Anatomy of the ear

The ear consists of three parts- the *outer ear* (outer ear and ear canal) which through the tympanic membrane leads to the *middle ear*, which include the hearing bones. The *inner ear* contains both the cochlea (hearing) and the vestibular parts (balance). From both parts the cochlear nerve is transforming the information to the brain.

All three parts can be affected in Turner syndrome.

Outer ear

Low set ears and a wide short ear canal is common, this, however, do not effect hearing. (Figure 1).

Figure 1

A young Turner girl with low set ears (arrow).

Middle ear

In Turner syndrome recurrent otitis media (OM) (infection of the ear) is frequent, starting early in childhood (<6 months of age) and continuing late up in adolescence, and is more common than among other otitis media prone children. It is not uncommon that a girl with short stature and frequent otitis media, if still undiagnosed, can direct the thoughts toward Turner syndrome. The girl should then be referred to an endocrinologist and a chromosome test will reveal the syndrome. The cause of recurrent OM is still unknown, but growth retardation of the temporal bone (the part of the skull containing the inner ear) may be important. Aggressive treatment of otitis media is appropriate, and insertion of ventilation tubes (grommets) should be considered. Careful follow-up is important. (4). Levels of immunoglobulins (proteins involved in the immune system) called IgG, IgA, IgM, IgD and the four IgG subclasses as well as T- and B-lymphocyte (white blood cells also involved in the immune system) subpopulations has been investigated in young girls with Turner syndrome to examine whether a deficiency in the immune system may be the cause of their high record of otitis media. No major immunological deficiency was found that could explain the increased numbers of OM (5).

Even if treated according to guidelines, some of the affected ears will finally result in chronic ear difficulties. These middle ear diseases can lead to a hearing loss, due to as well as subsequent problems with discharging ears, destruction of the hearing bones, tympanic membrane perforations etc. (Figure 2). These chronic consequences can be repaired surgically, because the inner ear is still intact. Patients with chronic middle ear problems should be operated on without delay to prevent further problems.

The frequency of OM usually declines after adolescence and is not common in the young and elderly Turner syndrome woman.

Inner ear

In the inner ear two problems can develop. At first a large proportion of adult Turner syndrome women develop a mid-frequency sensorineural hearing loss (a "dip"). There may be a genetic background, because this "dip" is usually connected to the different phenotypes (more common among females with 45,X and karyotypes with isochromosomes) (Figure 3a). In the audiogram the "dip" is most commonly found in the 1,5 and 2 kHz regions. The gene location (locus) for the hearing impairment in Turner syndrome is thought to be situated on the p-arm of the X-chromosome (6). The "dip" has first been visualized in the audiogram in girls at the age of 6. This is usually not a problem for the Turner girl as long as the high-frequency region is still intact. This "dip", however, progresses over time (gets deeper) and can later in life lead to hearing problems (Figure 3 b). The presence of a dip is an especially strong predictor for future hearing deterioration.

Secondly, an early (>35 years of age), high frequency hearing loss can frequently be found resembling the developing hearing loss found in the normal ageing population (>60 years of age) called presbyacusis. Women with Turner syndrome develop a moderate to profound high-frequency loss, thus oftentimes leaving only the low frequencies spared. The hearing impairment has a cochlear (inner ear) origin, and is called sensorineural (7). This loss of hearing in the high frequencies is added to the "dip" earlier developed, together leading to a quite rapid progression, which is often followed by social hearing problems (Figure 4). The trouble often start with difficulties to hear in the so called "cocktailparty situations"

i.e. noisy environments. The person is more dependent on lip reading to compensate. At this time in life, when hearing is rapidly deteriorating, these women usually experience severe tiredness. This tiredness is due to exhaustion of trying to hear and listen throughout the day. This association between hearing problems and being tired is not often noticed. It is important to contact an experienced Ear-Nose- and Throat doctor in order to perform a hearing test and given information about hearing aids. It is known that only 13% of women with Turner syndrome aged 40 and above have normal hearing thresholds. Hearing aids are used by 3% of the women in the normal population, at the age of 65 or older, but in women with Turner syndrome 27% are wearing hearing aids. The rate of decline in hearing threshold in adult Turner syndrome women is comparable to that in a normal female population aged 70–90 years, regardless of initial age, initial hearing levels and karyotype (Figure 5). The rate of decline is especially high in the high frequency region.

A contributing cause for the sensorineural hearing loss in Turner syndrome women has been proposed to be the lack of endogenous estrogens (estrogens produced in the body). Estrogens have so-called neuroprotective and neurotrophic effects on the brain, which means that estrogens can be presumed to have positive and protective effects also on the hearing function.

Figure 2

a) Normal eardrum, b) Otitis media, c) Chronic perforated ear drum, d) Chronic perforation with affected hearing bones
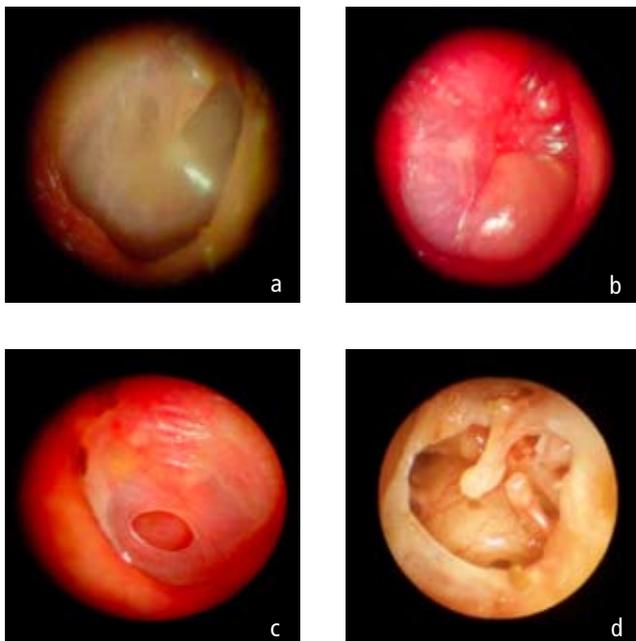
The "dip" and the connection to karyotype.
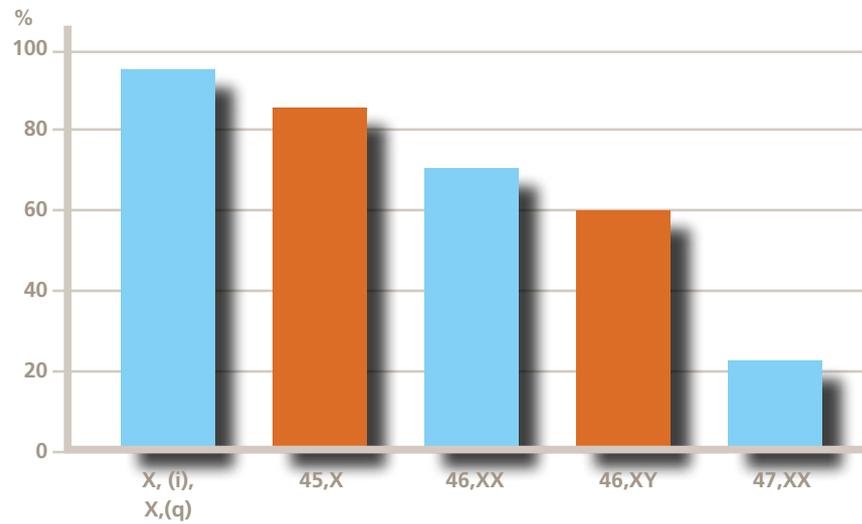
The "dip" deepens with age.
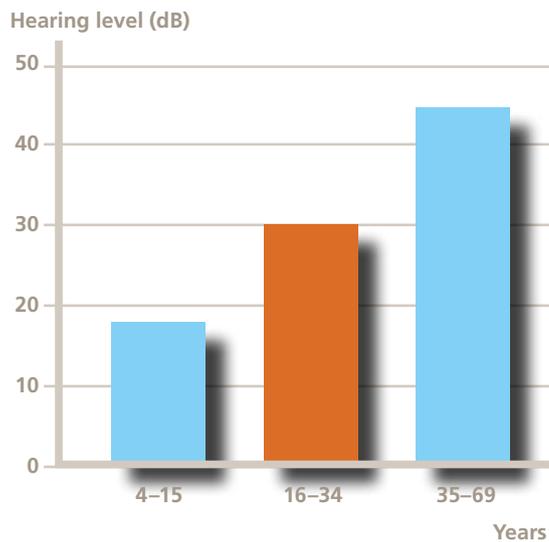
Other functional problems associated to ear-nose and throat

Swallowing

In early childhood swallowing and vomiting during breastfeeding and feeding can be a problem. This usually resolves within the first year of living. The cause is not yet fully known yet.

Speech

Girls with Turner syndrome often have speech problems. A high arched palate is common and might have some impact. If speech problems occur, referral to an Ear-Nose- and Throat clinic and a speech therapist is recommended.

Neurocognitive

The Turner syndrome-associated neurocognitive phenotype generally includes normal verbal function but with relatively impaired visual-spatial and visual-perceptual ability, attention, and working memory (8). Thus, the ways the brain understands and copes with visual impressions are impaired. It is not known if these difficulties in Turner syndrome represent central auditory functions (function of the ear) besides the visual. In adult age many of these disabilities are not as apparent, and may be due to the hormonal treatment. The visual-spatial and visual-perceptual abilities, however, seem to remain decreased in adulthood despite hormonal treatment, therefore giving rise to speculations that the decline in these functions has a genetic aetiology.

Sound localization provides information about the direction to sound sources. Normal sound localization is dependent on fairly intact peripheral hearing and on normal processing in the central auditory system. Aural orientation is an integral part of orientation, since it monitors the surrounding soundscape. Mild disturbances of sound localization are seen in Turner women who have not been substituted with estrogens during puberty. (6).

Recommendations

Be aware of the hearing problems connected to Turner syndrome and always refer a child with Turner syndrome to an Ear- Nose- and Throat specialist

Be careful and meticulous when handling the frequent otitis media during childhood-adolescence, in order to avoid chronic consequences.

Hearing problems is more frequent in the karyotypes 45,X and those containing iso-chromosomes.

Regular audiograms, testing both bone and air conduction during childhood/adolescence, can reveal a "dip" which is a strong predictor for future hearing problems. Advice for future profession can be valuable. On the other hand - if no dip is seen, hearing problems are infrequent

When the high frequency loss is rather rapidly added to the "dip" (over the age of 35) perform regular audiograms in order to be "in time" with hearing aids

Audiogram. The "dip" is shown in an audiogram from a 12 year old Turner syndrome girl (red arrow). The early high frequency loss is added (two arrows) to the earlier dip, resulting in a rather sudden severe hearing loss (blue arrow)
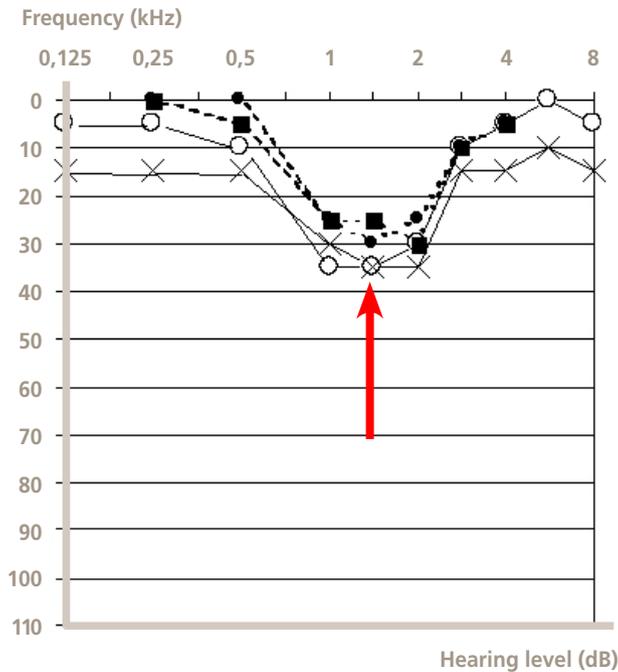
12-year old Turner girl
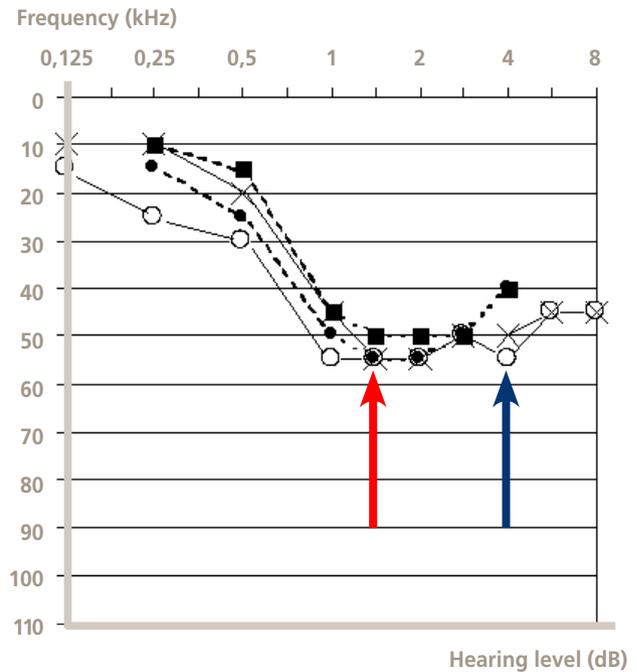
Middle aged Turner woman

Figure 5

In thin lines a reference material of hearing loss over time in five different age groups in the normal population of women is shown. In thick lines is the deteriorating hearing loss among Turner syndrome women in 2 age groups (27,8–42,7 and 43–51,8). It is concluded that women with Turner syndrome have a more severe hearing loss and at the age of 43–61 have a hearing comparable to a 71–80 years old woman in the control group.
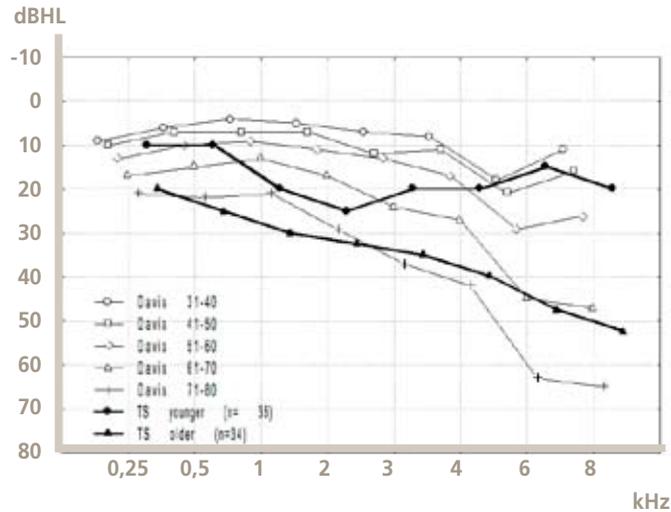
**Baseline median hearing threshold levels, two age groups, with Davis' references**

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part

3

Fertility and psychology

Sex hormone treatment

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After puberty, most women with Turner syndrome will require treatment with female sex hormones (replacement therapy), regardless of whether puberty was spontaneous or induced using estrogen. Adult women normally produce estrogen, progesterone (gestagen) and testosterone (androgen), as well as many other weaker estrogens and androgens. These hormones are produced in the adrenals and ovaries (Figure 1). As you can see from the illustration, both men and women produce the same hormones, so the designation "male" and "female" sex hormones is a misnomer, and is used primarily for want of something better. Women produce most of their estrogen and progesterone in the ovaries, while almost one half of their testosterone comes from the ovaries and the remaining half from the adrenals. In theory, this means that women with Turner syndrome, in whom the ovaries do not function, lack almost all of the estrogen that should be present, while they lack only half of the testosterone that should be present. Scientific studies have revealed that this does in fact apply to women with Turner syndrome.

By the end of the pubertal period, appropriate breast development, growth of sexual hair, and menstruation will have taken place. Maintenance of these characteristics will require therapy with estrogen and progesterone. This treatment also ensures that the uterus grows and attains the normal adult size (1). This type of treatment is called "hormone replacement therapy" – HRT. However, this treatment also affects a wide range of other body functions.

Why are sex hormones important?

The scientific basis for the importance of the sex hormones in maintaining good health is not completely understood, but there is no doubt that these hormones do play an important role. Figure 2 illustrates several of the relationships in which lack of sex hormones in Turner syndrome affects other body functions. We do not understand the details of all these relationships, and not all causal-relationships have been definitively proven.

Body shape and development of diabetes

The female sex hormones are important in the development of a female fat distribution pattern and continued therapy as an adult contributes to maintaining this fat distribution. In addition, estrogen has a weak, muscle-developing effect and contributes to maintaining muscle mass of the body. Several studies have looked at the effect of female hormones on glucose metabolism and, consequently, development of type 2 diabetes. There is no proven relationship, but treatment with estrogen appears to reduce the number of new cases of diabetes; a factor that is important in Turner syndrome where the incidence of diabetes is highly elevated.

Uterus

Many women with Turner syndrome can today choose egg donation (see chapter 22) and thus have the possibility of having children. After puberty, the uterus continues to grow for a few years. Some studies indicate that women with Turner syndrome will often require more estrogen than the dose which is conventionally given if the uterus is to attain its adult size.

Sexual function

Female sex hormones are not necessary to have sexual thoughts or sexual intercourse, but are necessary for the normal function of the vagina so that it can become moist at sexual stimulation. The male sex hormone, testosterone, also plays a part in normal sexual function, as do several other factors such as personality, childhood, and the first sexual experiences.

Breast development

After puberty, hormone replacement therapy is necessary if the shape and size of the breasts are to be maintained. Estrogen is necessary if pregnancy is desired, and estrogen also plays a part in normal milk production during the breastfeeding period.

Bone density

After puberty, estrogen is the most important hormone for the maintenance and continued calcification of bones, thereby preventing osteoporosis. We have recently shown that hormone replacement therapy in women with Turner syndrome prevents loss of calcium from the bones.

Blood vessels and blood pressure

Elevated blood pressure is frequently seen in both pubertal girls and adult women with Turner syndrome. Long-term elevated blood pressure is a highly significant factor for health of all people, but particularly for women with Turner syndrome, who can also have problems with dilation and dissection of the aorta. Estrogen has a small blood-pressure reducing effect which, together with the positive effect on the composition of the walls of the blood vessels and on inhibition of early stages of atherosclerosis, is positive. We do not yet know the full extent of this positive effect on the blood vessels and blood pressure. Neither do we know which type, or duration of estrogen therapy would be optimal, but future studies will hopefully clarify this question.

Liver

The liver has many functions: It produces a series of important proteins, takes care of the breakdown of various substances (detoxification of these substances); and it excretes gall into the intestine and is thus involved in uptake of nutrients. Liver function can be measured by determining the content of various enzymes, proteins and gall precursors in the blood. Altogether, these substances can be called "liver tests". In particular, in women with Turner syndrome the results for liver enzymes measured in blood samples are often

Figure 1

Estrogen and androgen – women and men. Sex hormones are produced by a complex enzyme system that converts cholesterol via several steps to the various sex hormones. Parts of this process take place in the adrenals and ovaries, while the other steps can occur in many of the body tissues. The hormones dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA) and androstenedione have very little androgenic effect, in contrast to testosterone and DHT.

Calling estrogens and androgens female and male sex hormones can be misleading because men have significant estrogen production and women have significant androgen production.

Normal levels in women:
Testosterone (nmol/l): 1 (0,55–1,8)
Oestradiol (pmol/l): 120–770 (<40–2400)

Normal levels in men:
Testosterone (nmol/l): 14,6 (8,4–25,4)
Oestradiol (pmol/l): 110 (48–170)

Cholesterol

Pregnenolone → **Progesterone**

17-OH-pregnenolone → **17-OH-progesterone**

DHEA → **Androstendione**

DHEAS → **Testosterone**

**Dihydrotestosterone (DHT)**   **Oestradiol**
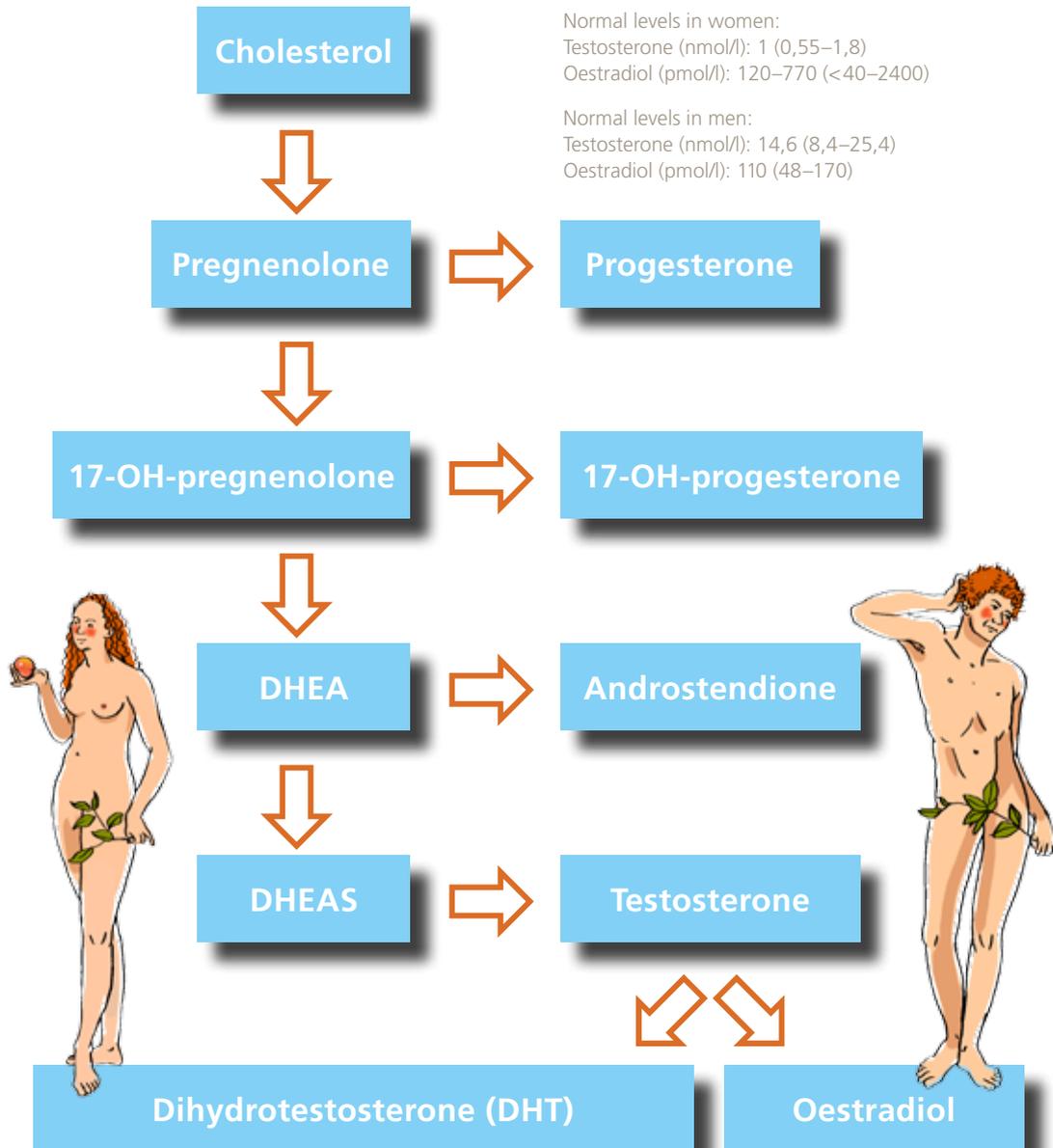
Figure 2

The serious effects of lack of genes on the X chromosome and/or premature ovarian failure (POF) and thus of female hypogonadism (absent estradiol), as seen in Turner syndrome, is illustrated in this figure. Hypogonadism has pervasive effects, affecting (1) different hormone levels, (2) cardiovascular features, (3) metabolic features and (4) features related to sex hormones, such as infertility. In addition, mounting evidence suggests that hypogonadism in Turner syndrome leads either directly or indirectly to a reduced quality of life. Lack of genes from the X chromosome has been implicated in the presence of an increased risk of congenital malformations, although no specific genes have been identified so far. Arrows indicate possible consequences – not all interactions have been shown in scientific studies. Not illustrated in the present figure are effects on the central nervous system. VO2max, the maximum capacity to transport and utilize oxygen during incremental exercise; IL-6, interleukin 6; IL-8, interleukin 8; TNF-a, tumor necrosis factor-a; PTH, parathyroid hormone.

Lack of genes from the X chromosome

Premature Ovarian Failure

Hypogonadism

Cardiovascular features
⇧ **Blood pressure**
⇩ **Aortic reactivity**
⇧ **Carotid intimal thickness**
⇨ **Endothelial function**
⇧ **Congenital malformations**
   Others?

Metabolic features
⇧ **Osteoporosis**
⇧ **Liver enzymes**
⇧ **Liver fatty tissue content**
⇧ **Fasting glucose and insulin**
⇧ **Cytokines and inflammation markers**
   (IL-6, IL-8, TNF-ß, C-reactive protein)

Body composition:
⇧ **fat mass**
⇩ **lean body mass**

⇧ **Morbidity**
⇧ **Mortality**

⇩ **VO2 max**
⇩ **Muscle strength**

⇩ **Insulin sensitivity**
⇧ **Diabetes**

too high (see chapter 17 on the liver function). Several studies have demonstrated that estrogen therapy has a positive effect on these liver enzymes. Whether, in the long term, fewer liver problems will be observed in women with Turner syndrome when more are treated with sex hormones is not known.

Brain

As described in the chapter on puberty (see chapter 5), sex hormones exert an effect on brain development. Whether this development stops after successful puberty or whether there is a continued positive effect of sex hormones, in particular estrogen, is still unclear. But several studies indicate that in adult life sex hormones do have a positive effect on a number of important brain functions (2).

Hormone levels
⇩ **Estradiol**
⇩ **Testosterone / androgens**
⇧ **FSH**
⇧ **LH**
⇩ **Growth hormone**
⇩ **IGF-I**
⇧ **PTH (Turner syndrome only?)**
⇩ **Vitamin D (Turner syndrome only?)**

Features related to sex hormones
Infertility
Lack of female secondary sex characteristics
⇩ **Sexual activity, thoughts and fantasies**
⇩ **Uterine size**

⇩ **Quality of life**

Which type of hormone replacement therapy should be prescribed?

Once the pubertal process has obviously finished and breast development has progressed well; the first menstruation has taken place; and the uterus has grown; hormone replace-

ment therapy should be regulated as desired by the woman. The purpose of treatment is to ensure optimal health for many years to come. Therefore treatment should be discussed in detail with the doctor, and the patient should switch between products if necessary. Because treatment will be given for many years, it may well be worth investigating which products suit the patient best. Typically, a product should be tried for 3 months before deciding whether it is optimal, or whether a different product should be tried.

There are numerous products available. There are many different products in Europe, some of which vary from those available in the US and Japan. The core products are the oral contraceptives which prevent pregnancy, and hormone replacement therapy. In Europe, oral contraceptives are comprised of a synthetic estrogen and gestagen, and hormone replacement therapies are comprised of human estrogen and a synthetic gestagen. The latter do not act as a safe contraceptive pill, and should therefore not be used by those few women with Turner syndrome who can become pregnant unless there is an actual desire to become pregnant. Hormone replacement therapy can be given as pills (oral administration), plasters (transdermal administration) or as a gel for application (transdermal administration). Finally, it is also possible to take estrogen as a nasal spray for inhalation through the nose – a product which however does not seem to have found wide acceptance.

In the US, hormone replacement therapy is mostly given as estrogen extracted from horse urine and a synthetic gestagen. In some cases, a gestagen coil that is inserted into the uterus can be a good alternative to pills, in particular if menstruation is irregular.

It is important to point out that we still lack knowledge on the many possibilities within hormone replacement therapies. Thus, it is not possible at present to state with certainty which form of treatment is best. Neither in the short-term, or the long-term.

What is the treatment outcome and how long should you continue hormone replacement therapy?

There is no agreement as to the treatment outcomes, but there is substantial evidence that those doses that have been given traditionally over the last years have been too low, and recent studies indicate that larger doses

of sex hormones should be given to ensure satisfactory growth of the uterus and calcification of the bones.

We believe that for women with Turner syndrome, the aim should be normalised female hormone levels (oestradiol, FSH and LH) (3). This means that many young women with Turner syndrome require estrogen doses greater than the 2 mg dose that has been traditionally given. In practice this means that many women will require 3–4 mg oestradiol (17ß-estradiol) and a gestagen.

Neither is it known with any certainty how long women should be treated with female hormone replacement therapy. Due to the lack of absolute knowledge on this topic, the current consensus is to mimic the conditions in women with normal menstruation. This means that women should undergo hormone replacement therapy for 40 years (first menstruation – 13 years old; menopause – 53 years old – Danish data). If puberty starts around 12–13 years of age, hormone replacement therapy should cease at around 53 years of age. However, if treatment does not start until later or much later in life, as has happened for many women with Turner syndrome, treatment should be continued until the woman is considerably older.

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Quality of life and sexual life in young adulthood

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Introduction

Turner syndrome influences growth, development, puberty and fertility and has therefore profound consequences on psychosocial life. Medical management aims at correcting as well as possible these aspects to improve health status and also alleviate the psychosocial consequences of the syndrome. Although quality of life can be easily conceptualized by everyone, it is difficult to measure for several reasons, including the fact that everyone of us put different practicalities behind this concept. However, it is important to formalize the evaluation of quality of life if one wants to evaluate it in a structured fashion and try to decipher its components and the variables that influence its variation. Evaluating quality of life in women with Turner syndrome is needed to better analyze the aspects that should be prioritized to improve their health status and measure the impact of medical care, in particular growth promoting treatments in childhood and pubertal management in adolescence. In this chapter, we briefly review the concept of quality of life and its measurement and we summarize some of our studies performed in France.

Evaluation of quality of life

There are more than 70 different quality of life instruments in the international literature. They can be administered as self-administered questionnaires or as interviews performed by trained personnel and will generally address specific aspects of quality of life such as health-related quality of life, self esteem, depression or social adaptation. All the instruments have clear limitations and scores are compared to a control group or to general population standards.

Health related quality of life

Health-related quality of life scores of young adult women with Turner syndrome are not different, on average, to those of women of the same age in the general population. The StaTur study (1) is the only prospective population-based study of women with Turner syndrome. It was made possible by the collaboration of several pediatric endocrinology centers in France and was based on the national registry of patients treated with growth hormone. A group of 891 young women, 22,6 years old in average (± 2,6 years), having been growth hormone treated from 1985 to 1997, were contacted to participate in a questionnaire study. The Short Form 36 (SF-36 (2)) was used to evaluate self-perceived health related quality of life. About 70% of the women contacted responded and no difference was found between women with Turner syndrome

and women at the same age from the general population for all the dimensions of quality of life (Figure 1) (3). The strength of our study is the use of a well validated questionnaire that was proposed to all women included in a national registry, unlike most studies where patients are recruited through one or several clinics or support groups, introducing involuntary biases. The main limitations are the fact that only 70% of the women responded (one can assume that those who did not want to respond would have responded differently to the questionnaire than those who did) and the fact that all patients had been treated with growth hormone (one can discuss whether those who did not use growth hormone or whose parents declined the use of growth hormone would have answered differently).

Similarly, in a clinical trial performed in Holland, Bannink et al. (4) found similar scores in 49 women with Turner syndrome and in a ref-

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Figure 1

Health related quality of life in young women with Turner syndrome in the StaTur study (3).
 Scores for the 8 dimensions of the self perceived health-related quality of life scale SF-36 (2) are shown for 568 young women with Turner syndrome, in comparison with women of the same age from the general population; higher scores indicate better quality of life; there were no differences between affected and unaffected women; with permission Journal of Clinical Endocrinology and Metabolism.
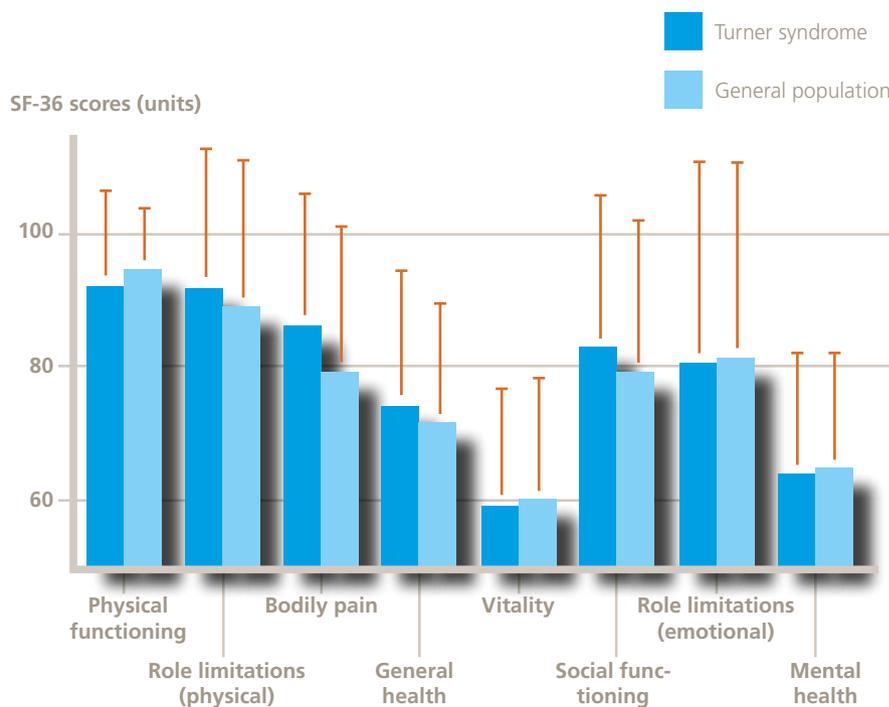
erence population, using SF-36 and another instrument called TAAQOL. These women had been treated with growth hormone, had had their puberty induced with estrogen starting at a mean age of 12,9 ±1,1 years and were 19,6 ±3,0 years old in average.

Evaluation of depression and anxiety

Several studies have presented controversial results on depression and anxiety, with some concluding that depression is increased (5–6) others decreased (7) and others comparable to controls (8). In the StaTur study, minor psychiatric disorders such as anxiety and depression were detected using the General Health Questionnaire 12 (GHQ-12). We found that the proportion of women with such problems was lower in women with Turner syndrome (24%) than in unaffected women of the same age (31%) (3). Therefore we can safely conclude that at least anxiety and depression is not increased in our population of patients.

Self-esteem

Self esteem was decreased in Turner syndrome in several studies (9). In the StaTur study, we used the Coopersmith Self-Esteem Inventory (SEI) (10) and found markedly decreased scores, in comparison with the general population (Figure 2). Similar conclusions were reached by the Dutch group using the Harter Self percep-

Figure 2

Self esteem in women with Turner syndrome in the StaTur study (1).
The Coopersmith Self-Esteem Inventory (SEI) (10) was used; results are expressed relatively to a reference population in standard deviation scores; "normal" results would be close to 0 ± 1 ; in contrast, here all results are significantly decreased.

Self esteem dimensions	Self esteem scores expressed in standard deviation score
General	-1,3±1,5
Familial	-0,3±1,1
Social	-0,8±1,4
Work	-0,3±1,3
Global	-1,1±1,5

tion profile (8). Infertility is certainly a major factor contributing to decreased self esteem. Indeed, in a study where women with Turner syndrome and women with primary ovarian failure due to other causes were compared, similarly decreased self-esteem, anxiety and shyness scores were detected (11–12).

In conclusion, recent studies on young women who have been managed by pediatric endocrinologists and have been treated with growth hormone and sex steroids show that health related quality of life scores are similar to the general population but that self esteem scores are decreased. However, it should be argued that so far we have only discussed mean scores and that women with Turner syndrome are like everyone else in the population: Some are happy and some are sad, some are successful and have a high self-esteem and other are depressed and have a low self esteem. Our aim as pediatric endocrinologists, was not just to describe the situation to characterize women with Turner syndrome, but rather try to analyze the factors that influence it with a special emphasis on the factors that were directly influenced by health care providers and therefore modifiable.

Determinants of quality of life?

Statistical models were used to decipher the factors influencing the scores that were discussed above.

Heart and ear problems

Turner syndrome increases the risk of heart and ear problems and we wondered whether these problems influenced quality of life. In the StaTur study, 26% of women (149/568) had ear problems (hearing loss, recurrent otitis) that were associated with a significant decrease of health related quality of life and self esteem (3). Similarly, heart problems (12% of the patients) were associated with decreased quality of life (3).

Height

One of the premises of growth hormone treatment in Turner syndrome and in short stature in general is that increasing height will be beneficial for the wellbeing of the individual. However, exploring this paradigm has mostly yielded negative results (13). The mean adult height in the StaTur study was 150,9±5,6 cm and the mean gain induced by growth hormone was estimated at 8,9 cm (14). This mean adult height is a few centimeters below the lower limit of normal height in French women (153 cm), meaning that more than half of the women remained short despite growth hormone treatment. When we

looked for a relationship between height or height gain induced by growth hormone and several aspects of quality of life, we found absolutely none. Similar results were found in the Canadian randomized study (15) where 12 untreated (mean height 143,7±6,1 cm) and 21 treated (mean height 148,9±5,7 cm) women were compared at the age of 20 and had absolutely similar health related quality of life scores measured by SF-36.

Other factors influencing quality of life

As expected, quality of life scores are not only influenced by factors that are specific to Turner syndrome (height, puberty) but also to a variety of non specific factors including paternal socioeconomic class, educational level, professional situation and adiposity (presence of obesity) (1; 3).

Puberty, sexuality and fertility

Turner syndrome has a profound influence on puberty and fertility and it is essential to analyze if these components influence quality of life and to use this information to improve pubertal management and fertility counseling. It is known that women with Turner syndrome are less likely to get married or cohabit and have sexual relationships later than unaffected women (16–17). We therefore included in our questionnaire questions regarding sexual life. The responses to these questions are shown in figure 3 in the context of self esteem and social adaptation scores. Although we do not have normative responses to the same questionnaire for unaffected women, it is clear that sexual experience is delayed in this population of women with Turner syndrome. In addition, those with less sexual experience had lower self esteem and impaired social adaptation both in univariate and multivariate analysis.

We also analyzed the onset of pubertal development in the StaTur cohort (Figure 4) (1). In more than 75% of the women, puberty had to be induced with sex steroids, while in the remaining 25%, some form of spontaneous pubertal development occurred, although half of these had to use sex steroids later to induce the onset of menses. Importantly, the mean age at starting sex steroids to initiate breast development in those with induced puberty was very late, on average 15 years.

Given the influence of sexual experience and the obvious relationship between pubertal maturation and sexual experience, we analyzed the determinants of sexual experience in the StaTur cohort, with particular emphasis on the influence of pubertal management. One difficulty in the analysis was to incorporate the fact that all women pooled together did not have the same age (actually ranging from 18 to more than 30 years) and that sexual experience obviously depends on time (more sexual experience with age). We therefore designed

Figure 3

Sexual experience, self esteem and social adaptation in the StaTur study.

Questions regarding sexual experience were answered by 568 women with Turner syndrome aged more than 18 years and 22,6 ± 2,6 years on average; they also responded to the Coopersmith Self-Esteem Inventory (SEI, higher values, higher self esteem) (10) and to the Social Adjustment Scale Self-Report (SAS-SR, lower values, better social adaptation); results are presented relatively to a reference category that was arbitrarily selected as those having no sexual experience, i.e. those who have an experience of sexual intercourse have in average 2,7 more points in the self esteem scale going from 0 to 50.

*p<0,05 ; **p<0,01

Type of sexual experience	n (%)	Global self esteem score (0–50)	Global social adaptation score (0–5)
Married	42 (8%)	2,9±1,4	-0,22±0,06**
Sexual intercourse	172 (30%)	2,7±0,9**	-0,22±0,04**
Kissing and dating	165 (29%)	0,8±0,9*	-0,18±0,04**
No experience	187 (33%)	0	0

Figure 4

Pubertal development in the StaTur cohort

	Spontaneous puberty		Induced puberty
	no secondary estrogen treatment	secondary estrogen treatment	
Number of patients (%)	69 (10%)	84 (12%)	522 (77%)
Age at onset of puberty (years)	12,5±1,6	13,6±1,7	15,0±1,9
Total pubertal growth (cm)	15,0±5,9	12,5±6,7	8,7±5,9

Figure 5

Influence of age at induction of puberty on age at first sexual intercourse in women with Turner syndrome from the StaTur study. Kaplan–Meier curves are shown, to take into account the fact that all women were not of the same age when they responded to the questionnaire; the curves show the probability for participants to remain without sexual intercourse (virgin) at a given age, in relationship to the age when estrogens were prescribed to induce puberty.

▪▪▪▪▪▪▪▪) Pubertal induction after the age of 14,5 years.

————) Pubertal induction before he age of 14,5 years.

⦿) Proportion of women without sexual intercourse at the age of 18,5 years in the general population in France; with permission Journal of Clinical Endocrinology and Metabolism.
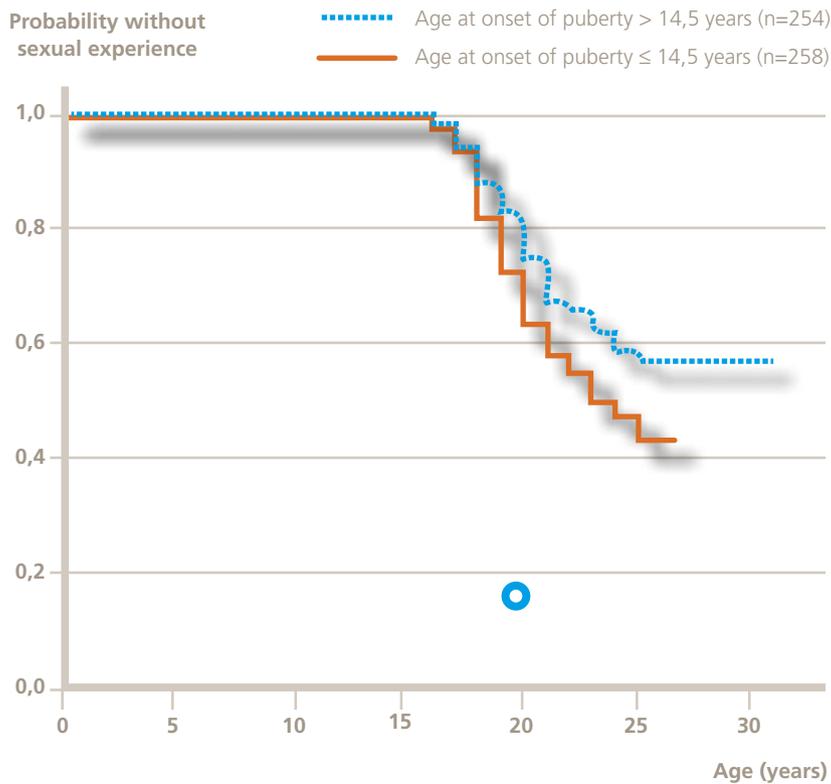
"actuarial curves" showing the proportion of women with or without experience at a certain age such as the one shown on figure 5.

These curves allowed us to detect 4 factors associated with delayed first sexual intercourse or first date: The presence of a heart malformation associated with Turner syndrome, being in a family where the father is a manual worker, having induced (as opposed to spontaneous) puberty and having a late pubertal induction (1). Every one of these factors would need a separate comment, but the age at pubertal induction is certainly the most important to us since it is the only modifiable factor. As shown on figure 5, we separated the women between those who had their pubertal induction started before and after the age of 14,5 years (median for the whole stature population). The first result is the marked delay of first sexual intercourse relative to unaffected women where approximately 85% of women have experience by the age of 18,5 years. In addition, the curve for those with later pubertal induction is delayed to the right and the difference remains visible at the age of 25 years.

Conclusions

In conclusion, our studies on several aspects of quality of life in a large population of young women with Turner syndrome are globally reassuring and carry important messages for all those who care for girls or women with Turner syndrome.

First of all, height should not be the primary focus of care although it is often put forward as one of the modifiable aspects of the syndrome. For instance, otological problems are certainly more important in the long term and visits to the ear nose and throat specialist should be as frequent as those to the pediatric endocrinologist.

Second, sexual life in adolescence and early adulthood is different (increased age at first experience) from other girls. This implies counseling the young girls on normal aspects of puberty and sexual life, so that coping with infertility is improved. It is also essential to prescribe a progressive regimen of sex steroids at the normal time of puberty, starting not later than 12 years as discussed in details in another chapter of this book. One part of this is to convince the parents that indeed prescribing estrogens will not decrease adult height in their child but rather reach the same adult height earlier, as now demonstrated by several publications (18).

Third, delaying the onset of puberty and first menses in adolescents with Turner syndrome will have long lasting effects on sexual life and

quality of life, alluding to a possible "window of opportunity" when puberty has to be induced, with irreparable damage taking place if this "window of opportunity" is missed.

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Psychological and psychiatric aspects of Turner syndrome

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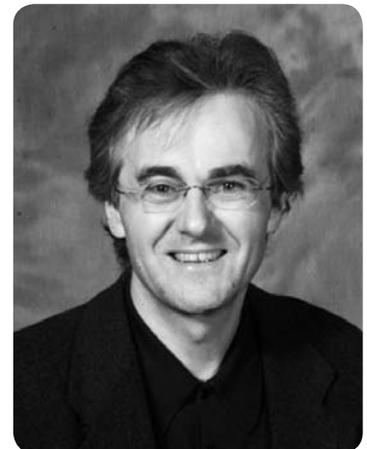
Social adjustment and behaviour

Turner syndrome can cause difficulties for a small number of children and adults, in terms of their ability to fit into our educational and social world. We don't know for certain how common these problems are, because no comprehensive survey has been done of a representative sample of females with Turner syndrome. Those who are not identified at birth are usually initially seen by clinicians because of an associated growth problem or a lack of spontaneous onset of secondary sexual characteristics in puberty. The accepted figure for incidence is around 4 per 10 000 live female births. There are around 20 million females in the UK under the age of 50 years, implying there should be 8 000 with Turner syndrome. Few of those who are seen by doctors for their condition ever get referred to a psychologist or psychiatrist. In research done by our group at the Institute of Child Health in London over the past 15 years or so, we attempted to identify all known children and adults with Turner syndrome from specialist clinics for paediatric and adult endocrinology in the United Kingdom. Perhaps surprisingly, we could not find more than 2 000, implying that far from all females with the syndrome ever come to medical attention. There is a risk that any conclusions drawn from an atypical sample run the risk of

"ascertainment bias', meaning that only those with the most obvious signs or symptoms will be identified. That could mean the psychological problems discussed here apply only to a minority of people with the condition. It is possible that there are many others with less significant social and cognitive impairment, which might be considered part of the normal range of personality and temperament. On the other hand, rarely within our sample of Turner syndrome females was a psychological or behavioural factor the presenting difficulty; intellectual impairment in association with ring chromosomes is the exception (5). In general, there was no correlation within our case series between the severity of the physical condition, and associated psychological problems.

Genetic and hormonal influences

The X-chromosome possesses a greater concentration of genes that are important for the development of our brains, and our mental functions, than any other chromosome. Whilst there is still controversy about which genes regulate "the social brain" (specific regions associated with social functions), there is no doubt that having the wrong number of sex chromosomes disrupts its physical and functional development. This is because gene dosage is normally very precise, and our capacity to compensate for having a single X-chromosome when two were expected is limited. Because maleness is determined by the presence of the complete Y-chromosome, and specific genes on the Y chromosome cause a cascade of events to take place that result

in the development of the testes and male sex hormones, so any foetus with just one X-chromosome will develop as a female. In rare cases, females with Turner syndrome do retain fragments of a Y-chromosome, but this does not make them any more "male" than those with a single X-chromosome.

One issue which is so complex that it would not be possible to do it justice here, is the role played by genetic mosaicism in the psychological features shown by females with Turner syndrome (7). By mosaicism, we mean the observation that in many people with Turner syndrome some cells (usually derived from the blood) are seen to have a different chromosomal constitution to other cells. There are subtle differences in the psychological characteristics of women who are monosomic for the X-chromosome (i.e. 45,X, meaning that all observed cells have a single X-chromosome) and those who have one normal sex chromosome, but the second X is structurally abnormal in some or all cells (for example, an isochromosome). The two situations are not the same genetically, for women with a single X have just one copy of all genes that are expressed from the chromosome.

In 46,XX females, one of the two sex chromosomes is inactivated. But it is not wholly inactivated, and there are up to a couple of hundred genes expressed from both of the X-chromosomes – effectively doubling their dosage. Regulation of the dosage of genes is of critical importance to normal development. Having too little gene product from a large number of X-linked genes accounts for all the

symptoms of Turner syndrome, either directly or indirectly. It may do so indirectly by affecting hormonal controls over development.

In the case of an isochromosome, there are effectively three identical parts of an X-chromosomes in all affected cells (although it is usual for such cases to be mosaics, with some cells containing just a single X – 45,X). The only variants that are likely to have a major impact on developmental progress are: First, mosaicism in which there is a normal cell-line (46,XX) in which the symptoms of Turner syndrome are much more mild if a substantial proportion of cells are quite normal in their complement of X-chromosomes. Second, where the abnormal second X is in a ring shape. This is known as a "ring-X" and if it is small it can be associated with non-inactivation and hence expression of many genes that ought to be silent. The dosage imbalance leads in almost all cases to mental retardation. It is important to note that this is the only variant of Turner syndrome in which there is likely to be significant learning difficulties in all domains, including language development.

In virtually all females with Turner syndrome, the ovaries do not develop normally which leads to insufficient production of the female sex hormone, estrogen, and absent pubertal development. Possibly, estrogen is also needed for some aspects of brain development too, even before the onset of puberty, and that many girls with Turner syndrome have insufficient quantities even during infancy and early childhood. Whilst this is a theoretical risk,

there is no evidence that providing very early hormone replacement therapy has substantial benefits on either behaviour or cognitive development, and it can have disadvantages. Normally, estrogen replacement therapy commences around 12 years of age.

Once the potential medical complications of the disorder have been managed (very often associated with congenital cardiac defects) the emphasis is on growth. The most common reason for children with Turner syndrome being identified, other than by prenatal screening or during the neonatal period (when the alert obstetrician should notice peripheral edema), is because of failure of growth in stature. It is important to emphasise that the textbook pictures of females with Turner syndrome with striking webbing of the neck, and a low-set ears, and skeletal abnormalities, are by no means typical of people with Turner syndrome seen in everyday clinical practice. Less than 50% have such features, although the majority have a distinctive facial appearance that a skilled clinician could identify. In order to enhance growth, treatment with growth hormone is standard practice, and this continues for many years until the long-bones have fused and further growth in stature is not possible. The treatment usually increases final height, but there is as yet no evidence to document that this additional stature has any major impact on quality of life.

For over 20 years, it has been known that many (perhaps most) females with Turner syndrome have difficulties in their social relationships with others, not only in childhood but also in adulthood. These difficulties are relatively subtle, and would rarely be obvious in the course of a paediatric or other medical consultation. They are, however, often the main cause of concern to families, after medical treatments have been established. If the parents raise their concerns with a consultant, the response is usually that such difficulties are understandable in light of three factors: First, the child's short stature relative to her peers; second, the fact that she looks dysmorphic; third, the fact that she feels different from her peers on account of her infertility. In recent reviews on the subject of Turner syndrome and its management (1; 6; 11; 13) there is no mention of impaired social perception and responsiveness except in the context of the three factors outlined above (i.e. short stature, infertility, and an unusual appearance). There is overwhelming evidence that for a substantial minority of people with Turner syndrome, the social difficulties are due to misperception of other people's social cues and a failure to respond appropriately. They are primarily due to differences in the way in which the brains of people with Turner syndrome process social information and do not result from the indirect influence of short stature or of self-esteem issues associated with infertility.

Childhood

Language development

The centres of the brain used for the expression and comprehension of language are normally situated on the left side (the left cerebral hemisphere). In Turner syndrome these centers may be less "lateralized" and so do not work as efficiently as they should. The brain normally requires language to be processed on the left side in specific areas. If those specialist brain regions do not develop normally, and language has to be processed in a more widely distributed network - perhaps involving the right cerebral hemisphere too – delays and dysfunction can result. Normally, a child's first words (other than "mama" or "dada" which are effectively babble) are heard around 12 to 18 months but in nearly half (40%) of girls with Turner syndrome the onset of language is delayed. Phrase speech, which has usually been heard by 36 months, is delayed beyond this point in development in around one in five girls. On the other hand, eventually verbal skills usually become relatively more competent than non-verbal skills (such as constructional or numerical abilities), which are adversely affected in four out of five cases.

We can classify expressive language skills in various ways, but the simplest might be to draw a distinction between "structural" (using grammar correctly, understanding the meaning of words, remembering what someone has just said to you and replying appropriately) and so-called "pragmatic" abilities. The latter term encompasses aspects of language that are essential for social communication. We learn how to use language to make our needs known as toddlers, but as we get older we normally want to be able to engage in social conversations too.

Children with Turner syndrome have subtle difficulties in both the expression of socially appropriate language and its comprehension, although the "nuts and bolts" of language are generally intact. The domains affected include:

- Inappropriate initiations.
- Interrupting people who are talking to someone else, which is linked to a tendency to be impulsive.
- Difficulty constructing a coherent account, such as an explanation that is easily comprehensible to the listener.
- Tending to focus on one favoured subject and bringing the conversation round to that subject over and over again.
- Not setting a context for what is being talked about, for example might introduce names of people which are not familiar to the listener without further explanation, or introduce a subject unrelated to the preceding conversation "out of the blue'.
- A lack of rapport, and relative insensitivity to non-verbal and verbal cues from the person being addressed, which is linked to a more general tendency to lack social perceptiveness.

About 25% of females with Turner syndrome have some difficulties, which are within the probably clinical range of severity, in terms of the use of language for social communication.

Besides the expressive language characteristics of Turner syndrome, affected girls may also have a literal comprehension of language, and limited "verbal working memory'. Parents soon learn that their daughter finds it hard to understand instructions when they are not precisely expressed, or not very specific. The term "working memory" refers to our ability to hold information on-line whilst we are processing it. The skill develops during childhood; by the time they reach school-age most children would be able to remember three linked instructions quite easily ('go upstairs, find your dirty washing, and bring it to me'). About three in five girls with Turner syndrome would have difficulty with this task. The problem would often be associated with poor attention to the instructions in the first place. But even if they are able to repeat the injunction back accurately immediately after it has been given, they would not necessarily complete the task; within a minute they only recall the first instruction and would have forgotten the rest. Breaking down instructions into simple elements, ensuring each is completed sequentially is essential; teachers need to be aware of this as well as parents. Difficulty holding information "on-line" has particular significance when attempts are made at mental arithmetic. This is a major challenge for many females with Turner syndrome, both at school and in later life.

Other autistic-like behaviours

Some girls with Turner syndrome have quite restricted interests. They tend to dwell on the same subject in their conversations and, rather than playing imaginatively, they have oddly formal play. A tendency to adhere to rigid routines can be both a strength and a weakness. Many girls with Turner syndrome (around a third) are typically upset by changes in a routine and prefer the rigid organization of a day in temporal terms (e.g. leaving for school at the same time precisely), or the organization of place (e.g. taking the same route to school, sitting in the same place at a table). On the whole, their repetitive behaviours, restricted interests, inflexibility and adherence to rituals, are rather mild and we do not tend to see the stereotypical motor behaviors we associate with autistic children. However, this aspect of the behaviour of girls with Turner syndrome has never been investigated sufficiently systematically to be certain whether the symptoms are rare. They could just be different in kind to the autistic features of behaviour that are found among children on the autistic spectrum. There is no doubt that overall there is a higher risk of autistic disorders than is found in the general population of girls of normal intelligence, being at least 5% (Creswell and Skuse, 2000).

Social skills

Many girls with Turner syndrome are popular with their peers and have no difficulty making friends. They have engaging personalities, and they are exceptionally trusting. Because they are small in stature, they tend to be "ba-

bied" by other girls at school, and this may have some adverse impact upon their social development. On the other hand, they may also be teased and there is a tendency for adults to ascribe such teasing to their short stature. Teasing is a problem for many children of school age, and it is by no means clear that girls with Turner syndrome are teased because of their stature or their odd appearance more than many other children who do not have the syndrome. We suspect that inappropriate social behaviour may be a more salient risk factor.

One of the most common stories parents recount about their daughter with Turner syndrome is the observation that she may make friends easily, but she also loses friends easily, for reasons that are often hard to ascertain. There are several associated characteristics. First, it is hard for many girls with Turner syndrome to manage relationships in groups. They feel much more comfortable with one special friend, and it may be that the special friend will introduce them to other girls and protect them in group situations where they can easily feel out of their depth. This phenomenon seems to be due to a combination of factors: Lower speed of processing social information; lack of skill in deciphering social cues in terms of gesture and subtle characteristics of language; difficulty understanding nuances of a social hierarchy). They often become dependent on that single friend, and if the relationship should break down (sometimes, because the friend feels it is just too intense) there can be major emotional consequences. All these factors have an impact

upon self-esteem: It is an over-simplification to attribute self-esteem issues to short stature or infertility concerns.

With respect to specific difficulties in social relationships, which can in adulthood lead to withdrawal, and depression, around one in five of children with Turner syndrome have abnormalities in their reciprocal social relationships that are of probable clinical severity. These are not associated with intellectual impairment; they appear to be linked most strongly to a relative lack of understanding of other people's thoughts and feelings. As many as a quarter persist in telling people things they already know, a figure that is over double that of typically developing children, and a characteristic that could irritate people. Girls with Turner syndrome are aware of their deficient social skills, and they may try to model their behaviour on that of a sister or their closest friend in an effort to become accepted. A tendency seldom or never to look at the person she is talking to is characteristic of nearly one in five females with Turner syndrome but is found in less than 5% of the general population, a factor which also militates against the development of normal social relationships (4; 8). Nearly one in six females with Turner syndrome do not have even one or two close friends.

Motor skills

There may be some differences from most girls of their age in respect of their motor skills, and these encompass both fine motor skills and gross motor abilities. Their hand-eye

coordination is not developed to a normal extent, and their spatial awareness is poor. All this means that many Turner syndrome children would not be represented in sports teams. Their relative clumsiness and small stature can be a handicap, but a contributory factor to children not being picked for school teams relates to their processing of social information. When we play in a team successfully, we need to be able to read the mind of the team and to measure our contribution against the progress of others in the team towards a shared objective. For many girls with Turner syndrome that process would represent a huge challenge. Nearly a third of females with Turner syndrome cannot ride a bicycle competently, and about one in six cannot confidently eat with a knife and fork. These motor skill deficits are little discussed in the reviews of "challenges" associated with Turner syndrome, but they clearly could have a major impact on social development.

Communication

When we communicate with other people face to face, we need accurately to decipher their facial expressions, and to use appropriate facial expressions ourselves in order for a genuinely reciprocal social relationship to develop. Girls with Turner syndrome tend to lack a full range of facial expressions compared with others of their age, and may not spontaneously use social smiling to guide their interactions. They may also have difficulty reading other people's mood: This can become a particular problem with peers who tend to be rather less tolerant than adults

of someone who appears to be slightly out of kilter with them. The ability to recognize when someone is getting bored listening to you talk about your favorite subject is rather important, but it is common for them to go on rather longer than is socially appropriate. Around 15% do not use non-verbal gestures and other non-verbal cues to scaffold their communications appropriately, and 25% are relatively socially inexpressive, not using appropriate smiling or facial expressions to the same extent as typical females of the same age (9).

Their relatively poor set of expressive characteristics can lead to difficulties in social interactions with other children and potentially to conflict with teachers. At home, parents can feel frustrated that their daughter not responding appropriately to their mood, and can seem unduly focused on her own interests. Despite these characteristics, girls with Turner syndrome are typically very willing to please and appear superficially charming and friendly.

Females with Turner syndrome typically have difficulty reading facial emotions, especially negative emotions as shown in the figure below, which depict sadness, fear, anger and disgust. The reason for this is unknown, but it is likely to be associated with a lack of normal connectivity between regions of the brain that are normally concerned with emotion recognition. The biggest problem is with the recognition of fear: On average 45,X females are less accurate in this ability than over 90% of the general population. It is likely

Emotional faces, from series of 60 faces prepared by Paul Ekman. (Pictures of Facial Affect) http://www.paulek-man.com/research.html)
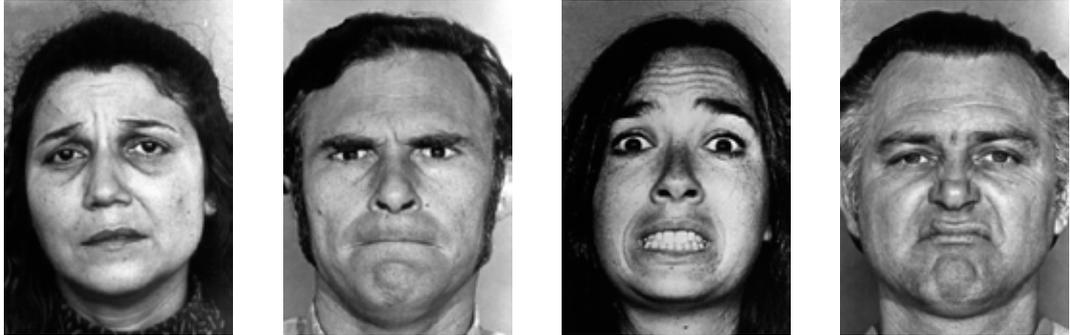
that one contributory factor is their failure to use information from the eyes to give clues as to the underlying emotion. Interestingly, the very experience of fear is one that many Turner syndrome females do not have, even in situations that most people would regard as fearful. It is perhaps for this reason that they rarely enjoy "being scared" by entertainments such as movies which are designed to evoke those sensations.

Making friends

Girls with Turner syndrome are often popular with other children at primary school, because they tend to be tolerant and gentle toward other children, particularly children younger than themselves. In later life, in our extensive experience, the favourite profession for women in adulthood concerns caring for preschool children, especially nursery nursing. This has many possible reasons, not least of which is their infertility, but their kindly tolerant nature

is another positive factor. This occupation is also relatively structured and does not include complex adult interpersonal work relationships.

Most children with Turner syndrome are very keen to make friends among girls of their own age; they appear more stereotypically female than most girls. This is, we suspect, because they are keen to observe female behaviour and model their own behaviour on it, requiring a conscious appreciation of what makes girls distinctive. It is hard for them to learn social skills, and thus to acquire friends, without some effort. Because of their diminutive appearance, they appear younger than their age and this can be a handicap in many ways. In general, we tend to respond to children according to their size (and assume age from that social cue). Consequently, girls with Turner syndrome are often treated by adults as if they are younger than they really are.

Difficulties may arise if social skills are impaired for the reasons discussed, and parents may be uncertain whether the resulting social isolation is related to their medical condition. This becomes much more of an issue in adolescence, because the social world becomes so much more complex. It is harder to sustain an exclusive relationship with one "special friend" and there is an increasing tendency for girls to go out in groups. There is also the burgeoning interest in boys, in typically developing girls, but it is common for those with Turner syndrome to be relatively detached from the sexual preoccupations of typical girls at this time. Psychosexual immaturity is recognized as a feature of Turner syndrome, but a lack of interest in sex is often ascribed to short stature and/or infertility. That seems very unlikely. Short women, who do not have Turner syndrome, are certainly not uninterested in sex. Women who have been found to be infertile for reasons other than Turner syndrome are also sexually active. It seems probable that the explanation lies in the differences in development of brain regions that are normally activated by sexual interest in women with Turner syndrome, and in the lack of their integration with higher brain (cortical) areas that turn arousal into action.

It should be possible to address some of the reasons for a lack of friendships, in those few girls who are finding it difficult to keep friends, by teaching some simple rules:

- There is a need to listen to the other person and to respond to what they are interested in, rather than persistently imposing your own preoccupations on them.

- Second, to remember that all social conversations involve turn-taking, which is often poor in Turner syndrome.
- To learn to read other people's body language so that you can judge when they are getting bored, or irritated with you.

Remember that for children with social skill deficits, these will be amplified in groups: Most girls with Turner syndrome would feel more comfortable interacting with one other child.

Attention deficits, impulsivity, hyperactivity

Attention problems are often reported from home and from school, among children with Turner syndrome during early and middle childhood. The severity of the associated hyperactivity then tends to diminish, although poor attention can persist into adolescence, and even into adulthood. The proportion with significant attention problems during childhood is over 75%, and the short attention span associated with Turner syndrome can have an impact on educational progress. It is not known whether it responds to stimulant medication, such as Ritalin.

Mathematical and non-verbal cognitive skills

For most females with Turner syndrome there are major difficulties with mathematical abilities. There are several reasons for this. The most important is that, for reasons we do not understand, Turner syndrome is associated with a fundamental problem in the appreciation of number magnitude. Normally, when we are asked if one number is bigger or smaller than another number we place those numbers on a "number line" in our mind. We probably learned to do this when we were children before we went to school. But girls and women with Turner syndrome usually cannot use this technique to solve basic questions about number size, because the way their brain has developed does not allow them to imagine a number line. Consequently, even very simple decisions about numbers will take them very much longer than an average person. The speed of processing issue is of huge significance, and there is no way round it – girls with Turner syndrome ought to be given longer to finish examinations that require them to use mathematical skills. A second reason why they have difficulties with mathematics is that they cannot hold information "on-line" as easily as other people, so mental arithmetic is almost impossible unless the calculation is very simple or can be rote-learned. The third reason has to do with cognitive development in the skills required to appreciate the spatial relations of objects, one to another. Across the whole range of non-verbal skills, females with Turner syndrome are likely to have poorer performance than typical females of the same age.

It is possible to gain a sense of the degree of difficulty experienced by females with Turner syndrome by looking at the results of a copying task, using a complex figure that is commonly employed in neuropsychological research. The task is first simply to copy what is seen. Coloured pencils are used, so that the order in which the various elements of the figure are copied can be determined afterwards. Then, after a delay of 30 minutes, the person is asked to reproduce the figure from memory. Examples of figures drawn by females with Turner syndrome and normal verbal intelligence are shown below in comparison with figures drawn by typically developing children.

Rey-Osterrieth complex figure

In the figure below examples are given of the ability of typically developing children between 6 and 10 years of age to copy the figure directly and to remember that copy after a delay. There are standard ways of scoring the accuracy of the reproduction of this figure by the person being tested.

In figure a) a girl with Turner syndrome of 7,5 years has copied the complex figure, and in b) she has reproduced it after a delay of 30 minutes. She has normal verbal and non-verbal intelligence. Her copy is not as detailed

Figure

Rey–Osterrieth complex figure. Representative drawings that illustrate age-related changes in products and process beween the copy and memory conditions. http://www.cogsci.ucsd.edu/DCNL/research.normal.htm
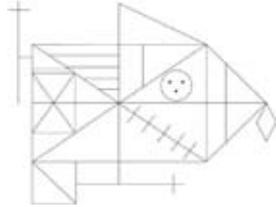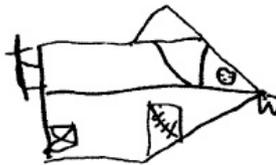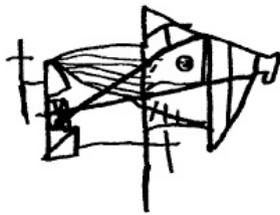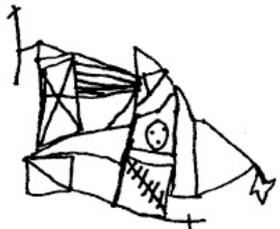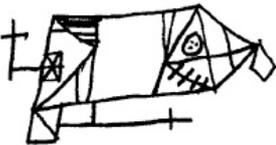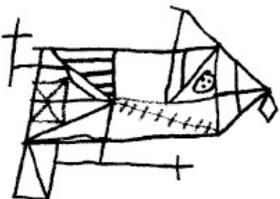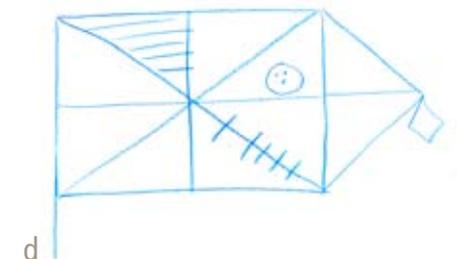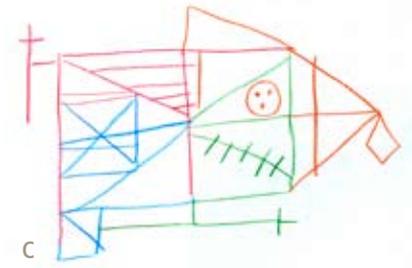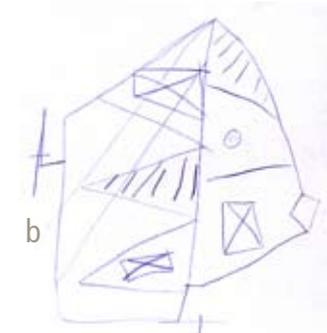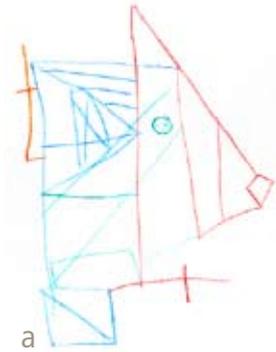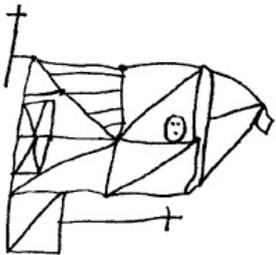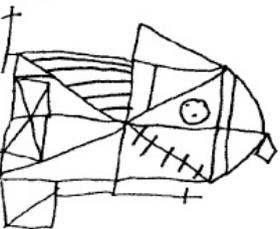
as the example given above, and her recall is poorer than we would expect, given the fact that on an IQ test she has nearly average ability. Note that the usual way to start drawing this figure, during the initial copying phase, is to create the body, which looks like a rocket on its side, using the pink pencil. Most of the children in the examples above do this, but neither the child nor the adult with Turner syndrome described here do so. This gives the impression that they are seeing the figure as the sum of individual parts, rather than as a whole shape with additional details. We do not know exactly why people with Turner syndrome have these visuospatial problems, but they indicate that critical regions of the brain which are concerned with the processing of visual information are not talking to each other. The tendency to focus on detail and to miss the bigger picture may influence other aspects of the personality of people with Turner syndrome.

The pair of figures c) and d) were drawn by an adult with Turner syndrome, in her mid-twenties. She also has normal verbal and non-verbal intelligence, both close to average. Her initial copy of the figure (c) is relatively good, although not as accurate as we would expect given her ability. On the other hand, her memory for the figure is very poor with lots of detail missing (d). This is worse than the remembered figure drawn by a typical 10 year old child, which is also shown in the illustration.

Adulthood

Many with Turner syndrome go undiagnosed, we suspect. Therefore, any comments made about their behavior in general must be tempered by the knowledge that the relatively few who have discussed their social difficulties may represent a small proportion of the total. Despite an effort to recruit from all specialist clinics in the country, we were unable to identify more than 20% or so of suspected adult cases. A major reason for this lack of success could be that women with Turner syndrome in the UK are not coming back for medical attention to endocrinologists once they have left paediatric services. It could be that women who do continue to attend are more seriously affected in some ways, and this could lead to an ascertainment bias.

One often mentioned issue is a lack of assertiveness and undue inclination to trust others. At work this means difficulty to refuse a request, or to stand up for one's own rights. This may be related to the fact that in Turner syndrome emotional regulation is quite difficult, and so the idea of confronting someone in a superior managerial position and rationally arguing one's corner may be hard to contemplate. Whilst this lack of assertiveness is often ascribed, somewhat unthinkingly, to short stature there is no evidence to support the view that women who are short are less assertive than those who are of average stature. It seems far more likely that the problem lies in the development of brain circuits that are associated with assertiveness. The combina-

tion of having a single normal X-chromosome, and estrogen deficiency, adversely affects the development of brain circuits that are crucial for normal emotional regulation and social perception.

Some of the social issues that are relevant in childhood continue to pose problems in adulthood. Making close friends can be hard, because of the need to get on the "right wavelength" with other people. Although facial emotion recognition improves with practice, there may be a particular problem still in determining when someone is feeling irritated or angry. Also, the relatively slow processing of non-verbal and verbal (prosodic) cues in conversations, and the difficulties experienced when trying to link what is said to emotional indicators in the verbal and non-verbal domains (tone of voice, body language) can make it difficult to read other people's intentions accurately. This is all made worse by the tendency not to make eye contact with others directly (10).

Many women with Turner syndrome choose to work primarily with children. There are good reasons for this, as has been indicated previously. Coping within a complex social environment of adults can put a lot of strain on women with Turner syndrome because they have consciously to process information about their work colleagues in a way that most people would not need to do. For that reason, they may develop perceptual skills that are near-normal but at the expense of mental energy.

Mental health issues

Typically, women with Turner syndrome have high levels of social anxiety, which can be exacerbated by concerns about their own femininity and their infertility. Not surprisingly, some succumb to social withdrawal and into depression. Few studies have been published on the prevalence of significant psychiatric disorders associated with Turner syndrome that have used systematic methods of evaluation. At the Institute of Child Health in London, we conducted one of the only systematic studies of this matter, in which over 50 women with Turner syndrome were interviewed at length about their current and past mental health, using standardized procedures. The results are instructive, although they need to be evaluated in light of the fact that it was not possible to obtain equivalent information from women from the general population of the same age. Accordingly, we cannot be certain how much these women with Turner syndrome differed from the general population. We had hoped to address the question of whether knowing about one's infertility was relevant to mental health issues, by interviewing a comparison group of women with premature ovarian failure, but this proved impracticable. Such a comparison group was however used by Schmidt et al (2006), in a study with an emphasis on whether Turner syndrome was associated with personality characteristics of shyness and social anxiety. Interestingly, they found rather similar results in both samples,

which were equivalently shy and anxious. The evidence to date emphasizes the point that we should not assume that the prevalence of mental health difficulties is peculiar to women with Turner syndrome, although the reasons for their mental health difficulties may differ from others.

We interviewed women who agreed to take part in the study, from a database of those women with Turner syndrome who were known to adult endocrinologists at clinics with a special interest in that condition, in the United Kingdom. We do not know how representative the women who agreed to take part in our study were, of all who have had a diagnosis of Turner syndrome in their lifetime. However, they are likely to be more representative than those described by the only other project that used a standardized method of ascertaining mental health problems (3), because in that study, recruits had to agree to stay for 4–5 days at a research centre in the United States. This is likely to have biased against the recruitment of those women with severe social anxiety and social phobias (the proportions of which were found by those authors to be surprisingly low in their interviewed sample). In our study they were visited in their own homes.

In a recent study from our research group, nearly 40% of the women had current or previous significant mental health problems. In general, the later the diagnosis of Turner syndrome had been made, the more severe these problems were; they were most likely to be found among women whose diagnosis had not been made until they were in their adolescence.

Mental health disorders fell into two broad categories. First, many women had some form of intense anxiety. This manifested in most cases as agoraphobia (a fear of public spaces, hence reluctance to leave their home) and associated social anxiety (10%); they were reluctant to go out of their homes and to mix in social situations. Other women had specific phobias and intense associated anxiety amounting to panic attacks (5%), or generalized anxiety. The social phobias were related to a lack of social skills and a lack of confidence in social situations because of self-awareness, a realization that they are doing "something" wrong but a lack of clarity as to what that might be.

The second main category of disorder was depression. One in five women was either depressed at the time they were seen, or they had been treated for a depressive illness. This was often associated with anxiety. A few had been treated with antidepressants for several years. Some had an associated eating disorder, including anorexia nervosa and bulimia nervosa. It is not possible to identify any clear precipitating factors for this depression in most of the women who were interviewed. None of them spontaneously mentioned infertility as being an important factor, but several were concerned about their lack of social relationships. Late diagnosis did mean greater difficulty in coming to terms with the condition though, and it seemed to be a contributory factor. Few

women made mention of their relatively short stature, and it seems unlikely that this was of any great independent relevance to their state of mental health. Our finding was that current depressive illness of clinical severity affected 13% and that a further 7% had had a significant depressive episode. The proportion with current depression is similar to that reported by Cardoso et al (2004), although they found many more (36%) had had major depression during their lifetime. In a survey of females with Turner syndrome by Sutton et al (2006) the proportion identified with depression was much lower. In that study, there was a less systematic assessment of mental health, but the authors questioned their subjects (children and adults) about their concerns regarding their diagnosis of Turner syndrome. Infertility was persistently mentioned as the major concern, along with short stature. We could speculate that the difference in preoccupations between what was found in our survey, and the findings of the Sutton et al (2005) investigation, is attributable mainly to cultural differences. There is little doubt that adult stature is a more salient issue for both men and women in the United States than it is in the United Kingdom. There is evidence from other sources that both sexes in the USA regard an ideal adult height as being several centimeters taller than the ideal cited by populations elsewhere in the world. We do not know why women with Turner syndrome in the UK are apparently less preoccupied with their infertility than they are in the USA, but it may be that they receive more support from peer groups here, and there could be less of a cultural emphasis on the need to fulfill an ideal of womanhood.

Summary

People with Turner syndrome usually have entirely normal intelligence, and are capable of achieving success in many different fields in life, both in terms of their personal relationships, in academic achievements, and in the workplace. There are two main areas of vulnerability that are hardly recognized by professionals who care for girls and women with Turner syndrome, although they are known to parents and to individuals with the syndrome. First, there is the issue of social vulnerability. This is not due primarily to short stature or concerns about infertility. It has to do with the different development of key areas of the brain which process social and emotional information, in people with Turner syndrome. The social difficulties faced are often attributable to a failure to read accurately social cues (and to give the appropriate range of social signals to others). One consequence of this is that many females with Turner syndrome are too trusting of other people, and this can lead to significant problems in both childhood and adulthood. The failure to sustain friendships, which is an issue for children and adolescents in particular, can lead to a loss of self-confidence and ultimately to social anxiety and depression, or to an eating

disorder. In general, psychiatric problems are more common in women who had a later diagnosis, especially when this was not given until adolescence or early adulthood.

The second main area of vulnerability concerns the processing of visuo-spatial and numerical information. The reason why these issues affect nearly all women with Turner syndrome is because of developmental differences in those parts of the brain that are required to process this information. At school, if these issues are not appreciated (perhaps because the school is not aware the child has the syndrome, or they have not been supplied with any explanation concerning the associated specific learning difficulties) girls can find they are not achieving in subjects that draw on these skills – and can be accused of not trying sufficiently hard. In practical terms, parents will be aware of how easily their daughter can become disorientated in an unfamiliar place, and reading a map can present a huge challenge. Arithmetic calculations, such as "how much change am I due for this purchase?" can take far longer for someone with Turner syndrome than a typical female of the same age. All these factors can militate against the development of social confidence and in some vulnerable girls and women lead to agoraphobia, and withdrawal from society. It is essential that paediatricians and adult endocrinologists who are seeing women with Turner syndrome appreciate the range of their vulnerabilities, and the potential risks associated with them. So long as the anxieties and social phobias that are commonly reported from females with Turner syndrome are at-

tributed exclusively to their short stature, or their concerns about infertility, they will not receive appropriate help.

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Fertility, spontaneous pregnancies and egg donation

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Fertility

Ovarian failure is one of the characteristic features in Turner syndrome. In female foetuses with Turner syndrome normal numbers of developing eggs are seen during foetal life and up to week 18 of pregnancy. From the latter half of the foetal period, a massive progressive loss of ovarian follicles containing the small immature eggs occurs (1–2). A suggested reason for this loss has been directly linked to the missing X chromosome or more specifically the heterologous X chromosome pairing in 45,X-foetuses and lack of meiotic cross-over (3–4), when one X chromosome is missing. Such pairing of similar chromosomes (for example a pairing of the two chromosomes number 5) takes place in all cells, when the cell divides. It was unknown at which age the eggs totally disappear from the ovaries until our recent results (5) revealed that 15 out of 57 (26%) Turner syndrome girls, aged 8–19,8 years, referred to our hospital for evaluation of their fertility potential, had follicles in small biopsy pieces of the ovarian cortex, more closely described later on in this chapter. Follicles were similarly found in girls between 12 and 16 years of age, but after that there was a clear decline.

Of all Turner syndrome girls in our study, 39% had some signs of spontaneous puberty, while earlier studies have shown that some 30% had signs of pubertal development (6). The increasing proportion of Turner syndrome girls with at least some signs of spontaneous puberty is likely to be due to improved diagnostics of the syndrome. Now, also the girls with a mild phenotype or physical presentation become identified, and they are those who are more likely to have remaining ovarian function.

Some 2–5% of Turner syndrome girls have been evaluated to undergo spontaneous menarche (6–8) and have a possibility for spontaneous pregnancies, but this proportion is also likely to increase due to improved recognition of the syndrome. Without medical assistance or adoption, 95% of adult Turner syndrome women will remain childless. Infertility was regarded as the most harmful consequence of the syndrome by Turner syndrome women interviewed at adult age (9).

Possibilities for fertility preservation

Since the first reports of successful cryopreservation of human ovarian cortical tissue, fertility preservation in women facing premature ovarian failure has become a standard option in girls and young women facing chemotherapy (10). Cryopreservation is a technique that involves a biopsy of the ovarian cortex, followed by freezing of the tissue, and then, when relevant, transplantation of the tissue

after thawing, back to the woman who had the biopsy taken in the first place. Healthy babies have been born after transplantation of frozen-thawed ovarian tissue back to the ovary. For the time being, some 30% of the re-transplantations have resulted in pregnancy. Re-transplantation to one woman can be repeated several times when necessary if there only is a sufficient amount of frozen tissue available.

The immature eggs are located in the ovary as a thin layer one mm under the surface of the ovary – the cortex (Figure 1.). It is easy to take pieces of this layer by laparoscopy, which can be performed as day surgery. These tissue pieces can then be frozen and stored for use at the time when childbearing is desired.

In this light, it was natural to explore the possibilities of fertility preservation also in Turner syndrome (11). In our first mentioned survey, we found that many adolescent girls, indeed, had follicles in their ovaries (11) (Figure 2.). In the second and larger survey carried out by the support of several Swedish paediatric endocrinologists, we were able to define some prognostic factors for finding follicles in the ovaries (5) (Figure 3).

We can now recommend ovarian tissue cryopreservation for 12–16-year-old Turner syndrome girls who have Turner syndrome mosaicism, and/or who have any signs of spontaneous puberty. Normal serum concentrations of anti-mullerian hormone (AMH) and follicle stimulation hormone (FSH) are also positive prognostic signs. These hormones are involved

Figure 1

Location of the immature eggs under the surface of the ovary
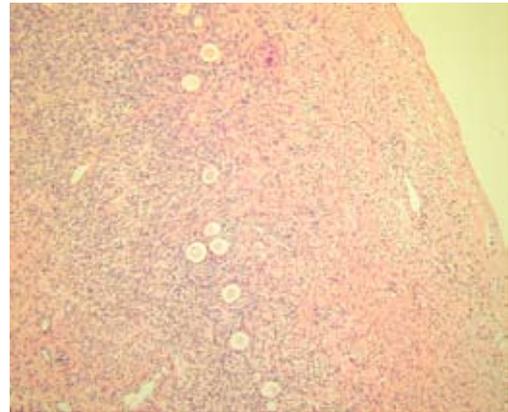
Figure 2

a) Primordial (immature) eggs in a 12-year-old Turner girl's ovary.
b) An almost mature egg follicle in a 15-year-old Turner girl's ovary
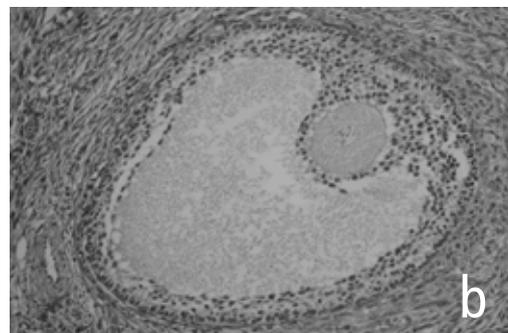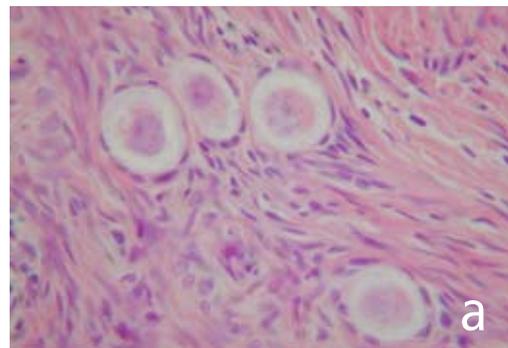
in the hormonal control of the ovary. However, using any of these prognostic factors, does not completely exclude the possibility of existing follicles. Follicles could be occasionally found in the ovaries of girls with karyotype 45, X, and in ovaries of girls who did not have any signs of puberty and who had high FSH and low AMH serum concentrations.

During an ovarian biopsy, it is often possible to collect mature or immature eggs which can be frozen and fertilised with sperm later on, when timely (11–13). In addition, freezing of mother's eggs for later use by her Turner syndrome girl has been reported (13).

The likelihood of pregnancy after transplantation of ovarian tissue to Turner syndrome women may be lower than that among those who have undergone chemotherapy because the numbers of eggs in the ovaries of Turner syndrome women are lower. Fertility preservation among Turner syndrome women is still regarded as experimental, and it is not included in the standard recommendations yet.

It is advisable to counsel menstruating and mosaic Turner syndrome women to not postpone childbearing for too long without good reasons, because premature ovarian failure before the average menopause age is so common. During fertility counselling, it is important also to explain about the risks of pregnancies in Turner syndrome women, and how to avoid possible complications.

Spontaneous pregnancies

Spontaneous pregnancies have been encountered in Turner women, reported as case reports and small surveys (7–8,14). Some early case reports arouse the suspicion of frequent chromosomal abnormalities among the infants of Turner women. This is certainly clear in some forms of structural abnormalities in the X-chromosome (8). The possibly of an increased risk of trisomy 21 (Down syndrome) is based just on a case report, and should probably not cause concern. Miscarriages or spontaneous abortions have been frequent among the spontaneous pregnancies of Turner women (7). They were supposed to be due to chromosomal abnormalities. But miscarriages were, however, also common in the pregnancies achieved using donated eggs in the early years of this treatment. More recently, the miscarried rate has become lower, and uterine causes due to insufficient estrogen supply have been suggested as their cause (8; 15–16). In other words, it seems as if the estradiol dose given in earlier years has been insufficient to allow normal growth of the uterus, which has many times not reached the normal adult size.

Irrespective of pregnancies being spontaneous or achieved using donated eggs, they are always high risk pregnancies, and they require meticulous special care (17). Before a planned

pregnancy, a health control examination carried out by a team used to follow Turner syndrome women is highly recommended.

The most severe complication during pregnancy is aortic dissection (18–19). Aortic dissection is common also in non-pregnant Turner women (6). Because it is possible to treat aortic dissection, and because it is not wise to expose a woman in risk to any increased circulatory load, a magnetic resonance imaging (MRI) should be carried out by a radiologist/cardiologist having experience from the disorder before and at least once during the pregnancy. Echocardiography for diagnosis of a bicuspid valve is necessary. Particular care is needed among women with hypertension and history of aortic coarctation. Thyroid status and glucose tolerance should also be monitored. All this best followed up in a multidisciplinary team (17).

Egg donation

Today, a good and feasible option for Turner women to get children is egg donation. In the early days of this treatment the pregnancy rates were lower than those among other women with premature ovarian failure. They have then increased to similar level as in other groups of women probably due to better hormonal replacement therapies (Figure 4). During most recent years, the pregnancy rates have varied between 40 and 67% per

embryo transfer. The miscarriage rates were first high, up to 50%, but have more recently come down to 25–40%. The reported numbers of live children have yet been low.

Before egg donation treatment, a very careful health control is necessary (see above), and the pregnancy follow-up needs to be meticulous and in expert hands. Aortic ruptures have been described also in egg donation pregnancies (19).

High blood pressure which is common in non-pregnant Turner syndrome women, may increase the risk of pregnancy hypertension and pre-eclampsia (8; 15–16). This is the main reason for the often seen small birth weight of some infants born to Turner syndrome mothers. Otherwise infants born to Turner mothers have been healthy.

Caesarean section has been very common in Turner syndrome women, mainly because of pelvic disproportion caused by short stature (8; 17). Turner syndrome women are also exposed to pregnancy induced glucose intolerance, which can progress to gestational diabetes.

Twin and higher order multiple pregnancies always increase the risk of any pregnancy complications among any women. Twin pregnancies should not be induced in Turner syndrome women because of the increased risks already encountered in pregnancies among them. This can be completely avoided without compromising the possibility of the women achieving pregnancies by transferring only

a single embryo at a time. The remaining embryos can be cryo-stored and then transferred one at a time (20).

Adequate hormonal replacement therapy for several months before the planned egg donation and embryo transfer is needed in order to achieve a well functioning uterus with sufficient blood supply and receptive endometrium (6; 15).

Figure 3

Good prognostic signs for having eggs in the ovaries. None of these signs are exclusive.

Good prognostic signs for having eggs in the ovaries

Onset of spontaneous puberty

Mosaic Turner syndrome

Normal serum concentration of FSH

Normal serum concentration of AMH

Age 12–16 years

Figure 4

Pregnancies after egg donation in Turner syndrome. ET: Embryo Transfer, meaning transfer of one fertilized egg to the uterus.

Article	No. of women	No. of ET	Embryos /ET	Pregnancies	Miscarria-ges
Rogers et al. (21)	6	–	–	2	–
Yaron et al. (22)	22	58	3,1	14 (23%)	5 (36%)
Press et al. (23)	11	25	–	6 (24%)	3 (50%)
Khastgir et al. (24)	29	68	Up to 3	28 (41%), 2 triplets	14 (50%)
Foudila et al. (15)	18	33	1,5	22 (67%), 1 twins	8 (36%)
Delbaere et al. (25)	9	15	–	5	2 (40%)
Bodri et al. (16)	21	30	1–4	12 (40%)	3 (25%)
Hovatta et al., 2006	7	10	1	3 (30%)	0 (0%)

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part

4

The view of individuals with Turner syndrome

ADULT

Dorte's story

I was born 43 years ago in 1965 at Glostrup Hospital. In fact, my arrival was planned to take place at a maternity home, but when my mother started bleeding heavily three weeks before due date, she was taken by ambulance to Glostrup Hospital, where I was born the next day. My mother thought that my feet were very blue just after I was born, but the staff at the hospital didn't think so.

I had a lot of problems thriving in the first two years of my life, and gulped nearly all my food up again. My mother had to give me food every two hours all day long, and the health visitor came and visited regularly and weighed me, one time putting on a little weight and the next taking it off again. When I was two years old, my doctor and health visitor decided they couldn't be responsible for me any more, and I was admitted to Dronning Louises Børnehospital (Queen Louises' Children's Hospital). Seven weeks later, my mother was asked to come and talk with the doctor, and was told that I had a chromosome fault and a heart problem and that, later, I might need to have an operation. The name Turner Syndrome was not mentioned at that time.

After I came home from hospital, the vomiting suddenly disappeared as if by magic, and I actually started to eat all my food. I grew and thrived, and went regularly for follow-up, first to Dronning Louises Børnehospital and later, when that closed, to Fuglebakken Børnehospital (Fuglebakken Children's Hospital). At some time, I dropped out of the system at Fuglebakken, but my parents weren't particularly worried because I was thriving. They thought that Fuglebakken would react if relevant.

When I was 13 years old, I went for a check-up at the Dental College. They encouraged us to contact Fuglebakken and get an appointment there.

At Fuglebakken, the doctor wanted me to return later to see a heart specialist, and I will never forget the day when they said I needed

an operation. My mother told me it was up to us to decide whether I should have the operation or not, but when I heard the doctor's arguments (I wouldn't live to be much older than 30 if I wasn't operated), I was old enough to know there was no avoiding it. I had almost no blood pressure in my legs, and sky-high blood pressure in my head and upper body because I had a constriction of the aorta. I cried and yelled that I didn't want to die. The electrocardiogram they took of me afterwards must have looked very strange.

At school I had quarrelled with the "strong" girls in the class, and had the mental strength to manage right until I was told that I had to have an operation. Suddenly I didn't have the energy to fight on two fronts; the teasing affected me deeply, and I experienced the worst 18 months of my life.

Yes, it took almost 18 months, and I was almost 15 years old, before I was operated for the constriction on May 12 1980. The constriction that the doctors thought was about 1–2 cm long, proved to be 6 cm long when they opened me up, so they had to hold a conference in the middle of the operation.

After the operation things went really very well. I thought the chain had come off the bicycle the first time I tried to cycle when my blood pressure was properly regulated. I went for a follow-up because they wondered why they could still hear a heart murmur, and they found out that I had a two-flap heart valve. They didn't want to do anything at that time, but I did go for follow up.

In the last classes at lower secondary school I started to make a few friends, and sixteen years old I started to take estrogen. I am so glad that Turner girls today get much better information (as a rule) and treatment than we got back then. Because I didn't start taking estrogen until I was 16 (they wanted me to be finished with the operation first), I started on a very high dose of estrogen which meant that within six weeks I had developed breasts!!! I couldn't lie on my stomach because it hurt so much at times. Psychologically it wasn't the best form of treatment either. I was totally confused. Everything happened so fast that I actually couldn't keep up with it mentally.

All the time we were at Fuglebakken, my parents and I asked if there were other girls with Turner syndrome who I could get in contact with, but every time I was given the message that because of their oath of confidentiality they couldn't put me in contact with other patients. After I started estrogen treatment I went for follow up and had blood samples taken. One technician, who was the only one who was allowed to touch my arm, felt sorry for me and said that she was going to take a blood sample from another Turner girl immediately before me. I went over and looked in secret – and what did I see: My mirror image!!! It was a strange experience. I did not speak to her, but managed to wheedle out of the staff that she was the daughter of a pub owner from Fyn. At home we fortunately had a brochure on Danish inns with the telephone numbers. After pacing the floor a couple of times, I rang them and asked: "Do you have a daughter with Turner Syndrome?" It went

completely quiet on the other end, but the daughter took the phone and we became pen pals for several years.

When I was in the second year of my upper secondary schooling, my father was driving home from work one day over the bridge from Amager to Sjælland. Listening to the radio he happened to hear that Johannes Nielsen and Bente Konradsen were looking for members so that they could form a network group for Turner girls on Sjælland. Whilst he drove along with one hand, he wrote down Bente Konradsen's telephone number with his free hand. After some more pacing across the floor in front of the phone, I dared to call. After much encouragement from my parents, I called and talked with Bente, and we agreed that I would go to the next meeting that was to be held on Sjælland. I almost walked on air from that meeting. Now I was no longer alone!!

I passed my school exams in 1985, and then went to a College of Technology to become more independent. One weekend, when I happened to be home from college, I collapsed, and when I came to, I vomited. We called the duty doctor who said it was flu, and forgot to take my blood pressure and pulse. He advised me to get my appointment with my heart specialist brought forward.

Because I got worse and worse, my mother called my GP on the Monday who immediately said he thought it sounded as though I should be admitted to hospital. My mother called my heart specialist, and I got an appointment the same day. After I was admitted to Rigshospi-talet, a whole number of things happened very fast. It turned out that I had a ruptured aorta, and I was operated that night. They also put in a new heart valve, which has been my faithful companion now for 23 years.

Today, I live in a small, terraced house and work as a medical secretary. I have worked full-time for many years, but am now on flextime, mainly because of my hearing. I am glad to have something to get up for in the morning, but I am also enjoying having a little more energy for things other than work. I have been involved in the Danish Association for the Hard of Hearing, and have a large network.

Well, this was my life story. It all sounds very dramatic, and as though I have had a terrible time, but that's not true. I have had a very good life. It hasn't been a bed of roses, but whose life has? Haven't we all experienced things that we would have preferred not to? I think so. In spite of all the things I have been through, I am glad that I am alive. My biggest problem at the moment is not my heart, which in fact I don't notice, but is my hearing! Music has always been a very large part of my life, so it has been very hard for me to loose some of my hearing. So – other people cannot always judge what is or isn't a good life – that is up to the person that lives it.

DORTE BRODERSEN

Mathilde's story

My name is Mathilde, I am 18 years old and attend 2nd year of junior College. When I was 8 years old, I was diagnosed with Turner syndrome and low metabolism – my thyroid did not work, I had almost not grown in the previous years, and I was extremely tired. After starting treatment with thyroxine, and taking growth hormone for many years, I am now doing very well; I am 161 cm tall, and I do not think about Turner syndrome at all in my daily life. I am active in my school, in society and politics, interested in languages and play the piano in my spare time.

Living with Turner Syndrome

In some ways, being diagnosed with Turner syndrome was a relief. Before we knew that, my parents and I were worried about why I didn't grow and why I was tired, but being diagnosed and knowing exactly why I had these problems made many things much easier. I have never thought of it as an excuse not to fight for the things I wanted to achieve.

My parents have always told me that being a Turner girl is something very special, I am doubly lucky: The first miracle was that I was born, and the second was that had I been a boy with the chromosome fault, I would not have lived, so this was two miracles at the same time. As a Turner girl, you have to fight a little harder; you have to go the doctor often; you have to take medicines; and you cannot conceive in the normal way. Many girls have problems with their ears. I have always had problems with loud music, and have needed my friends to understand this and respect it. For some Turner girls, these physical facts are very overwhelming. I have been afraid of giving birth, and I use this as an excuse to adopt, but it is of course a fact that you have to accept, which is very difficult and hard. One of the worst things that I have come to realise is that almost 80% of Turner babies are aborted (Danish data reveals that 70–80% of parents with a Turner syndrome baby choose abortion). For me, this feels very wrong.

When I talk to my friends about Turner syndrome, they are often curious and interested in what the actual fault is, and why I have to take medicines, because their immediate impression is that I am a normal little girl who is even taller than two of my friends and who gets good grades at school. For many Turner girls, the brain functions perfectly well, perhaps in some ways slightly better than their peers' (at least as teenagers), and in general we grow 5–15 cm extra if we take our medicine, so height doesn't need to be a problem. At one time, when I was about 8 years old, I stopped growing completely, and was extremely tired. I was seen by several doctors, and it was discovered by Consultant Knud Kastrup that I had Turner syndrome and low metabolism. I

was given medicine for the low metabolism (Eltroxin), and growth hormone, and quickly improved and began to grow again.

This period was a great strain on my parents, my sister and me. It is always difficult to accept that some things have to be different. But I experienced that you can indeed live a completely normal life with Turner syndrome.

Consequences

Having Turner syndrome means that you have to take medicines, that there are some things that you have to be aware of and checked up for and, for most Turner women, means that they cannot have children in the normal way. It is important to remember that there are other methods by which you can become pregnant (there is a lot of research on artificial conception), perhaps also using your own eggs.

Turner syndrome is due to a chromosome fault. It is not a "disease", you are not "ill", but formed slightly differently because the chromosomes during the early cell division phase made some sort of mistake. There are many of us Turner girls around the world, and there are lots of opportunities to get in contact with each other.

Impact on the family

The effect on the family of having a child with Turner syndrome is difficult for me to describe, as I cannot put myself completely in somebody else's place, but I have always experienced love and support from the people around me. Sometimes I think that parents and siblings can have a tendency to want to protect a Turner girl too much. My friends and people around me ask what it is, and what it means to have Turner syndrome, and I often feel that they care and want to help, but really I don't like others feeling sorry for me, because that gives me poorer self confidence. A Turner girl should feel she can just ask for the help she needs.

School and self-confidence

As far as I can see, school is just as different for Turner girls as it is for everybody else. Some have it easy and others have more problems, some are good in some subjects, others in other subjects, and so on. For me, it was important that the teachers were aware of what was happening, so they didn't think that I didn't care about school when I had to go to the doctor instead of school or stayed at home

because I needed to. In my opinion, selfconfidence can be a problem for a Turner girl. What is required of the family and friends of a Turner girl is to support her in such a way that she doesn't feel that they feel sorry for her. It is important to be there for her if she needs it, but at the same time not to make a big fuss of growth hormone treatment, for example. Many of my friends and family were very interested in hearing about it, talking about it, and seeing how I did it, and so on. This is not necessarily nice for a Turner girl who perhaps is fed up with having to take it, and perhaps feels that others feel sorry for her, and so she then feels sorry for herself.

Throughout my school life, my friends have always been very good at making sure that I did not feel excluded. That was important, knowing that they were there, even if at times it was difficult to be on top of things. For example, I had low metabolism and for a long time did not have the energy to do anything, and then I was glad that the others continued to talk to me, did things with me, and invited me out when I got older and had more energy again. I have always been shy and quiet, and sometimes have had problems looking people in the eye. I don't know if this is a normal feature of Turner syndrome, but it is just something that has to be fought and worked on. Today, I am much more outgoing, and particularly like conversing in English, French or Spanish, because then I feel I'm on home ground, and feel I am good at it.

Independence from the family

Becoming independent from your parents can be difficult for a Turner girl. You are more tied to them than other girls because in some ways you are more dependent on their support, and need them to be around. I have always missed my parents when I have been away alone. Even when I was on a language trip to Oxford and during a High School stay in Cincinnati I called home often to speak to them. My message to parents is that they must give their child give time, only help when necessary and not to create a cocoon of immaturity. It can also be very difficult for siblings of a child who needs special attention to be heard, and it is therefore also very important to make time for them.

I would describe my relationship with my parents as something very special. They have always been there for me when I needed them; they have done things with me when I haven't had the energy to see friends; they have always accompanied me to the hospital because they could see that I needed it, and they have collected me from the strangest places because as a small child I needed to leave the summer camps and go home, and so on.

My advice

As a Turner girl, I believe that we must look after ourselves. Turner girls are all as different as everybody else. Some girls have more problems taking growth hormone than others and are more affected by it than others, and you must get your parents help to talk about it if you are fed up. Just keep thinking that it is important for you to grow, and that it is far more painful to fall and hit yourself. In general, I personally don't think it hurt particularly to take growth hormone. I believe it is important to be aware of how you feel in different situations, and to try and find out why it feels like that.

MATHILDE ANDRUP

CHILD

Sarah's story

Our story starts one beautiful spring day in 1996 at the hospital where we, Sarah's parents, waited in anticipation for the scan in the 18th week of pregnancy. When the scan was well underway, the midwife said "Now, you mustn't be nervous, but I am just going to get a colleague who I would like to look at the scan". They look and look, and then they tell us and show us on the screen that the foetus has an unexplained small fluid-filled area in the stomach. We were told to sit outside in the waiting room and wait for a doctor who has been called from the Paediatric department, and who is going to assist at a new scan.

That was most probably the longest hour we have ever had to wait, and so many ideas as to what could be wrong went through our heads. I felt as though I was sitting in some strange vacuum. We sat there in the waiting room, and watched as other parents went in and came out proudly with their first picture of their baby in the womb. I can clearly remember the feeling of suddenly not being part of that community any more. I have to admit that, in fact, I was sad and a little offended that we had to sit and watch them all get their clothes and go home.

But in the end, everything turned out very well that afternoon. The paediatrician told us that it was 99.9% certain that we were expecting a healthy baby. The doctor nevertheless asked us to pop in again in week 30 for a follow-up scan. We went home after a couple of hours, completely mentally exhausted and very tired. The following weeks went well, but there was always a tiny doubt lingering in our minds. Was everything really as it should be? That little 0,1% continued to fill our thoughts.

At the scan in week 30, our doubts were blown away, and we were sent home with the message that we could re-use the pale pink baby clothes from big sister born in '95. That was a very happy day, and the relief was endless.

But today, I still don't know whether the doctor did suspect something. I firmly believe that doctors should always tell the patient everything they know. On the other hand, I now know that the world is not black and white when it comes to a diagnosis such as Turner syndrome. Feelings, ethics and own expectations, the expectations of family and friends, and medical knowledge place us all, women/couples, in some almost inhuman dilemmas.

Looking back, I am very thankful that the doctor did not offer me an amniocentesis. He could well have done that, even on a very small suspicion.

The rest of the pregnancy went well and, 15 days late, our little mischief-maker, Sarah, was born. She was slightly chubbier, more

compact and not quite as long as her older sister was when she was born, but she was a beautiful little girl.

In 1996, when we were expecting Sarah, big sister was just one year old. The maturity and energy we have today as the parents of three delightful, half-grown children, we definitely did not have then. If a doctor had told us that we perhaps expected a child with a chromosome fault, we may not have had the strength or energy to go through with it. Hurrah that we were allowed to live the first years with Sarah in blissful ignorance. The girls got a beautiful little brother two years later. We were allowed to solve the problems and mysteries around Sarah afterwards, as they occurred. We can say that we have had the diagnosis served as small bits of a puzzle. The last piece fell into place when Sarah was 7 years old.

Big sister Charlotte was born in 1995, 11 days late and weighing 3890g and measuring 53cm. Sarah born in 1997, 15 days late and weighing 3820g and measuring 50cm. Baby brother Simon was born in 1999, 11 days late and weighing 4350g and measuring 55cm.

The only physical irregularity with Sarah, that our good, experienced health visitor found, was that her toe nails were very short. The growth curves were good, and various tests were passed with flying colours. Today, when we look at old pictures of our three beautiful children, and compare them at the various ages, we can easily see that big sister and little brother had a different physical build to Sarah.

Sarah is the little compact one compared to her two long rakes of siblings. But otherwise they were just as different as siblings are.

All three children had ear problems when they were small. Because we had been through several middle ear infections with our oldest daughter and had to insert a drain several times, we decided with the doctor to insert a drain in Sarah's ears as soon as she was old enough to take the anaesthetic.

This is a decision that we think has been very wise, because all the children in the family have had a lot of colds.

When Sarah was 1½ years old she had very large polyps removed, which for a long time had given her breathing problems especially when she was asleep. Six months later Sarah again had polyps removed, and aged 4 her tonsils were removed.

We are not lying if we say that Sarah had a *very* difficult relationship with the ENT specialist and people in white for many months afterwards. It was very traumatic for her every time she had to go for follow-up at our GP. Sarah was so small that we could not explain that the follow-up did not hurt. For a long time, we couldn't even go on an ordinary shopping trip to the local shopping centre because our ear specialist had a clinic there, and she just started screaming as soon as we neared the centre.

When baby brother was born, we took Sarah out of the nursery so that she could be at home for a year with mummy and the baby. That was a lovely year with lots of time for enjoyment and fun. When she was 3 years old she started in the same nursery as her big sister.

In 2001, we moved from Århus to Djursland, and I decided to use the remaining part of my childcare leave. I resigned my job and stayed at home – that was three wonderful years.

That was the turning point and the start of a completely different way of life. Three times a week the children and I drove to the playgroup – we had many fun hours here. When we were at the playgroup, I could see that Sarah was not so interested in the other children and their games. Sarah played a lot next to them and by herself. She could start off playing with them quite happily, but within a short time she would drop out of the game.

When Sarah started talking a lot, we could hear that she sometimes stammered, so we contacted the county speech therapist. She visited us very soon after our referral, and after a good hour's visit, she was in no doubt that Sarah did stammer.

After further investigations, we were offered a place with Sarah at the Speech Therapy Institute in Århus for an intensive week of lectures and mixing with parents and children who stammered. A psychologist was also associated with the Speech Therapy Institute. I aired my suspicions with her that I thought that Sarah was not like other children. By the end of the week, she had made some observations of Sarah, and had come to the conclusion that she had "semantic/pragmatic difficulties", whatever that meant, and recommended to let the Pedagogic, Psychological Advice Unit, PPR in our home county examine Sarah.

And I can promise you that we had a couple of exciting years ahead of us. Sarah started nursery school at 4½ years of age, and PPR visited Sarah there. The nursery school supported the idea that she should be examined further because they had also noticed that in some areas; Sarah did not always behave as you would expect a 4–5 year old to do. With regard to language, Sarah was way ahead of other children, but she had big problems when

it came to understanding a collective message. Getting dressed to go out could take half a day. On the other hand, she charmed everybody with her loving and humoristic manner. Even though Sarah at times was very troubled with her stammer, it didn't inhibit her in any way, quite the opposite: Sarah likes to talk a lot, and is particularly good at arguing for a very long time and very well.

The investigations by PPR confused everybody a little: None of the tests they performed explained why Sarah was the way she was; she didn't really fit into any of the boxes.

Sarah managed most of the tasks in the PPR tests for her age, but she did not manage tasks that were abstract. The results showed that she was well below average with regard to being able to concentrate; putting herself in another's position; and seeing the world from a wider perspective. Lack of a sense of occasion was another typical feature, and she also lacked the natural shyness with strangers.

We visited a neurologist who also couldn't find anything unusual in Sarah. But the PPR investigations gave us, the nursery school and, later, the school, a very useful tool to work with – we now knew where and in which situations Sarah needed support.

The investigations ended with a three-month stay at the Speech Therapy Institute, this time on a course for children with semantic/pragmatic difficulties. That stay gave Sarah, us, and the nursery school many good tools to work with. Two days a week, Sarah was collected and driven by taxi to Århus, which she thought was rather posh and exciting. We found out that Sarah benefited by having structure, short explanations and pictures for support. Pictures of outdoor clothes in the changing area helped Sarah get dressed more quickly in the winter.

If you ask Sarah now what the worst thing in the nursery school was, she will say having to go for walks and eating fruit in the morning. Sarah loves to explore new surroundings, but not having to walk there and back. Sarah can see absolutely no point in walking for the sake of walking; there are so many other exciting things you can be doing instead. There were many trips in the last six months of nursery school, and you could often see Sarah and her assistant for the trip walking along 10–20 meters behind the rest of the group.

An amusing story is of course "The apple war". When children eat fruit in the nursery school, they can't have just banana, for example. The agreement was that Sarah could only have banana after she had eaten a piece of apple. Subsequently, the nursery staff have told us many stories of her creative hiding places for uneaten pieces of apple.

Together with the nursery school, we decided that Sarah should have an extra year in nursery school, and the additional support that Sarah had been allocated in nursery school followed her through the pre-school year and gave Sarah an excellent start in school.

At the obligatory medical check-up in the pre-school class by the school doctor, Sarah was measured and the doctor found out that Sarah had not grown a single millimetre since her last check-up with our GP, and we had missed an annual visit. So now the school doctor sat there with a growth curve that was flat as a pancake and thought "There is something wrong here".

She sent us immediately to our GP who referred us to a specialist in childhood diseases in Århus. The specialist suspected gluten allergy. Blood samples were taken and allergy excluded. In the meantime we had been on the net and searched for "lack of growth", and had come across Turner syndrome. At our next appointment with the specialist, we asked her if Sarah could have Turner syndrome, but she did not think so. She did not think Sarah looked like a girl with Turner syndrome, but because she couldn't completely rule out a mosaic, it meant another trip to the outpatient clinic and more blood samples.

That day, the outpatients in Århus closed early, so we jumped into the car and drove to Randers, which was open longer. We just couldn't bear the thought of waiting another day. We already had the next appointment with the specialist in six weeks.

But after only two weeks, she called one afternoon at 17.00, and I can still hear her voice. "I have got the results, and I am very surprised. Sarah is a girl with Turner syndrome (45,X)." My answer was "Yes, but I knew that. I am so relieved."

When I had put the phone down, we lifted Sarah up, sat her in the middle of the breakfast table and told her that she had Turner syndrome, and that was why she hadn't grown. And that was why her little brother was about to outgrow her. From that moment, Sarah became a different girl. The next morning we went with her to the After School Activities, and she told the staff the news herself. I believe she was just so happy and relieved. My husband and I in the meantime had read a lot about Turner syndrome on the internet and were therefore quite well prepared.

We are so lucky that we live in a really good municipality that prioritises cooperation between PPR, nursery school, school, speech therapists and parents highly. We noticed this particularly when Sarah at the age of 6 was to start in the pre-school class. We were naturally allocated a case officer in the municipality, a really good specialist advisor who in fact had already been an advisor for an adult Turner girl.

The biggest problem Sarah has had in school is concentration; she was easily distracted by things around her. But with the help of teaching assistants, Sarah managed to follow the first couple of years very well. At the end of the 2nd year, Sarah became very tired of school. Greater demands in writing and maths were to much. At one time, she was so fed up with the fact that she couldn't keep up with the class that she just refused to take her books out of her satchel at home. There were many conflicts due to homework that did not get done. In the end we decided that

we did not want to be support teachers for Sarah any more. Our sensible school principal suggested that Sarah could start in a miniclass straight away – a fantastic solution. For a long time, we chose not to do homework with Sarah, and her little brother and big sister in particular benefited from this – they had been forgotten and overlooked for a long time. We had spent an awful lot of time with her for a very long time.

The arrangement was that, to start with, Sarah had all her maths and most Danish lesson in the miniclass. The class comprised between 3 and 5 children, all of whom needed intensive teaching for a shorter or longer period. In the other subjects, Sarah was with her normal class. Sarah's teachers were very aware of the areas and situations in which Sarah needed extra help. She often needed help to get going on a task and making a dent in it.

In connection with starting the miniclass, we asked the school if they could order a new PPR assessment of Sarah. That assessment finished autumn 2008, and clearly pinpoints the problems that need to be worked further with. Sarah now manages so well in Danish, that she can follow her normal class for most Danish lessons. For maths, she continues to go in the miniclass. Sarah now goes in the 4th year with 16 pupils at our local school, which only has classes up until 6th year. When Sarah starts in 7th year, she will naturally have to change schools to a much bigger school with larger classes. All the support she is now get-

Charlotte 10 years, Sarah 8 years and Simon 6 years. August 2005

ting will equip her well for further schooling, regardless of which school/school option she continues with.

We have chosen to be very open in our family and in our local community about Sarah's diagnosis. We wrote a letter about Sarah and Turner syndrome. This letter was distributed to Sarah's class, her parallel classes and to all friends and acquaintances, in fact, to everybody who has contact with Sarah. We have received praise from everybody for our openness.

When we got the diagnosis in 2005, Sarah started growth hormone treatment. In the three years since then, Sarah has grown

very well. We are not too concerned about whether Sarah is 150 or 165 cm tall. The most important thing is that she is a girl who enjoys life. Physically, Sarah is very well. She has a very small partial fusion of two heart valves, so she is followed-up every 3–4 years with a heart scan.

In our family, Sarah's diagnosis naturally involves us all, and this is because we have chosen to live with the diagnosis. It has been embraced in our family, with a number of challenges for everybody, and this we have to take into account. We are aware of the fact that Sarah's brother and sister also need attention.

We have chosen to be active in the Danish Turner Syndrome Society contact groups, not to nurture Sarah's diagnosis, but so that Sarah has a network around her, and we can be continuously updated on what is going on in research on Turner syndrome. Shortly after our daughter was diagnosed, we were contacted by the Parent Group. Our first family weekend was a fantastic experience. Over the last four years we have met and talked with many amazing families. Hearing about other people's experiences and their stories has been very rewarding for us.

ILSE, JOHN, CHARLOTTE, SIMON og SARAH CLAYRE

Notes

Turner syndrome

... is a complex condition that can, and should, be considered from many perspectives; only by taking a holistic approach is it possible to see the whole person. When all aspects of the syndrome are observed and acknowledged, girls and women with Turner syndrome can live a "normal" life just like other people.

Turner – know your body! is the result of many researchers' dedicated interest in girls and women with Turner syndrome – authors from Europe and the USA have contributed to this book.

Turner – know your body! provides inspiration, information and help for everybody interested in Turner syndrome, and explains the latest scientific knowledge for lay people. Turner know your body! can be read from cover-to-cover or as chapters on medicine, psychology or personal stories.

Turner – know your body! has been written for girls and women with Turner syndrome, for their families, for the GP who has a patient with Turner syndrome, for the paediatrician who meets the child with Turner syndrome, and for all doctors, nurses and care providers who come into contact with people with Turner syndrome.

CLAUS H. GRAVHOLT

THE EDITOR, CLAUS HØJBERG GRAVHOLT, PhD, MD is a Specialist in adult endocrinology and internal medicine and currently works as a consultant and senior researcher in the Department of Medicine (Endocrinology and Diabetes) at Århus University Hospital, Denmark. He has worked clinically and scientifically with Turner syndrome for the last 17 years, conducting clinical, genetic, epidemiological and experimental studies, and publishing more than100 original articles and review papers. He is an active participant in the international Turner syndrome research community, as well as in national and international research societies.

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