Turner Syndrome: Across the Lifespan

Editors: Jill Hamilton and Irena Hozjan

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Introduction

Turner Syndrome (TS) is a common genetic condition affecting 1 in every 2,000 to 2,500 females. TS girls and women experience a variety of medical and non-medical issues that impact their day-to-day functioning. The idea for this book came about as we were planning to update an older document for the Turner Syndrome Society of Canada that described the use of growth hormone in the TS population. As health care providers for many girls with TS and their families, we recognized that there was a lot of medical information in various formats describing health issues that may impact those with TS, however, most were written for medical professionals and not the individuals and their families dealing with TS. Secondly, the information was not collated in one place, and was sometimes difficult to access.

In this book, we have brought together experts from across Canada to cover a large array of health and wellness topics including genetics, growth, puberty, infertility and advanced reproductive technology, bone health, diabetes, hearing, school and learning, just to name a few. Updated health surveillance issues are also outlined.

We really wanted to include our patients, their families, and adult women with TS in the process of creating this book. Their contribution of personal perspectives, stories and drawings makes this project very special. We believe that this book is a useful resource for anyone wanting to learn more about TS.

There are many people to acknowledge. Roche Canada has generously funded the creation of this book through an educational grant. They gave us creative freedom throughout the entire process and were supportive in the best of ways.

We have worked closely with the Turner Syndrome Society of Canada and, in particular, the Executive Director, Mary Edwards. We would like to thank Mary for all of her wise suggestions, expert feedback and encouragement that helped to make this book happen.

A special thank you also goes out to the Graphic Designer, Mirja Kihlanki, who worked tirelessly with us to make this resource look as good as possible. This was clearly a labour of love for Mirja, and we were very fortunate to have someone with such commitment working on our team.

We would like to acknowledge all of the authors for their excellent contributions, and for putting up with our sometimes, manic edits!

A huge thank you also goes out to Amy Newcombe. Amy co-authored one chapter, but spent many hours assisting us in the development of the book. Her superior organizational skills and great sense of humour made a complicated project move along smoothly.

Finally, we would very much like to thank the many girls and women with TS, and their families, who submitted stories and drawings for this book. Some of these are quite personal, and must have been difficult to share. However, these entries will no doubt resonate with future readers who have faced similar encounters and perhaps even help others to understand their own experiences a bit better.

This book is dedicated to girls and women
with Turner Syndrome everywhere.

—Jill Hamilton and Irena Hozjan

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The Turner Syndrome Society of Canada

Beginnings

The Turner Syndrome Society of Canada was founded in 1981 by a woman with TS, Susan Charney, and a small group of others in Toronto, supported by the medical community at the Hospital for Sick Children and the Toronto General Hospital—the first self-help support organization for TS in the world. They formalized the incorporation of the early group into a charitable organization with a board of directors, organized a conference to recruit and inform more members, and set up a small office in donated space at York University. Funding for a paid Executive Director was obtained, the conference became an annual event, and a regular newsletter was established.

The aims of the organization from the outset have been to offer up-to-date information and mutual support to women and girls with TS and their families. Many women with TS felt isolated, without a safe place to discuss the personal issues that are associated with the syndrome, and many were uninformed or misinformed about the health aspects.

Mission Statement 

"The goal of the Society is to improve the quality of life for individuals and families affected by Turner Syndrome. This is accomplished through the provision of public and professional awareness about the needs and concerns of individuals with Turner Syndrome and their families. A mutual support network is available through local chapters."

Changing Times

Much has changed in the quarter-century since the Society was formed. The organization has grown to include chapters across

Canada, and has recently moved its national office from Toronto to Ottawa. There are currently five chapters; Toronto, Ottawa, Vancouver, Edmonton and Montreal, as well as local groups in other communities.

The medical understanding and treatment of TS has come a long way in the last twenty-five years as well. Diagnosis tends to be earlier, even pre-natal, and there are more options available to deal with every aspect of the syndrome. Growth hormone treatment is now an option for girls with TS, and *in vitro* fertilization technology has opened up new options for women with TS to become mothers, just to mention two of the medical advances. The medical community has become better informed about the condition, and there is a trend towards increased patient involvement in decisions about medical care. The internet provides a wide variety of resources and information as well. The role of the Turner Syndrome Society of Canada has shifted to include more support for families of young girls, and helping to answer increasingly detailed questions about medical issues.

Continuing Challenges

The initial issues that led to the formation of the Society still remain – a sense of isolation, even secrecy about TS can persist for individuals and families; there is still a need for up-to-date medical information from the basic to the very detailed. We are always working to keep our reference materials and conference topics current. Communication with our members now includes a website and other electronic formats. Funding challenges continue, and outreach and volunteer involvement are needed on an ongoing basis.

The Future of the Society

The Turner Syndrome Society of Canada still has a vital role to play in education about TS, at all levels, and in providing accurate, timely answers to specific questions from our members. Perhaps even more importantly, we help to make the personal connections

between individuals and families, connections that are so valuable in overcoming the feelings of isolation that ~~still~~ persist

The Turner Syndrome Society of Canada has enthusiastically provided support and feedback for this book, initially through a needs survey, and later through the inclusion of material reflecting the experience of individuals with TS. We are very pleased to be involved in the production of this volume—the most comprehensive and up-to-date source of information on medical and non-medical topics for girls and women with TS.

Mary Edwards

Executive Director

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Chapter 1

It's All About the X-Chromosomes: Genetics of Turner Syndrome

Cheri Deal, MD, PhD, FRCPC

Turner Syndrome (TS) is not a disease. It is a frequent, genetic condition that is present in about 1 in 2,000 to 1 in 2,500 newborn girls. This chapter will explain the biological basis for TS. If you have never studied genetics (the science of heredity and why one individual is different from another), the first section will give you the basics. It will then discuss how we diagnose TS, why TS occurs and what the study of chromosomes and genes can tell us. Finally, we will look into the future and see if genetics can eventually help us to better predict future health issues of girls and women with TS, and better tailor treatments to the genetic make-up of the individual.

A Few Facts on Genetics

Cells are the building blocks of our body, and we have billions of them in every organ and tissue (such as the heart, liver, kidneys, brain, muscles, bones and fat). Cells carry information that then tells the organ how to "behave" or function so that it can carry out its particular job.

The incredible amount of information needed to make a human and keep them in good working order is stored in structures called chromosomes found inside almost all cells. There are 46 chromosomes in a cell's nucleus. Two of these 46 chromosomes are called the sex chromosomes, or the X- and the Y-chromosome. The majority of females have two X-chromosomes and the majority of males have one X-chromosome and one Y-chromosome. Excluding the sex chromosomes, the remaining 44 chromosomes (called autosomes) in the cells of the body are present in pairs – one of the pair coming from the mother and the other one from the father.

An exception to the 46 chromosome rule is found in the germ cells (eggs and sperm), in which there are only 23. This is because cells giving rise to the germ cells undergo cell division to split up chromosomal pairs (termed meiosis). When a sperm fertilizes an egg,

23 added to 23 will restore the original number, 46 chromosomes, in all the cells of the future human being. Eggs and sperm usually carry only one sex chromosome: eggs contain only an X-chromosome but sperm can contain either an X- or a Y-chromosome.

If you think about each chromosome as being a book, then you can imagine that in each book there are instructions for a part of your body, such as what colour hair you have. The pages of the books are like genes, that is, the smallest unit of information that can help explain a trait, or characteristic of an individual. We have about 25,000 genes carried on our 46 chromosomes. The X-chromosome (the biggest chromosome) carries around 1,400 genes.

Genes are formed from DNA (deoxy-ribonucleic acid). DNA is the chemical material used for "writing" the instructions necessary to guide the formation and functioning of the body. You may have heard about the genetic code, an alphabet of 4 chemicals (called nucleotides) that are strung together into two, long strands in each chromosome. Each strand is complementary with the other; the strands are paired with each other. An important property of DNA is that it can serve as a template for duplicating itself because of its structure. This is very important because when cells divide, there has to be an exact copy of each DNA molecule that can be passed on to the "daughter" cells.

Chromosomes and therefore genes are inherited from our parents, and they form the basis for the transfer of characteristics from parents to offspring. The technical word for characteristic is phenotype. Phenotype can refer to something we can see, like eye colour or height, something we can observe such as musical ability, or something we can measure, like cholesterol in the blood. Phenotype is not entirely due to heredity and genes, but can be influenced by the environment (what kind of parents you have, your life experiences, the food you eat, medications you take, toxic things that you knowingly or unknowingly put into your body). It is an individual's phenotype that allows doctors to detect and ~~diagnosis~~ medical conditions and diseases.

All of us have some genes that are missing (gene deletion) or defective (gene mutation) or even present in too many copies (gene duplications). Going back to the "book", you can think about these

genetic problems as pages that might not have gotten the information perfectly right – maybe the pages are missing entirely, or maybe there are some spelling mistakes on the page that make them hard to understand, or maybe there are even extra pages. When this occurs, depending on which genes are affected, it can sometimes cause a serious disease, like cancer, or maybe just make you more likely to become overweight if you do not eat well and exercise. Sometimes these errors come from our parents. In other words, they are carried in the egg or the sperm. Sometimes they occur during the formation of the egg and sperm, sometimes they happen before birth, during the development of the embryo and fetus and sometimes they happen during our lifetime.

We can see the chromosomes in a cell but only with a microscope that can enlarge them at least 1250 times, and most often a sample of blood is taken for this purpose. The chromosomes are lined up in pairs by size from the biggest to smallest, numbered from 1 to 22, with the sex chromosomes put last. This procedure is called performing a karyotype (see Figure 1). Karyotypes can also be obtained from amniotic fluid which is the liquid surrounding the developing baby, from the cells lining the mouth or from a piece of skin. It is the karyotype that confirms the diagnosis of TS.

Where the Name "Turner Syndrome" Originated

As you may already know, scientists try to understand the world —and doctors, their patients—by classifying their observations into smaller bits of information, and by attaching a label that will help them identify similar patterns in the future. In the United States, back in 1938, Dr. Henry Turner described a series of characteristics that he noticed in some of his female patients who were very short compared to the other members of their families. In fact, Dr. Otto Ullrich had described similar patients in Germany in 1930, but English medical textbooks have dropped his name when referring to what we now know as Turner Syndrome. Neither of these physicians had any idea what caused the collection of features that they described: a short height, forearms that tended to stick out from the sides of the body when turned with the palms facing forward (called a wide carrying angle, or cubitus valgus), an absence of breast development and menstrual periods, and a shortened neck, sometimes with increased skin.

The term syndrome is used in medicine when doctors see several clinical features that tend to occur together such that the presence of one finding makes the physician look for others. These features can be symptoms reported by the patient, physical traits seen by examining the patient or results of examinations, like ultrasounds or X-rays, and tests of the blood or urine, for example. Not all features have to be present in order to make a preliminary diagnosis of TS, but there are some that usually prompt the physician to perform a karyotype, like unexplained short stature in a girl. Table 1 lists the features that doctors look for when considering a diagnosis of TS. The most common findings are an abnormal growth pattern leading to short adult stature and non-functional ovaries, resulting in absent pubertal development and infertility.

Table 1. Features of Turner Syndrome and Their Frequency

Features	**Frequency*** (one or more finding within in each category)
Chest Shield-shaped chest, nipples widely spaced and/or inverted	60-80%
Ears Mild deformation of the external ear, low-set ears	40-50%
Eyes Drooping eyelids (ptosis), Mongol folds (epicanthus), almond-shaped eyes Far-sightedness (hypertopia), Strabismus	20-40%
Growth Birth weight low for gestational age (average weight at term less than 2.5 kg) Failure to thrive in early infancy (slow growth and weight gain) Growth delay in late infancy and childhood with normal weight gain Short adult stature	80-100%
Heart and Blood Vessels Stenosis (coarctation) of the aorta, bicuspid aortic valve, aortic dilation/aneurism Intestinal telangectasia (abnormal, dilated blood vessels), abnormal EKG	40-50%

Features	Frequency* (one or more finding within in each category)
Intellectual Development and Behaviour Usually normal intelligence but some learning disabilities and difficulty concentrating Immature behaviour, over-activity, social withdrawal	60-70%
Kidneys Renal malformations such as horseshoe kidney, rotated kidneys or renal aplasia Malformations in the renal pelvis and ureters (duplications, dilitations) Renal vessel abnormalities	30-40%
Mouth and Jaw High-arched palate, small lower jaw (micrognathia), defective dentition	30-40%
Neck Short, thick or webbed neck (pterygium colli) Hairline low at nape of neck with "M" configuration	60-80%
Ovaries Abnormal ovarian development (fibrous bands)	80-100%
Skin, Hair and Nails Lymphoedema of hands and feet (swelling), increased number of birth marks (naevi) Spoon-shaped and/or small nails (nail dysplasia), alopecia (hair loss), vitiligo (loss of skin pigment) Excessive scar formation (keloid)	60-80%
Skeleton Wide carrying angle of arms (cubitus valgus), scoliosis Short bones in hands and feet (mainly 4th and 5th metacarpals/metatarsals)	40-60%
Major Health Issues Absent pubertal development (breasts, periods), infertility Frequent ear infections Increased blood pressure (hypertension), cholesterol, liver enzymes Impaired hearing: conductive (because of frequent ear infections) and/or sensorineural loss Increased risk of hypothyroidism, obesity, glucose intolerance Adult-onset diabetes, celiac disease, inflammatory bowel disease	

* The frequency and severity of these features changes dramatically depending upon whether the diagnosis of TS is made prenatally, during childhood, or later in adolescence and early adulthood. ALL of these features can be seen in individuals without TS but it is the presence of several at once that alert the physician.

Explaining the Diagnosis of Turner Syndrome to the Affected Child

> *"Yeah, the doctor told me. My parents didn't. I didn't know whether they felt it would hurt me or I would blame them or whether they were insecure. I mean it's a big thing to tell your child they've got something. It's not like it's a disease or it's a death sentence, but they might be concerned about the child's reaction or whether the child would blame them for it… Then again the doctor was pretty matter of fact. I felt actually very grown up because he considered me old enough to confide in. So I felt very grown up about this. You know, I was very reassured by what he said. He was a marvelous doctor."*
>
> —Christine, age 44, diagnosed at 1½ years of age, but did not learn of her diagnosis until age 14 (Kagan-Krieger S, p.94) *

Our current thinking is that the disclosure of this diagnosis is a gradual process, and something that is begun early and built upon at appropriate developmental stages. The child needs to be able to understand that they are coming to see a health care provider for a reason, such as delayed growth or development. Studies have shown that it is far more threatening for a child to feel that there is something "wrong" with them, and yet not be told directly by their parents why they are coming to see the doctor, or if their problem has a name. This situation can also cause resentment and mistrust later in life.

It is understandable that parents may not feel equipped to explain all of the implications of TS to their child, and the role of the treating pediatric endocrinologist and other members of the health care team to help in this process. Information is given to the child: (1) progressively at appropriate developmental stages. For example: infertility can be approached at the age when most children are curious about where babies come from – usually around the age of three – by discussing the various ways a family is formed, and by explaining that not all women can carry babies in their bodies like Mommy. The idea is planted as a positive factor, and at around 10, when more explicit information is being taught at school, explanations can be given as to how her own body works; a more complete description of the ovarian failure can be given around the time that medical treatment of delayed puberty is begun; (2) in a timely fashion. For example: discussions of the normal timing of puberty and the need for

pills to help this along should have begun by age 9 or 10 since other girls are developing at this time; (3) in a language that is understood. For example: a full discussion of karyotypes is usually more appropriate during adolescence when the concept of chromosomes has been learned in school, usually around grade 11; and (4) in an atmosphere which leaves open the possibility for questions. For example: when your child asks a question at home that you do not feel capable of answering, tell them that it is a good question, write it down with her, and bring it to the next visit. It is also helpful to find out exactly what is it that she is asking, by saying, "What do you think?" Other health care providers can also be consulted to help with some of the psychological issues that patients and their families may experience, to better prepare individuals with TS to deal with the implications of their diagnosis.

> *"I was diagnosed with Turner Syndrome at age thirteen when my mother began to wonder why I hadn't begun even the first stages of puberty. She happened to watch a television program that listed the signs of Turner Syndrome, and realized that they all applied to me. She took me to a paediatrician and a gynaecologist, and I remember breaking down in tears between the two doctor's offices because I was so scared that I had something very seriously wrong with me. She told me then what she was suspecting, and it was such a relief to put a name to it, and to realize that it wasn't nearly as bad as what my imagination had conjured up."*
>
> —Mary

What causes Turner Syndrome?

Turner Syndrome is caused by the absence of all or part of the second X-chromosome in some or all of the cells of the body. The missing chromosome can never be regained.

Doctors can confirm a diagnosis of TS by obtaining a karyotype. We can identify and count the sex chromosomes as well as look at their structure. We can do this because "colouring" the chromosomes with specific dyes help us see stripes of different widths, referred to as bands, that we can count and measure to see if any genetic information is missing (see Figure 1). These dyes do not allow us to see individual genes, however, it helps us put the chromosomes in order and look at their structure. In cases where only part of a second X-chromosome is missing, we can use techniques to try and determine what genetic material has been lost. About 60% of girls

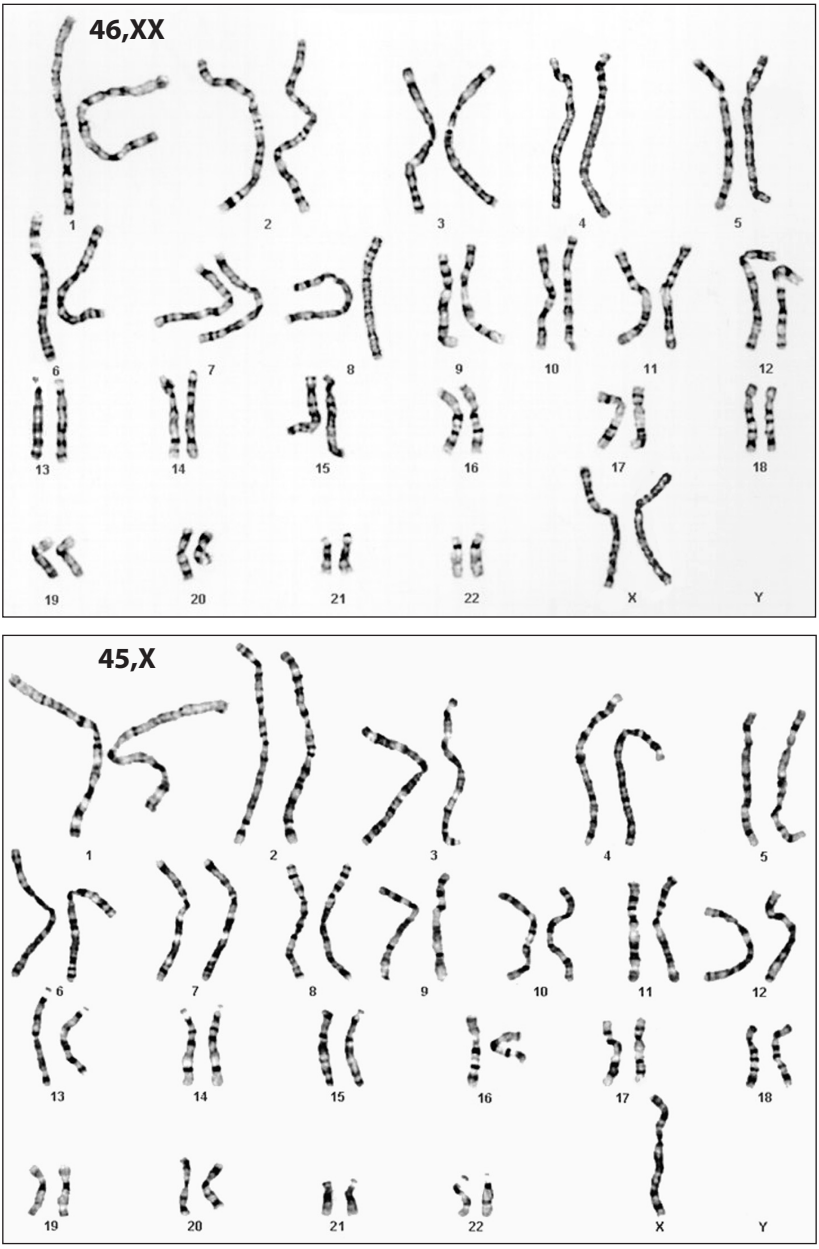

Figure 1. 46,XX Karyotype compared to the 45,X Karyotype seen in Turner Syndrome. Chromosomes are ordered from largest to smallest, then numbered. The sex chromosomes are placed last. The typical female karyotype (top image) contains two X-chromosomes. An individual with TS has only one X-chromosome as shown in the karyotype in the bottom image.

with TS have one of their sex chromosomes missing entirely; whereas 15% have some cells that have the normal number of chromosomes and the remaining 25% of girls with TS have both chromosomes but one of them is incomplete or altered.

The occurrence of chromosomal abnormalities in the developing fetus is actually quite a frequent event, and is the cause of more than half of all early miscarriages which are pregnancies that do not survive to term; TS can be diagnosed in about 20% of these. Loss of a sex chromosome or part of the X-chromosome is an event that happens at random, and is not caused by something that parents did – or did not do. Parents therefore should not feel that they are to blame, or that they could have avoided having a child with TS. Even parental age does not seem to be a risk factor for having a child with TS.

Prenatal Diagnosis of Turner Syndrome

The diagnosis of TS is sometimes found, after a women decides to have chorionic villous sampling which is the analysis of a small piece of the placenta, or an amniocentesis, the analysis of the liquid surrounding the developing fetus, because of the known increased risk of other chromosomal problems or another genetic condition in the family. Amniocentesis may also be performed after a fetal ultrasound reveals one or more of the following that may suggest TS: (1) the baby is not growing quite as well as it should; (2) there is excess skin or fluid accumulation in the neck region called nuchal translucency, suggesting cystic hygroma; (3) there is more generalized fluid accumulating in many parts of the body, such as around the heart or in the abdomen (hydrops fetalis); (4) there is a heart malformation; (5) there is a kidney malformation; and (6) the mother had an abnormal "triple or quadruple screen" blood test that measures various substances in the blood that can detect certain health problems in the fetus. Most of these findings will not hurt the baby, but hydrops fetalis and some cardiac malformations can cause more serious health consequences. When the diagnosis of TS is made prenatally, it is important to meet with an expert, usually a genetic counsellor or a geneticist, to explain the implications of all these findings. Pediatric endocrinologists can also answer questions these families may have concerning health issues and treatments in childhood and adulthood.

Why do individuals with Turner Syndrome have only 1 intact X-chromosome?

There are two times during development when the normal number of chromosomes can suddenly become altered. The first time is during the formation of the eggs and sperm. The second time is during embryo development, when the number of cells is increasing rapidly as each cell divides to make two daughter cells.

This type of error is called nondisjunction, and it occurs because the chromosomes are not distributed properly during cell division. Figure 2 shows how this can occur. It will be seen from Figure 2a that if the nondisjunction occurs before the sperm fertilizes the egg, all the cells in the body will have the same number of chromosomes. If it is one of the sex chromosomes that has been lost such that either the egg or the sperm does not contain a sex chromosome, then after fertilization there will be 45 chromosomes. If the embryo received only a Y sex chromosome, it does not survive, but if it receives only one X-chromosome, it may survive and develop as an individual with TS. Another way of describing this is X monosomy. We write this karyotype as 45,X, because there are 44 autosomes and only one X-chromosome. This is in contrast to the typical female karyotype of 46,XX. A 45,X karyotype is found in roughly half of the individuals with TS.

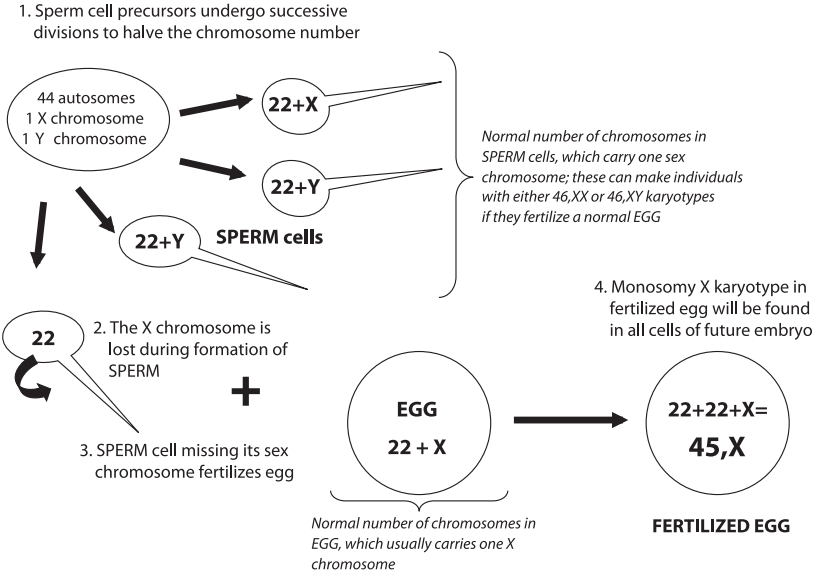

Figure 2a. X-chromosome loss during the formation of the germ cells

Suppose that the egg, carrying 22 autosomes and an X-chromosome, is then fertilized by a sperm carrying 22 autosomes and either an X-chromosome or a Y-chromosome. The rapid cell division quickly increases the numbers of cells in the embryo, with the chromosomes duplicating themselves prior to each cell division. One cell becomes 2 cells, then 4 cells, then 16 cells, then 32 cells, and so on. If at any time during embryonic development a sex chromosome is lost, then only the cells arising from that affected cell will have one less sex chromosome, and this condition is called mosaicism (see Figure 2b). When we perform a karyotype, we look at the chromosomes in many cells and then we can say what proportion of cells are 46,XX and what proportion are 45,X. For example, if we looked in 30 cells, which is the usual number we analyse, and saw that only 15 cells had 45,X and all the others had 46,XX, we would report that there was 50% X monosomy, and written as 46,XX[15]/45,X[15]. This is seen in about 15% of patients with TS.

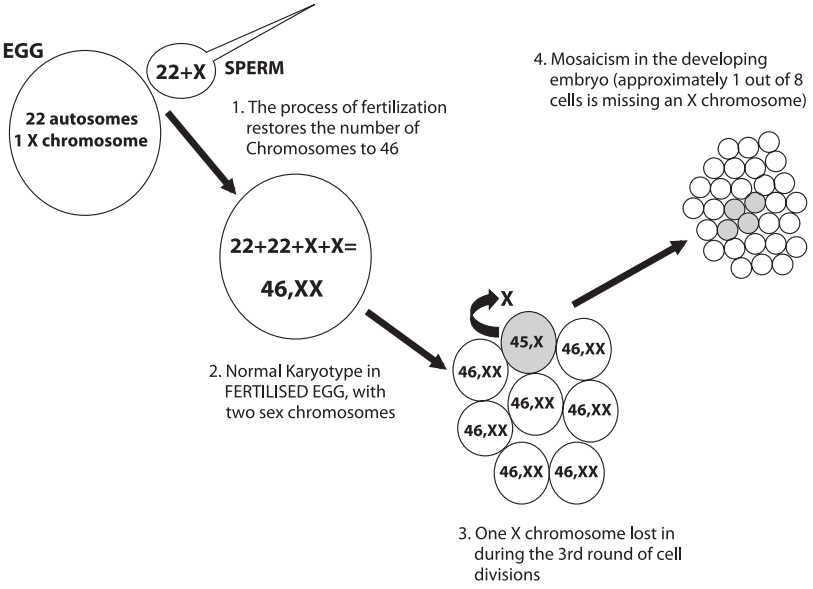

Figure 2b. Post-fertilization loss of an X-chromosome and resulting mosaicism

In some individuals with TS, the cause of the condition involves X-chromosome defects rather than loss of the complete chromosome. X-chromosomes can be found that have an abnormal structure, with some of the DNA missing or not "readable". Figure 3 is a diagram of some of the different types of X-chromosomes we can see on karyotypes from individuals with TS. They have specific names to describe them, depending on their shape and where the missing DNA is found. For example, a person missing the upper part of the chromosome (the short "arm" or p) in all of their cells would have a karyotype of 46,X,del(Xp). There may also be a number preceded by a "p" or a "q" [46,X,del(X)(p23)], which specifies exactly where the chromosomal break has occurred.

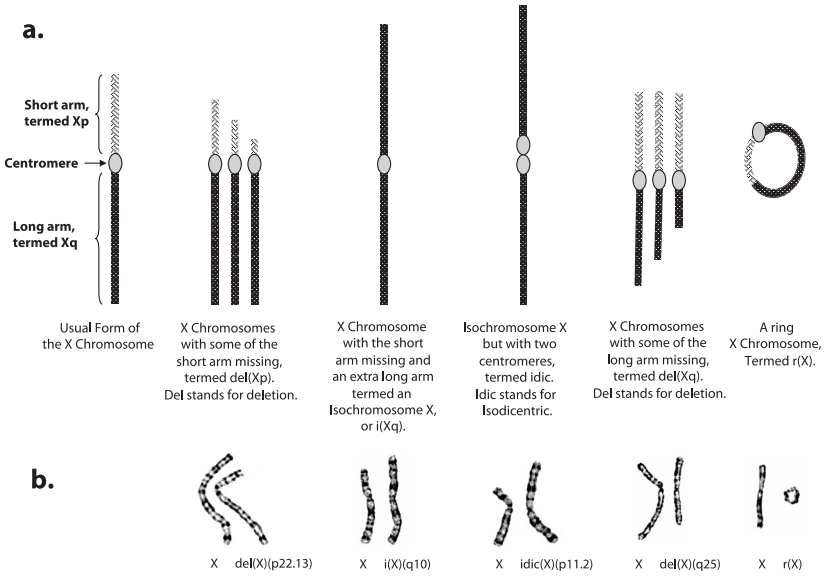

Figure 3

Normal and Abnormal X-Chromosomes.

(a) Cartoon drawings.

(b) Actual chromosomes, showing intact X-chromosomes adjacent to abnormal X-chromosomes. Chromosomes are examined for their structure, including the length of their long (q) and the short (p) "arms", their banding patterns and the placement of their centromeres (the central portion of the chromosome that plays an important role in helping the chromosomes move appropriately during their partitioning into egg and sperm or into daughter cells during development. The dicentric (idic) chromosome results from the abnormal fusion of two chromosome pieces, each of which includes a centromere. The ring (r) chromosome results from the fusion of the two ends of the chromosome following loss of material at both ends. Some Xp or Xq deletions are so small that special techniques like fluorescent *in situ* hybridisation (FISH) are needed to see them.

Even these abnormal X-chromosomes may not be present in all the cells of the body, because they can be lost during cell division (leaving a cell with a 45,X karyotype). Depending on when the loss occurs, there can be quite complex mosaicism, and we sometimes see individuals with not only two different cell lineages in their bodies but even three or four. An example of this would be 46,XX[20]/46, X iso(Xq)[9]/45,X [1]. This is seen in about 10% of patients with TS.

When mosaicism arises because of X-chromosome loss in a 46,XY embryo, it can result in an individual with a 45,X/46,XY karyotype. You may sometimes hear this called mixed gonadal dysgenesis. The development of the fetus' sex glands, also called gonads at very early stages of development because they are neither testicles nor ovaries, depends on where the cells with each of these chromosomal patterns are found. In the case where most of the cells of the body are 45,X, the individual will present the typical findings of TS and the gonads will not develop into normal ovaries; they are called dysgenetic and are often little more than bands of fibrous tissue. A sign that doctors look for, however, is the presence of any enlargement of the clitoris in these patients, because this means that some of the 46,XY containing cells may have found their way into the gonads and may be directing the production of male hormones. In a girl with a 45,X/46,XY karyotype and these findings, it is indicated to remove the gonads to prevent the formation of tumors called gonadoblastomas. In addition this will also prevent any further effects of male hormones.

Very rarely, small fragments of chromosomes, termed marker chromosomes, that are not easily identifiable by standard techniques are observed in an otherwise typical TS karyotype. This finding requires additional studies to try and identify the origin of this genetic material, mainly to rule out the presence of any Y-chromosome material containing genes that may make the individual more at risk for gonadoblastomas. Because the risk may be as high as 1 in 10 individuals with the presence of Y-chromosomal material, our current thinking is that the gonads should also be removed in these patients. Table 2 gives the relative frequency of different karyotypes seen in TS.

Table 2. Frequency of Karyotypes Found in Turner Syndrome

Karyotype	Frequency*
45,X	60%
45,X mosaicism with normal cell line (45,X/46,XX or 45,X/46,XY)	15%
Anomalies of structure (46,X,del(Xp); 46,X,i(Xq))	10%
45,X mosaicism with abnormal X cell line (45,X/46,X,i(Xq); 45,X/46,X,r(X))	10%
Other karyotypes	5%

*The frequency of these karyotypes changes depending upon whether the diagnosis of TS is made prenatally, during childhood, or later in adolescence and early adulthood.

Individuals with mosaic karyotypes may have variable numbers of the features that are present in TS depending upon the numbers of cells that retain the usual 46,XX karyotype and their distribution within the body. For instance, if there are mostly normal 46,XX cells in the ovary, there is likely to be preserved ovarian function, although this is not very often seen. In individuals with abnormal X-chromosomes such as those depicted in Figure 3, there can be variable numbers of genes that are no longer present or may not function correctly. Depending on their number and their function, the affected individual may have many features of TS or very few features. If there are few features, it may make the diagnosis harder for physicians to make. Similarly, if the abnormal karyotype is found in only a few cells, say less than 2% of blood cells, but there are many suggestive features of TS, the physician may ask that more cells be examined, or that the chromosomes of cells other than the white blood cells be examined.

How the Karyotype Can Predict Health Issues

We can not yet explain all the features of TS by relating them to specific genes on the X-chromosome, although we have identified some genes of interest that most likely participate in biological functions as diverse as hearing, ovarian function, growth and even certain brain functions.

Many genes on the X-chromosome have long been known to cause disease (such as muscular dystrophy and hemophilia) if they are missing or abnormal. Why don't we see these diseases in TS? Females with the usual 46,XX karyotype will have two copies of every gene

on the X-chromosome. Luckily, many but not all of the genes on the second X-chromosome are inactive. The process whereby most genes on the second X-chromosome are made to stop working is termed X-inactivation and it is a normal part of X-chromosome biology. It implies that we need only one copy of these normally inactivated genes to be healthy.

When the second X-chromosome is abnormal, sometimes the process of X-inactivation does not occur normally, and this can cause problems. This is believed to be why individuals with ring X-chromosomes may have more health issues than those with just deletions on their second X-chromosome.

One gene which we do need to function on both X-chromosomes is a gene called SHOX (short stature homeobox gene on the X-chromosome). Individuals with only one functional copy of SHOX, such as in those with TS, are much shorter than expected for their family; missing two copies causes an even more severe short stature along with other skeletal problems. The SHOX gene is also found on the Y-chromosome, so men also have two copies (one on their X-chromosome which is always active, and an active one on the Y-chromosome). Of course, many of the genes on the Y-chromosome are not found on the X-chromosome, and vice versa, which helps to explain why men and women are different!

Several genes on the X-chromosome have also been linked to ovarian failure and infertility, including BMP15, POF1, POF2 and FMR1. Three of these are on the long arm of chromosome X (Xq), which may explain why individuals with isochromosomes that have no short arm (Xp) but two long arms (see Figure 3) can sometimes have ovaries that function, giving them enough female hormones to develop breasts, have periods and, in rarer cases, even become pregnant.

There are also many genes on the X-chromosome that have been linked to different forms of familial deafness. It is not yet understood whether their absence contributes to the sensorineural hearing loss seen in over 50% of older women with TS, although one or more of them may be important.

Other genes are candidates for some of the difficulties that individuals with TS may experience with tasks requiring socialisation abilities, visual and spatial abilities, memory and attention, although it is unlikely that a single missing gene leads to a particular difficulty, such as performing a mathematical problem, understanding facial expressions or copying a geometric drawing.

One subject of interest is whether the X-chromosome coming from the father behaves exactly as the X-chromosome from the mother. In order to study this question, researchers have looked at individuals with a 45,X karyotype, and asked the question whether there is any phenotypic difference between those that retain the X from their mothers and those that retain an intact X from their fathers. This phenomenon is referred to as genomic imprinting, that is, the behaviour of a gene or genes depends on the sex of the transmitting parent. There is some suggestion that this is, indeed, the case in girls and women with TS, although more study is needed before this information could be used to counsel patients and their families.

Genetics in the Future: To Better Tailor Drug Therapy, Disease Prevention and Counselling to the Individual

Because there is such a variation of findings among individuals with TS, it is clear that not all patients need the same medical interventions and preventive therapy. Even the response to drugs and hormones may not be exactly the same for each person with TS. It is hoped that understanding the X-chromosome fully will enable us in the future to tailor our treatments to those individuals that will benefit the most, and to find novel approaches for treating individuals that respond less well to current therapies. This century will be an exciting one for genetic discoveries, and we remain very optimistic that this will improve the health of all people, not just those living with TS.

> *"I still feel special with Turner Syndrome because it's not my life. Other people have things that get in the way of their life, like people who have disabilities. They can't talk, they can't write, they can't read; I can do all those things. That's why I feel special even with Turner Syndrome. I am just happy to be who I am."*
>
> —Julia, age 8

Key Points

- A karyotype (study of chromosome number and structure) confirms the diagnosis of TS; the defining feature is the absence of all or part of the second X-chromosome, in some or in all cells of the body.
- The occurrence of chromosomal abnormalities is frequent; TS occurs in 1 out of every 2,000 to 2,500 newborn girls. It is not the fault of either parent.
- Disclosure of the diagnosis to the child is a gradual process that should be started early; the treating pediatric endocrinologist and other members of the health care team may facilitate this process.
- Patients with mosaic karyotypes may have less obvious clinical features of TS, as may patients with karyotypes showing smaller amounts of missing X-chromosome material.
- In girls with karyotypes containing part or all of a Y-chromosome, the gonads are usually removed to prevent excess production of male hormones and the development of tumors.
- Increased knowledge about the genes on the X-chromosome will help us to better counsel, treat and follow our patients with TS.

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    These two articles show that historically, individuals who are diagnosed by clinicians represent a different population from those who are diagnosed incidentally because of prenatal diagnosis or unexplained short stature, with the former group having more health issues.

Basic science articles discussing X chromosome genetics

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15. Ross MT et al. The DNA sequence of the human X-chromosome. Nature 2005;434: 325-37.

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In addition to the hallmark article on the sequencing of the X-chromosome, these papers discuss the mechanism of X-inactivation and its implications, the pseudoautosomal regions that contain the same genes on both the X- and Y-chromosomes, and how errors in the number of chromosomes in a cell can occur.

* Susan Kagan-Krieger, "The struggle to understand oneself as a woman: Stress, coping and the psychological development of women with Turner Syndrome" (EdD dissertation, University of Toronto, 1998).

Chapter 2

The Long and the Short of It: Growth in Turner Syndrome

Teresa Pinto, MD, FRCPC and Alexandra Ahmet, MD, FRCPC

Artist: Katelynn, age 7, standing on a hill next to her younger sister

At least 95% of girls with Turner Syndrome (TS) have short stature.[1] The cause of short stature is likely related to a complex interaction of various hormonal and genetic effects.[2] Studies have shown that growth can be affected in all stages of life in an individual with TS. The mainstay of treatment for short stature in TS is growth hormone therapy. The following chapter will review the different stages of growth in a child with TS, the current available treatments as well as their risks and benefits.

Fetal and Infant Growth

Fetal growth in the womb is influenced by maternal, placental and fetal factors. Intrauterine growth restriction (IUGR), referring to abnormal growth in the womb, has been reported to occur in newborns with TS. The exact cause of this growth restriction is unknown but may be related to the type of chromosomal abnormality.[3] On average, studies have revealed that newborns with TS are born in the low normal range for length compared to newborns without TS, approximately 2.8 cm, which is just over an inch, below average.[4-7]

Poor growth may start to be evident in infants with TS. In the past, it was thought that girls with TS only began to slow down in growth in later childhood, however more recent studies have documented a slower growth rate as early as under 1 year of age.[2,4,5,8]

Poor growth *in utero* and infancy may also be affected by other factors often seen in TS. These include abnormalities of the heart, gastrointestinal system and kidneys as well as poor feeding. These often affect weight more than height and are discussed in detail in other chapters of this book.

Growth in Childhood and Adolescence

The poor growth that occurs in girls with TS is felt to be composed of two main features. The first is a delay in the onset of the childhood component of growth and the second is related to a decreased growth velocity throughout childhood and adolescence.[7,8] Growth velocity or growth rate refers to the number of centimetres grown over a year. The childhood component of growth refers to an increase in growth velocity, called a growth spurt, seen in children around 6 months to 1 year. In girls with TS this growth spurt starts later. After one year of age, average growth velocities are typically

10 cm, or 4 inches, per year from 1 to 2 years, 8 cm, or 3 inches, per year from 2 to 3 years and 5 to 6 cm, or 2 to 2.5 inches, per year from 3 to 10 years of age. Girls with TS obtain maximal growth rates less than girls of the same age without TS. In fact, growth seems to progressively slow down throughout childhood in girls with TS.[7] Often, the diagnosis of TS is made when girls are referred to a specialist for poor growth.[1,6,9]

Puberty marks the beginning of the changes that a girl experiences in becoming a woman. It typically starts with breast development and ends with the onset of menstrual periods. Girls usually have an increase in their rate of growth early in their puberty, at an average age of 10 to 12 years. This is referred to as the "pubertal growth spurt". At that time they will grow up to 9 cm per year. Most girls with TS are unable to make the hormones necessary for complete pubertal development. Consequently, they do not have the typical growth spurt associated with puberty.[1] Once again, their growth velocity is noted to be significantly lower than that of their peers.

Due to the less than optimal growth that can occur at all of these stages, TS final adult height is significantly shorter than the average female height. On average, girls with TS will be 20 cm, approximately 7.8 inches, shorter than women of the same ethnic background.[1,9] Untreated, girls with TS will therefore reach an average height of 144 cm, approximately 4 foot 9 inches.[7] When measured by their pediatrician, girls with TS should have their height plotted on a specific growth chart standardized for girls with TS.[7] *See Image A on page 43 and a colour version on page 61.*

> *"Hi, my name is Alexandra. I was diagnosed with Turner Syndrome when I was 6 years old and now I am 10 years old. One thing you are not going to like is that with Turner Syndrome you are small. If you have a younger sibling, people might think you are younger because of your height. I have a younger sister and she is a bit taller than me, but you can hardly tell and some people ask if we are twins sometimes! Sometimes people will make fun of your height. Perhaps they may say "you're a shrimp". But what I do is I ignore the nasty comment. I sometimes have difficulty making friends but I have 7 good friends and that is really nice. That is all for now, I hope you find this helpful."*
>
> —Alexandra, age 10

Factors Affecting Growth

Many different factors play a role in determining final height. These include familial genetics, ethnicity, nutrition, general health, hormones and in the case of TS, specific genetic components.

Familial and Ethnic Components

The precise influence of genetics on final height cannot be determined definitively. However, an estimate of genetic height potential can be made based on the height of one's parents. This means that an individual with shorter parents is more likely to be short and those with taller parents will likely be tall. This is also true for girls with TS. Therefore, a TS girl with parents of above average height, is likely to be above average in height for a girl with TS. Similarly, a TS girl with parents of average height, or below average height, will also likely fall in the same corresponding range on the TS growth curve.[7] Race or ethnicity may affect growth potential, as some races are historically taller than others.[7]

Hormones

Many hormones play a role in the growth process. Only a few key hormones will be discussed here.

Growth Hormone

Growth Hormone (GH) is the most important hormone contributing to linear growth, or height, after the initial 6 to 9 months of life.[10] It is made in a small gland in the brain called the pituitary gland. Complex interactions between different signals allow for GH to be released in a well-controlled manner. The release of GH increases at puberty contributing to the pubertal growth spurt.[10] GH acts on different areas of the body including muscle, liver, bones and fat. GH increases the growth of bones and muscles. It also increases the production of other hormones called insulin-like growth factors, which also act on bone and muscle to increase growth.

Girls with TS generally make appropriate amounts of GH however there may be an abnormal response to it at the level of the bones, playing a partial role in the short stature of TS.[7]

Thyroid Hormone

Thyroid hormone is made by a gland in the neck called the thyroid gland. Thyroid hormone has many important roles, one of which is normal growth. It acts together with GH as well as independently on bones.[10] It is therefore crucial to have normal levels of thyroid hormone for normal growth to occur. Girls with TS are at an increased risk of having an under-active thyroid gland and less frequently, an over-active thyroid gland.[7] Physicians of girls and women with TS should do routine thyroid checks along with a blood test to ensure normal thyroid hormone levels.

Sex Hormones

Puberty is marked by an increase in the production of sex hormones. These include estrogen, the female sex hormone, and androgens such as testosterone, the male sex hormone. Both girls and boys make both female and male sex hormones in varying proportions. Both types of hormones contribute to the increase in growth velocity that occurs during the pubertal growth spurt, as well as to the maturing of the bones that also occurs at this time.[10] Estrogen, at low levels, contributes to the increase in growth velocity while at higher levels is responsible for the fusion, or closure, of growth plates.[11] Growth plates are the areas of bone that allow for growth to take place. As a child ages, these growth plates gradually close. Once this is complete, growth is finished. Estrogen plays an important role in the fusion of the growth plates and thus influences final adult height.[10]

Estrogen is also required for breast development as well as other female changes.[10] Girls with TS do not make sufficient amounts of estrogen and therefore require estrogen supplements to progress through puberty. Physicians taking care of girls with TS will therefore prescribe estrogen therapy starting at approximately 12 years of age, in gradually increasing doses to help promote appropriate female pubertal changes. Estrogen is started in small doses so as not to cause early fusion of the growth plates.[11]

SHOX Gene

The SHOX gene is a gene located on both the X- and Y-chromosome. Two copies of it – either on the X and the Y for boys, or on the 2 Xs

for girls – are necessary for its normal function. The SHOX gene is responsible for the creation of proteins necessary for normal growth.[12] Girls with TS are typically missing one X chromosome and therefore are missing one copy of the SHOX gene. This results in girls with TS having only half the amount of SHOX gene necessary for normal growth.[7,12] It is this genetic abnormality that is felt to contribute primarily to the short stature seen in girls with TS[12]. However, individuals with conditions other than TS who are missing the SHOX gene have average heights taller than girls in the TS population.[12] This suggests that there are other factors, including those discussed above, which contribute to height. There also may be other genes on the missing X chromosome that may affect growth in girls with TS that have yet to be discovered.

Skeletal Growth

Girls with TS classically have a wider body and shorter neck than other girls. Their hands and feet are often large in comparison to their height. Scoliosis, or a curvature of the spine can be seen in 10 to 20% of girls with TS. These features, along with other less common bony abnormalities, can contribute to the short stature seen in TS.[7]

Treatment for Short Stature in Turner Syndrome

Turner Syndrome was first described in 1938 and the most common finding noted was short stature.[7] Although growth hormone deficiency is not a typical feature of TS, GH therapy began to be studied as a possible treatment for short stature in TS starting in the 1960s. As GH therapy has become more available, many studies have been performed to determine whether or not GH therapy improves the final height of girls with TS. Now, over 40 years later, it has been determined that GH therapy increases final adult height in TS.[1,6,7,9,13-20] It is estimated that girls with TS can reach an average adult height of 150 cm, approximately 4 feet 11 inches, with GH therapy; usually about 5 to 10 cm, 2 to 4 inches, above expected final height without GH treatment.[7] This is partially dependent on when the treatment is started as well as the timing of puberty or estrogen replacement therapy.[7]

History of Growth Hormone Therapy

The method of obtaining GH for use in treating short stature has changed significantly over time. Starting in the late 1950s, the initial method of obtaining GH was through extraction from pituitary glands of human cadavers. This process was stopped in 1985 because of concerns regarding spread of disease, in particular Creutzfeldt-Jakob Disease, known as "mad cow disease", which can be spread through human tissue.[7] Since the mid-1980s, GH is produced in laboratories and uses complex laboratory techniques, designed to produce synthetic GH that looks and acts like human GH. It can be made without the risks associated with human GH. This is the form of GH used today to treat short stature in TS.

When and how is Growth Hormone given?

GH therapy should be considered in girls with TS once there is evidence of growth failure on the standard female growth chart.[21] It has been suggested that the earlier that treatment is started and the taller the girl is at onset of treatment, the better the outcome for final height.[13] GH is currently given as a nightly injection under the skin. It is given at night in an attempt to mimic the natural production or secretion of GH in the human body, which peaks at night. There are injecting devices especially designed to give GH that are easy and convenient to use. A girl with TS and her parents will be instructed on how to give the injections at home.

Other means of giving GH are currently being researched. These include liquid formulations and inhaled forms of GH. These may offer more convenient methods of administration of GH in the future.

Dose of Growth Hormone

Different doses of GH have been studied to determine which dose provides the greatest benefit with respect to height with the least side effects. The current recommended dose is 0.375 mg per kg per week given daily, which is higher than the standard dose used for short stature due to GH deficiency.[21] Different centres may use slightly different administration schedules, for example administering GH 6 versus 7 times per week. Girls with TS on GH therapy should be monitored every 3 to 6 months by a pediatric endocrinologist. Adjustments in the dose will be made based on height, weight ~~and~~ growth velocity measurements.

How long does treatment last?

Girls with TS typically continue GH therapy until their growth velocity has decreased to less than 2 cm, just under an inch, over the previous year with a bone age of at least 13 to 14 years.[1] The bone age is an x-ray of the hand which assesses the growth plate to determine how much growth potential is left. As most girls complete growth soon after starting their menstrual periods at an average age of 12.7 years.[7] It can be expected that growth will be close to complete at a bone age of 14 years. Bone age is related in part to estrogen exposure and does not necessarily match actual age, therefore girls with TS may continue to grow and be treated with GH beyond 14 years of age. GH therapy can be discontinued at an earlier time if there are side effects, if a satisfactory height is already reached or if the girl with TS chooses to discontinue it.

Risks

Side effects of GH therapy are rare but it is important to be aware of them prior to starting treatment. GH therapy may cause salt and fluid retention. This typically occurs early in treatment and may lead to swelling of the lower limbs or hands and wrists. It may also lead to a condition referred to as pseudotumor cerebri or benign intracranial hypertension.[22] This results from an elevated pressure in the fluid circulating in the brain and may cause a severe headache. These side effects are rare and reverse when GH therapy is stopped.[22]

GH therapy may lead to higher blood sugars, and rarely cause impaired glucose tolerance or pre-diabetes, or type 2 diabetes mellitus.[22] This risk is also very low and may improve with discontinuation of GH.[22] Girls with TS are at an increased risk of developing diabetes regardless of whether or not they receive GH therapy and should be monitored for this regularly by their physicians while maintaining a healthy diet and active lifestyle.[7]

Slipped Capital Femoral Epiphyses (SCFE) is another possible side effect of GH therapy.[22] This refers to the displacement of the growth plate at the femur – the long bone of the upper leg – at the hip. This may manifest as hip pain, severe knee pain or limp. If these symp-

toms were to occur, x-rays of the hips should be done as soon as possible with discontinuation of GH therapy.

GH therapy may increase the number or size of pigmented *nevi* present.[22] These are what are commonly referred to as moles. Despite this increase there has not been any noted increase in transformation to skin cancer of these moles.[22] Pigmented *nevi* should be monitored regularly by a physician for changes in size or colour regardless of whether or not one is on GH therapy.

Individuals who produce too much GH are at an increased risk of developing certain cancers but this increased risk has not been reported in girls with TS treated with GH. While being treated with GH, insulin-like growth factor (IGF-1) is monitored by a simple blood test. IGF-1 is a hormone that is stimulated by GH. Monitoring IGF-1 helps to ensure that GH levels remain within a safe range.[22]

> *"'Honey, do you know what growth hormone is?' I didn't know yet but this question would have a huge impact on my life. I was diagnosed with Turner Syndrome when I was only about 4 years old and except for the occasional, 'Wow! She's short,' it had hadn't really affected me. But when I was 7, my mom sat me down and told me how I was going to have to take needles with growth hormone everyday, so that I could grow more, of course I cried and screamed, but it didn't matter, I knew that taking the GH was best for me. I started on the GH as planned and I hated it, and sometimes I hated my mom for making me take it, but now that I'm finished, I'm glad. Having to take those needles made me stronger, even after just a year or so I was able to give the needles to myself. And because of them I'm 4 inches taller than what I was expected to be for my adult height."*
>
> —Brittany, age 16

Other Treatments for Growth

Androgens

Androgens are so-called male hormones, though both males and females produce them. It has been shown that oxandrolone, an androgen, may improve growth when given in combination with GH in girls older than age 9 years at the onset of GH treatment or in those with severe short stature.[18,23] This is something that can be discussed with your pediatric endocrinologist.

Estrogen

Estrogen replacement is necessary in most girls with TS in order to allow them to develop through puberty. Estrogen is also an important hormone that contributes to the closure of growth plates in bones, thus completing growth. Though in the past it was thought that estrogen replacement should be delayed to optimize growth, current guidelines recommend starting lower doses of estrogen at about 12 years of age. Recent evidence suggests that this approach does not affect growth and allows a girl with TS to begin pubertal changes at around the same time as her peers.[11,21] This is important for both her psychological and social well-being.

Key Points

- Short stature is the most common feature in girls with TS. It is characterized by intrauterine growth restriction, slow growth in infancy, a delay in the onset of the childhood component of growth, a poor growth velocity and absence of the pubertal growth spurt. Other factors such as parental heights and general health are also important in determining height potential.

- Treatment with growth-promoting therapies, in particular, growth hormone, has been shown to improve final height in girls with TS.

- The use of growth hormone, and potentially the addition of other therapies such as androgens, as well as the timing of estrogen therapy, are important factors that may be individualized to optimize growth and the general well-being of a girl with TS.

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Beginning Growth Hormone Therapy in Turner Syndrome

Answers to Frequently Asked Questions

What is Growth Hormone?

Growth Hormone (GH) is a natural protein hormone made up of amino acids, secreted by the pituitary gland. Somatropin is a synthetic form of human growth hormone which has the same chemical structure as the GH produced by the pituitary gland using recombinant DNA technology. Synthetic GH has been used in Canada since 1986. **GH is not a steroid.**

Why is Growth Hormone necessary?

In order for children to grow to their full genetic potential their bodies need to produce adequate amounts of GH. Therefore it is often indicated as an appropriate treatment in children with:

- GH deficiency
- Children with chronic diseases or syndromes that may impact growth like Turner Syndrome (TS)

For those with Growth Hormone deficiency, how is it diagnosed?

Assessment of growth rate and evaluation to rule out other causes of slow growth. Growth hormone testing is often done to help confirm GH deficiency. Some individuals with TS may undergo growth hormone testing if they have very poor growth velocity over time.

How is the Growth Hormone dose for each child determined?

Various dosage ranges depend on:

- Diagnosis
- Literature recommendations

- Level of GH deficiency, chronic disease or syndrome
- Goals of treatment

Generally, for individuals with TS the dose starts at 0.05 mg per kilogram body weight per dose and moves upwards depending on response and goals of treatment. Thus, weight and growth velocity will determine the dose of GH each child will receive.

How is Growth Hormone given?

As GH is a protein it can be digested in the stomach and does not work if taken by mouth. It must be given under the skin by subcutaneous injection to allow for it to get directly into the bloodstream where it travels to the liver where it stimulates insulin-like growth factor-1 (IGF-1) that, in turn, causes cells in bones, muscle and tissue to grow.

Where are the injections given?

GH is given by subcutaneous injections to arms, legs, buttocks or abdomen. Injections are rotated between these sites. You may be encouraged to keep a log of the injections sites.

How often are injections given?

Injections are given 6 to 7 times per week. **GH therapy requires long-term commitment by children and their families.**

When are Growth Hormone injections given?

GH injections can be given anytime of day however, it is generally recommended to be given in the evening prior to bedtime to help mimic and add to the body's natural tendency to secrete most of its GH at night.

How much growth can we expect?

Generally, prior to GH therapy growth is less than 4 cm per year. During the first year of GH therapy growth can be up to 8 to 10 cm and then usual growth of 5 cm or more per year, following the first year. The general expectation is that there is "catch up" growth during the first year and better than 5 cm of growth each subsequent year until puberty when there should be more.

How often will we need to be seen in a clinic for follow-up?

Generally, clinic visits are scheduled every 4 months during the initial year of GH therapy. This may then be decreased to once every 6 months following the first year of treatment if growth, development and health are stable. During the induction and progression of puberty, your child may be seen every 4 months to ensure optimal treatment during this period of accelerated growth and development.

What can I expect at these clinic visits?

- Assessment of height and weight
- Review of health and side effects
- General physical assessment
- Bone age x-rays taken once every year or two
- Blood testing approximately once per year
- New dose and prescription of GH based on new weight

How long will my child be on Growth Hormone?

Your child will be on GH until full growth has been attained as measured by ~~no~~ recent growth and a bone age x-ray showing closure, or near closure, of growth plates and a corresponding bone age of 13 to 14 years, or when you and your child are satisfied with the current height and are no longer wishing to continue with therapy.

What effects can we expect while my child is on Growth Hormone?

- Increased height
- Increased weight
- Increased muscle mass
- Increased bone mass
- Increased strength
- Increase balance and coordination in some girls with TS

You may also notice:

- Reduction of adipose, or fat tissue
- Increased metabolism along with increased appetite
- Improvement in mood

Strategies for Giving Injections

Giving your child an injection requires patience, practice, knowledge and a consistent approach that is most supportive of your child's particular age, temperament and developmental level. It is important to remember that injections are a routine part of the lives of thousands of children and along with the support of your health care providers, you and your child will learn to accept it as a part of your normal daily routine.

Toddler or Preschooler

Before the injection:

- Establish consistent routines for after dinner, before bedtime, and after tooth brushing, for example.
- Explain what you are about to do and make it clear that it is not a punishment for bad behaviour but medicine to help them grow. Ensure her that the discomfort will soon be over.
- Let them help decide the injection site to use such as the area on the leg, arm or buttock, if your child is willing.
- Prepare the injection prior to getting your child.
- Give the injection quickly. Prolonging may only make your child more anxious.

During the injection:

- When you have to restrain your child, explain that you are helping her to "hold still".
- Teach your child to relax. Wiggle toes when injecting into the thigh; take a big breath and blow; close eyes; look in another direction; hug favourite toy; or sing a funny song.

After the injection:

- Cuddle and hug your child. Praise them.
- Allow your child to play. This relieves tension.

School Age

Before the injection:

- Establish and stick to a consistent routine. Allow them to choose their day off, if you are injecting 6 days per week.
- Prepare injection prior to getting your child.

- Explain that the injection is "medicine to help you grow".
- Let your child help select the area in which you'll inject. Remember to rotate sites.

During the injection:

- Let your child take part in the injection process.

After the injection:

- Encourage your child to talk about any feelings or anxieties, and reward positive behaviour.
- Encourage and support them to take some ownership of the process such as a nightly reminder of the injection, keeping track of injection site rotation and under supervision, trying to give themselves an injection.

Teenager

Before the injection:

- Establish and stick to a consistent routine.
- Have your teen prepare and give the injection under supervision until they are proficient with the process.
- Respect your teenager's decisions about whether friends and relatives should or should not know about her therapy.

During the injection:

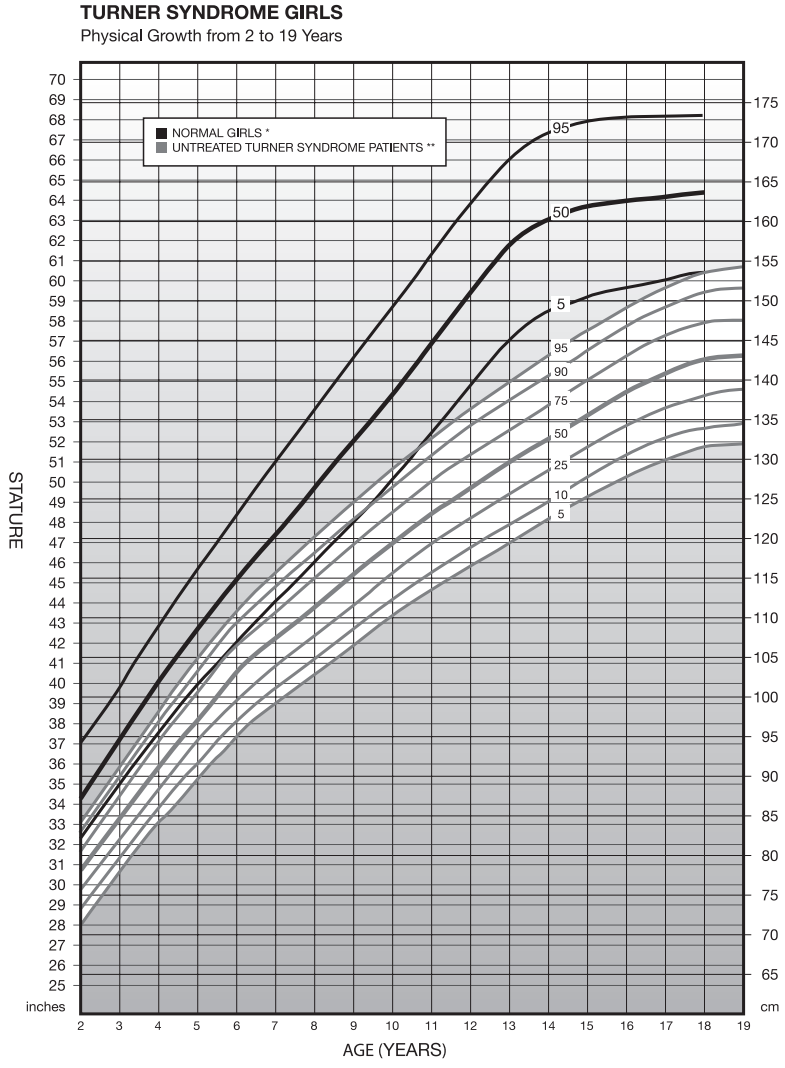
- Let your teen take part in the injection process as much as she wishes to with your supervision.
- Reconstituting GH should be done under adult supervision.

After the injection:

- Praise and reward your teen's consistent commitment to the therapy.
- Encourage your teen to talk about any feelings or anxieties.

Image A: The Turner Syndrome Growth Curve

The black growth curve shows the growth pattern for a girl without TS. The curve in grey shows the growth pattern for a girl with TS, untreated with growth hormone. See the colour version of this Growth Chart on page 61.



* Percentiles derived from National Center for Health Statistics
** Turner Percentiles from Lyon, A.J., Preece, M.A., and Grant, D.B. Growth curve for girls with Turner Syndrome. Archives of Disease in Childhood 1985;60:932-35

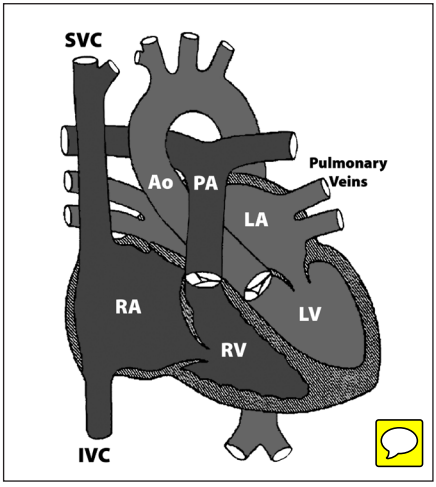
Chapter 3

The Beat Goes On: The Heart

Timothy J. Bradley, MBChB and Leland N. Benson, MD

The Normal Heart

First, it is important to understand the basic anatomy of the heart. The heart is 2 pumps in series. Each pump has filling vessels (veins), filling chambers (atria), pumping chambers (ventricles) and outlet vessels (arteries). Between the filling and pumping chambers are the atrioventricular valves, the right-sided tricuspid valve and left-sided mitral valve, which close to prevent the blood from going backwards when the ventricles contract (systole). At the same time the semilunar valves, the right-sided pulmonary valve and left-sided aortic valve, leading to the arterial outlets open so that the blood can be ejected to the pulmonary artery (lung circulation) and the aorta (body circulation). When the ventricles finish contracting the pulmonary and aortic valves close, the ventricles relax (diastole) and the tricuspid and mitral valves open allowing the ventricles to fill with blood.



The Normal Heart

The heart functions to pump oxygenated blood, or "pink blood", to the body where oxygen is removed in the tissues and to pump returning dexoxygenated blood, or "blue blood", to the lungs where more oxygen is added. Blue blood returns from the body via the systemic veins or superior/inferior vena cava (SVC/IVC) to fill the right atrium (RA), then drains via the tricuspid valve to the right ventricle (RV), and is then pumped via the pulmonary valve and the pulmonary artery (PA) to the lungs. Pink blood then returns from the lungs via the pulmonary veins to fill the left atrium (LA), then drains via the mitral valve to the left ventricle (LV), and is then pumped via the aortic valve and the aorta (Ao) to the body.

The Abnormal Heart in Turner Syndrome

The heart can be abnormal in Turner Syndrome (TS) due to congenital heart disease, conditions that we are born with – see Table 1, or acquired heart disease conditions that develop after birth – see Table 2.

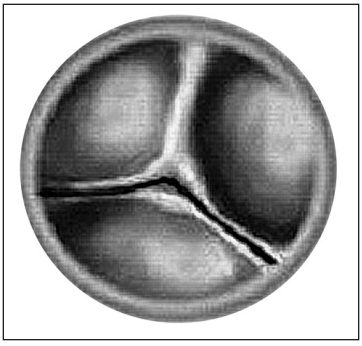
TABLE 1	TABLE 2
Congenital Heart Disease	**Acquired Heart Disease**
• Bicuspid Aortic Valve	• Hypertension
• Aortic Valve Stenosis	• Atherosclerosis
• Coarctation of the Aorta	• Ascending Aortic Dilatation/Dissection
• Hypoplastic Left Heart Syndrome	

What is the Risk?

The risk of congenital heart disease in the general population is approximately 1%. Approximately 35% of girls with TS are born with congenital heart defects.[1-4] Most commonly observed are obstructive lesions of the left side of the heart, including bicuspid aortic valve of 20 to 30% with or without aortic stenosis, and coarctation of the aorta of10 to 15%. If the obstruction is severe in fetal life the left-sided heart structures may not have grown adequately resulting in hypoplastic left heart syndrome. Mitral valve prolapse, atrial septal defects, ventricular septal defects, partial anomalous pulmonary venous connection have also been described. The most common congenital and acquired heart problems in TS will be discussed in this chapter.

Congenital Heart Disease in TS

Bicuspid Aortic Valve



There are often actually three leaflets, but two of the leaflets are fused along the edges, causing the valve to open "functionally" as a bicuspid aortic valve. The relative sizes of the cusps may also vary causing turbulent blood flow across the valve. When the aortic valve does not open freely, the left ventricle must work harder to eject blood into the aorta.

Bicuspid aortic valve occurring in approximately 20 to 30% of girls with TS is also one of the most common congenital heart anomalies in the general population being found in 1 to 2% of all adults. It is a frequent cause of progressive aortic valve narrowing, called stenosis and leakiness (insufficiency) and is often associated with other forms of left heart obstruction. It is also now recognized as causing progressive enlargement of the first part of the aorta, called ascending aorta dilatation, in both adults and children.[5, 6]

Evaluation

If isolated, it is usually discovered during a routine examination when a cardiac murmur (turbulent blood flow crossing the valve) and/or ejection click (additional heart sound as the valve opens) are heard and confirmed by ultrasound of the heart (echocardiography).

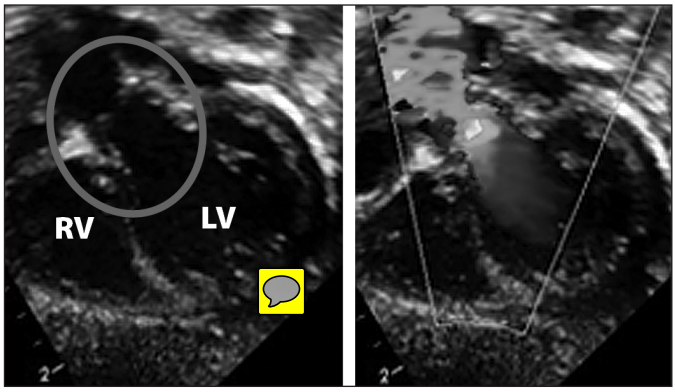
Management

The frequency of need for follow-up is determined by the severity of any associated stenosis or insufficiency. Early recognition and management of any co-existing high blood pressure (hypertension) is essential. Some women and girls will require antibiotics at the time of surgical or dental procedures to lower the risk of bacteria infecting the heart valve. See guidelines for antibiotic prophylaxis in Table 3.

Aortic Valve Stenosis

Aortic stenosis is often associated with a bicuspid aortic valve as in this case (below). In the left panel the left ventricle is mildly thick-

ened and hypertrophied and the aortic valve circled in the middle of the picture is not opening fully. On the colour image on page 63, it can be seen that this is where the narrowing occurs.



The most severe form, critical aortic stenosis, presents in the newborn period and the affected infant develops heart failure in the first days of life. This is an emergency situation that requires immediate medical treatment. Fortunately this can be diagnosed in TS before birth by fetal echocardiography. Severe stenosis in fetal life results in increased left ventricular pressure and muscle thickening (hypertrophy). The resultant oxygen supply and demand mismatch may result in scarring and fibrotic replacement of the muscle. However, in the fetus the right ventricle is capable of handling the entire cardiac output and a special blood vessel (the arterial duct), which is open normally during fetal life, allows the right ventricle to pump blood indirectly into the aorta. Then when baby is born and this arterial duct closes, sometimes up to 8 to 10 days after birth, the left heart function is inadequate to maintain the entire cardiac output and baby presents in circulatory collapse (shock). Initial management of this so called duct-dependent systemic perfusion requires treatment with an intravenous medication, prostaglandin E1, to maintain or re-open the arterial duct and then once baby is stable, a ~~more invasive intervention~~ is undertaken to relieve the obstruction. The prostaglandin E1 given is a synthetic form of the maternal hormone that keeps the arterial duct open in fetal life.

After the neonatal period, severe aortic stenosis in infancy presents as congestive heart failure with increased respiratory effort, poor feeding and failure to thrive. Beyond infancy, most children and

even adults with severe aortic stenosis remain asymptomatic and may only be found incidentally as a cardiac murmur on routine examination. Early fatigability, breathlessness with exercise (exertional dyspnea), chest pain (angina pectoris), and fainting (syncope) are rare and require prompt evaluation and treatment.

> *"I have a heart problem. The valve in my heart doesn't open very well for my blood to go through. In gym, about twice every day, I pretend to go to the bathroom and I take a huge drink of water from the water fountain. When I come back I see all the kids having fun, but I'm working so hard to even run with the kids. Then I go back on the court. When I take huge breaths, my teacher lets me sit down. Even though they can run longer than me, it doesn't affect my life. I could be better than them at dance or piano."*
>
> —Julia, age 8

Evaluation

Echocardiography is used to confirm the diagnosis. The aortic valve may be small, have fewer (2-bicuspid or 1-unicuspid), thickened or fused leaflets or extra fibrous attachments to the aortic wall. Any or all of these elements may combine to narrow the effective opening of the aortic valve and restrict blood flow out of the left ventricle of the heart. The severity of the narrowing determines the pressure gradient across the valve. Pressure gradient estimations are based on Doppler and color imaging. In childhood, the severity of the pressure gradient is used to determine the need for intervention, but in adults valve area calculations are used.

On the electrocardiogram (ECG), a special test done to evaluate the electrical impulses of the heart, left ventricular hypertrophy with a strain pattern may be seen. Twenty-four hour ECG monitoring (Holter), to assess for abnormal ventricular electrical rhythms (arrhythmia), and exercise testing, to demonstrate inadequate blood pressure response to exercise or ECG changes suggestive of inadequate oxygen supply (ischemia), may be useful indicators of the need for intervention in older individuals. Chest X-rays may demonstrate an enlarged heart. In particular, enlargement of the left atrium or congestion of the lungs indicate severe stenosis and left ventricular dysfunction.

Management

In critical aortic stenosis, sometimes the left ventricle is too small or the function deemed too poor and palliative surgery may be the

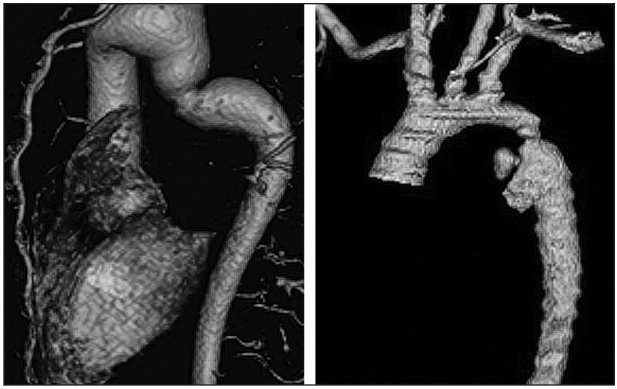
only option. If the left heart structures and function are adequate, cardiac catheterization and balloon dilation of the valve (balloon aortic valvuloplasty) is now the treatment of choice. In this procedure, a thin tube (catheter) with a deflated balloon at the tip is inserted into a blood vessel in the groin and, using a special X-ray machine and video monitor, threaded up through the blood vessels to the heart. Once there, the balloon can be expanded to stretch the valve. Sometimes the process of the balloon dilating and splitting the narrowed leaflets may be complicated by aortic insufficiency which can progress.[7] Similarly, in older individuals balloon dilation is now the usual initial treatment.[8] It can also be repeated if significant stenosis recurs dependent on the degree of aortic insufficiency.

Aortic valve surgery is indicated with recurrent stenosis that has been unresponsive to balloon dilation or with progressive aortic valve insufficiency. Repair may be possible, but often valve replacement may be required. Mechanical valve replacements are more durable in older individuals, but require life long blood thinning medications (anticoagulation). Tissue valve replacements are therefore the treatment of choice, especially in younger individuals to avoid the need for anticoagulation, but have the disadvantage of not lasting as long and needing repeat operations and further replacement.

Congenital aortic stenosis and any associated insufficiency are always progressive and require lifetime monitoring. After balloon aortic dilation, particularly in infancy, frequent monitoring is required in the first few years to assess any recurrent stenosis or associated insufficiency. After valve surgery similarly long-term monitoring is required to assess valve function. See guidelines for antibiotic prophylaxis in Table 3.

Coarctation of the Aorta

Coarctation of the aorta is a narrowing of the upper thoracic aorta (in the chest area) next to the entry point of the arterial duct in fetal life (juxtaductal coarctation). This is seen in the first of these 3D volume-rendered MR images (see next page), but is sometimes also associated with a preceding longer segment narrowing of the transverse aortic arch like in the second image.



Coarctation of the aorta occurs in approximately 10 to 15% of girls with TS. On fetal echocardiography, aortic coarctation may present simply as a smaller left ventricle indicating left heart obstruction. If more severe, a short segment of narrowing of the aorta next to the insertion point of the arterial duct (juxtaductal coarctation) can be seen. Longer segment narrowing in the aorta above this point (transverse arch hypoplasia) can also occur. In the presence of a coarctation, the left ventricle must work harder to generate a higher pressure than normal to force blood through the narrowed segment of the aorta to the lower part of the body. If the severity is not recognized *in utero*, when baby is born, she would appear well and when arterial duct closes, again sometimes up to 8 to 10 days after birth, the cardiac output (blood-flow) to the lower body would be inadequate and baby will present rather rapidly and severely with congestive heart failure, shock and multi-organ system failure, particularly kidney failure or poor blood flow to the gut or other organs of the body. Blood flow to the body is again duct-dependent. This requires treatment with intravenous prostaglandin E1 (PGE-1) to maintain or re-open the arterial duct and once baby is stable early surgery to relieve the obstruction.

In infancy beyond the neonatal period and in older individuals, coarctation of the aorta usually presents as a cardiac murmur, diminished lower limb pulses or high blood pressure in the arms and lower blood pressure in the legs. Delayed diagnosis is common because most children and even adults are asymptomatic, because the narrowing is generally less severe or has progressed more slowly and the left ventricle has had time to thicken (hypertrophy) to pump

against the narrowing of the aorta. Older individuals sometimes complain of leg muscle cramps with exercise (claudication) due to inadequate lower body perfusion and frequent headaches due to upper body hypertension.

Evaluation

Echocardiography is used to confirm the diagnosis and determine whether there is short or longer segment coarctation. The status of the arterial duct in infancy and the presence of any prominent arteries bypassing the obstruction (collaterals) in older individuals and the heart function also need to be assessed. Doppler and color imaging is used to estimate the pressure gradient. The severity of the pressure gradient determines the need, timing and type of treatment.

On examination in infancy, the classic features are diminished lower limb (leg) pulses and differences between arm and leg blood pressure measurements indicating the degree of obstruction. Older individuals will also have delayed lower limb pulses, high blood pressure (hypertension) in the upper body and blood flow through collateral vessels may be heard as continuous flow murmurs in the chest especially at the back. The ECG in infancy is often normal, but an older individual with long-standing hypertension may demonstrate left ventricular hypertrophy. A chest X-ray may demonstrate an enlarged heart and congestion of the lungs in an infant, but in an older individual it may be normal or demonstrate a classic "3 sign" with an indentation of the aorta at the site of coarctation and then a prominent descending aorta due to so-called post-stenotic dilation. With chronic obstruction, collateral arteries may also develop to help deliver indirect blood-flow to the descending aorta by bypassing the obstructions or area of narrowing. Over time as these arteries become more evident and enlarge, they may ultimately erode the undersurface of the ribs producing the classic sign of "rib notching" on chest X-ray. Magnetic resonance imaging (MRI) and computed tomography (CT) scans are now used for planning interventions in more complex cases in older individuals.

Management

The initial goals of management in the newborn period are to improve ventricular function, restore blood flow to the lower body. Newborns presenting with coarctation can be stabilized with med-

ical therapy, but then usually need surgical repair.[12] If the coarctation is over a short segment, surgery is performed through a lateral chest incision (thoracotomy) and involves resection (removal) of the narrowed segment and then the aorta is sewn back together. For this operation, surgical mortality and complication rates are very low (less than 1%) and the need for retreatment is in the range of 2 to 5%. For more complex coarctation, with underdevelopment of the arch of the aorta or additional heart defects, surgery is more extensive and performed through an incision in the front of the chest. The surgical risks are higher according to the complexity of the associated lesions and the need for retreatment in more extended repairs is in the range of 10 to 15%. Surgical risks particular to coarctation repair include interrupting the blood supply (with clamps that are placed on the aorta briefly interrupting the blood flow to downstream areas) to the kidneys or spinal cord with lower body paralysis, damaging the nerve supply to and also causing paralysis of the diaphragm muscles with respiratory complications and a period of post-operative rebound hypertension sometimes worse than preoperative levels.

In older infants and beyond, balloon dilation of a coarctation can be performed (balloon angioplasty).[13, 14] The balloon expands the narrowed portion of the coarctation by splitting the inner lining and producing linear tears in the wall of the aorta. Residual gradients in up to 25% or recurrent coarctation can occur even after apparently successful angioplasty, and probably more so in infants younger than 1 year of age, but usually respond to repeat balloon angioplasty. Aneurysm formation is less common, occurring in 5 to 10% of cases. An aneurysm is a localized balloon-like bulge of a blood vessel caused by weakening of the vessel wall. If this occurs further treatment with placement of a stent or surgery is needed (see below). A stent is a small mesh tube inserted into the vessel to stabilize the wall and keep the vessel open. Death from coarctation surgery is very rare. In infants younger than 12 months, there is the risk of femoral artery injury, and rarely of stroke. Balloon angioplasty can also be performed for recurrent postoperative coarctation.[15] Complication rates and possibility of repeat treatment being required are also similar. Balloon-expandable stents can also be used in older individuals to support the dilated aortic segment after the balloon angioplasty and decrease rates of residual gradients and recurrent coarctation.[16]

After successful management of coarctation the short- and intermediate-term prognosis is excellent, but regular monitoring is required to detect any residual or recurrent coarctation. Milder associated transverse arch hypoplasia has the potential to remodel and for normal growth. Long-term prognosis following coarctation repair may be affected by increased risk of hypertension and early onset atherosclerosis (see below). See guidelines for antibiotic prophylaxis in Table 3.

Hypoplastic Left Heart Syndrome

Hypoplastic left heart syndrome (HLHS) is a rare, but known association with TS. HLHS represents one of the most complex heart defects seen in the newborn and remains perhaps the most challenging to manage of all the congenital heart defects. In a child with HLHS, all of the structures on the right side of the heart are usually normally developed however the structures left side of the heart are severely underdeveloped resulting in a situation where the left side of the heart is completely unable to support the circulation needed by the body's organs. HLHS is fatal without treatment, often within hours to days of life. Infants with HLHS require many operations and spend long periods in hospital and intensive care situations[17] and have long-term outcomes of between 50 to 70% survival at 10 years. This heart defect is readily diagnosed with a fetal ultrasound. Early diagnosis of this defect allows for prompt intervention and stabilization at the time of birth and requires an infant being delivered at a hospital capable of aggressive newborn resuscitation in order to improve outcome. Termination of the pregnancy or compassionate palliative care following delivery are management options offered to families when HLHS has been diagnosed. Palliative surgery involves 3 major operations, as a newborn, at 6 months and at 2 to 4 years to convert the heart, major arteries and veins into a circulation supported by the single right ventricle pump.

Acquired Heart Disease in Turner Syndrome

Hypertension

High blood pressure (hypertension) is thought to be present in around 25% of girls and 50% of adults with TS.[20, 21] Although occurring often with coarctation of the aorta, kidney development defect or abnormal cholesterol and blood sugar metabolism such as dia-

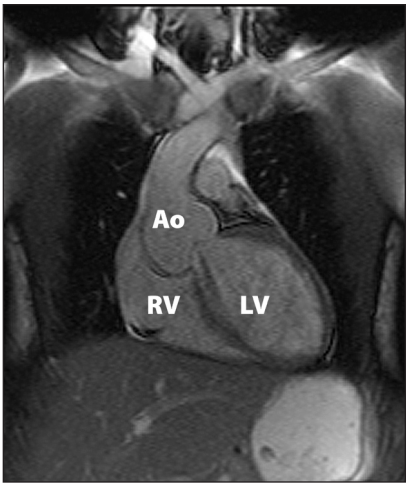
betes, it also appears that hypertension can occur in TS in the absence of these conditions and that there may be something specific to TS which further increases this risk. Hypertension is a known risk factor for atherosclerosis (hardening of the arteries) and ascending aortic dilation and dissection (see below) so blood pressure should be monitored frequently and aggressively managed.[22,23]

Atherosclerosis

The risk of early atherosclerosis, coronary artery disease leading to heart attacks and cerebral vascular disease leading to strokes, also appears to be increased in TS.[21] However, it remains unclear whether this is due to the known increased prevalence of cardiovascular risk factors in TS that are also common to the general population (obesity, insulin resistance, diabetes, lipid abnormalities and hypertension) or again whether there is something specific to TS which is contributing.[1] Recent studies do suggest that the larger arterial walls are structurally and functionally abnormal in TS.[24,25] Avoidance of smoking, a heart-healthy diet, regular exercise and frequent monitoring and aggressive management of obesity, lipid and metabolic abnormalities and hypertension are essential.

Ascending Aorta Dilatation and Dissection

Ascending aorta dilatation in TS usually involves the initial portion of the aorta (aortic root) and particularly the tubular portion (ascending aorta). With significant dilatation, a tear or dissection in the internal lining of the aortic wall can occur creating a false space in the aortic wall. The dissection can also extend back into the coronary arteries causing a heart attack or forward into the carotid arteries causing a stroke.



Ascending aortic dilatation originally thought to occur in approximately 10 % of older patients with TS, may be more frequent. Most patients with moderate aortic dilatation will remain asymptomatic and only be detected on routine screening. In an individual with known

significant aortic dilatation, symptoms of severe chest pain radiating through to the back constitutes a medical emergency and requires urgent evaluation and a CT of the chest to exclude aortic dissection. Medical alert identification should be strongly considered for any individual with TS with known aortic dilatation or dissection risk.

Ascending aortic dilatation and dissection in TS is almost always associated with a risk factor such as bicuspid aortic valve, coarctation of the aorta or hypertension or a combination of these findings, and the few individuals without an underlying cause may reflect inadequate examination.[2,23,26-28] Additionally there may be something intrinsic to the aortic wall in TS, as structural and functional abnormalities have been demonstrated to occur in the larger arteries.[24,25]

Evaluation

Echocardiography is used for routine surveillance of the aortic root. MRI is particularly used for older individuals with difficult Echo images or serial imaging of patients with known significant aortic root dilatation, more distal aortic involvement or post-surgery. Aortic diameters ~~can~~ be compared to body size and compared with age-matched control data for both Echo and MRI.[29] A recent prospective study demonstrated performing MRI doubles the rate of echo detection for ascending aortic dilatation (33% versus 16%).[29]

Management

With significant ascending aortic enlargement, more frequent serial imaging is indicated and medical therapy recommended. Aggressive control of blood pressure should aim for low-normal values. Experience from treating Marfan syndrome, a connective tissue disorder also prone to aortic root dilation and dissection, suggests beta-blockers can be used to slow aortic root growth. However, their benefit in treating ascending aortic dilatation in TS has not yet been investigated. Similarly indications for surgical intervention in the Marfan syndrome experience, would suggest aortic root replacement at a dimension approaching 50 mm, but may be indicated at lesser dimensions in TS. Fatal aortic dissection has been described in pregnancy, so any woman with TS planning to get pregnant, should have a cardiology evaluation with MRI of the aorta before pregnancy, and close cardiology follow-up throughout the pregnancy.[30] See guidelines for antibiotic prophylaxis in Table 3.

TABLE 3

Cardiovascular Screening and Follow-Up Recommendations for Children, Adolescents and Adults with Turner Syndrome

	Children & Adolescents	Adults
Screening at Diagnosis	Clinical assessment by a Paediatric Cardiologist Blood pressure all 4 limbs ECG - rhythm, timing intervals and voltage assessment Baseline Echo	Clinical assessment by an Adult Congenital Cardiologist Blood pressure all 4 limbs ECG - rhythm, timing intervals and voltage assessment Baseline Echo and MRI if indicated
Normal Heart and Aorta and Blood Pressure Follow-Up Every 5 to 10 Years	Clinical assessment by a Paediatric Cardiologist with expertise in TS Blood pressure all 4 limbs ECG Echo and MRI if indicated	Clinical Assessment by an Adult Congenital Cardiologist with expertise in TS Blood pressure all 4 limbs ECG Echo and MRI if indicated
Abnormal Heart or Dilated Aorta or Hypertension Follow-Up Every 1 to 2 Years	Clinical assessment by a Paediatric Cardiologist with expertise in TS Blood pressure all 4 limbs ECG & Echo 1 to 2 yearly MRI if indicated 1 to 3 yearly Consideration of beta-blockers for aortic root prophylaxis ± other antihypertensives	Clinical assessment by an Adult Congenital Cardiologist with expertise in TS Blood pressure all 4 limbs ECG and Echo 1 to 2 yearly MRI if indicated 1 to 3 yearly Consideration of beta-blockers for aortic root prophylaxis ± other antihypertensives
Special Considerations	Exercise and activity restriction with significant aortic root dilatation: avoid heavy isometric exercise (resistance training), competitive contact sports and activities involving sudden deceleration Antibiotic prophylaxis to prevent infective endocarditis for invasive dental or other minor procedures: only required for a prosthetic cardiac valve, previous endocarditis, repaired congenital heart defect within 6 months of placement of prosthetic material or after 6 months if a residual lesion persists adjacent to prosthetic material [31] Pregnancy: avoid unplanned pregnancy and plan cardiology review pre-conception and need regular cardiology follow-up during pregnancy Medical alert identification of aortic disease or dissection risk	

Key Points

- Congenital heart defects occur in approximately 35% of girls with TS and are mainly various forms of left heart obstruction.
- Bicuspid aortic valve with or without aortic stenosis (narrowing) occurring in approximately 20 to 30% of girls with TS is the most

commonly associated congenital heart defect and requires lifelong monitoring.

- Aortic stenosis, if severe, may need balloon valvuloplasty in the newborn. It often requires subsequent interventions and if associated with significant aortic insufficiency (leakiness), may need surgical repair or replacement.
- Coarctation of the aorta occurs in approximately 10 to 15% of girls with TS. It can be short segment narrowing or a longer segment narrowing (hypoplastic transverse arch) and if severe requires surgical repair in the newborn period. Otherwise it may be amenable to balloon angioplasty in older infants as a first intervention or as a follow-up intervention to surgery plus or minus stent placement.
- Hypoplastic left heart syndrome (HLHS) is a rare, but known association with TS. It represents the most severe end of the spectrum of left heart obstruction often at multiple levels.
- Hypertension occurs in approximately 25% of girls and 50% of adults with TS. It is often associated with coarctation of the aorta, kidney anomalies as well as abnormal lipid and glucose metabolism, but may also occur in isolation.
- Early atherosclerosis (coronary artery disease leading to heart attacks and cerebral vascular disease leading to strokes) appears to be increased in TS, mainly due to all of the associated cardiovascular risk factors that are prevalent in TS like obesity, insulin resistance, diabetes, lipid abnormalities and hypertension.
- Ascending aorta dilatation and dissection are strongly associated with bicuspid aortic valve, coarctation of the aorta and hypertension or a combination of these and so more frequent serial imaging is indicated when these conditions are present, particularly if pregnancy is being considered.
- Healthy-heart lifestyle modification, diet and exercise are essential for maintaining long-term cardiovascular health.
- Appropriate follow-up of congenital heart defects and frequent monitoring and aggressive management of diabetes, lipid abnormalities and hypertension in TS are essential to prevent complications.

Additional Resources on Cardiovascular Health

1. **The Turner Syndrome Society of Canada**
   21 Blackthorn Avenue, Toronto, ON M6N 3H4, Canada;
   Tel: 800-465-3744 or 416-781-2086 Fax: 416-781-7245;
   or see *http://www.TurnerSyndrome.ca*.

2. ~~**SickKids Website**~~
   This site has user-friendly diagrams and a description of how the heart works.
   http://www.sickkids.ca/childphysiology

3. ~~**PediHeart**~~
   ~~This is an excellent site for parents and children. It offers information about the heart as well as heart defects. It provides links and allows you to ask questions.~~
   ~~*http://www.pediheart.org*~~

4. **International Society of Adult Congenital Cardiac Disease: Especially for Patients**
   The ISACC is an organization for heath care providers of adults with congenital heart conditions. ~~This link is for their "Especially for Patients" site, which~~ has an excellent FAQ section, and other useful resources for adult patients living with congenital heart disease.
   ~~*http://www.isaccd.org/patients/index.php*~~

5. **Heart and Stroke Foundation of Canada**
   The Heart and Stroke Foundation provides information for children and adults about healthy living and avoidance of risk factors for heart attacks and stroke in Canada.
   http://www.heartandstroke.ca

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Chapter 4

Blood, Sweat and Tears: Puberty Initiation and Hormone Treatment

Bojana Babic, MD, FRCPC and Sari Kives, MD, FRCSC

One of the main features of Turner Syndrome (TS) is ovarian failure due to the lack of estrogen. The remaining external and internal genital structures such as the uterus, fallopian tubes and vagina, are normally formed, but do not grow to adult size without adequate estrogen exposure. As a result, many girls with TS do not enter or progress through puberty independently. Estrogen therapy is often initiated to allow puberty to occur and it is continued until menopause. This chapter will review estrogen use in girls and women with TS, including the benefits and possible side effects of estrogen therapy.

What is puberty?

Puberty is defined as the period of time during which sexual development occurs and a girl's body matures into a body of a young woman. Puberty follows a fairly consistent sequence in girls. Health care providers stage the physical changes of puberty on a scale of 1 to 5, called Tanner staging. Young girls who do not show any physical changes of puberty are at Tanner stage 1, while adult women who have completed puberty are at Tanner stage 5. For girls, Tanner staging is done to assess both breast and pubic hair changes –see Figures 1 and 2.

The first visible change is usually the development of breast buds, known as thelarche. This usually occurs between ages of 8 to 13 years and it marks the transition to Tanner stage 2. At the beginning of puberty, hormones in the brain called gonadotropins send signals to ovaries to start making estrogen – see Figure 3. Under the influence of estrogen, breasts start to grow. In addition, estrogen promotes growth of the uterus, the uterine lining, called the endometrium, and vagina.

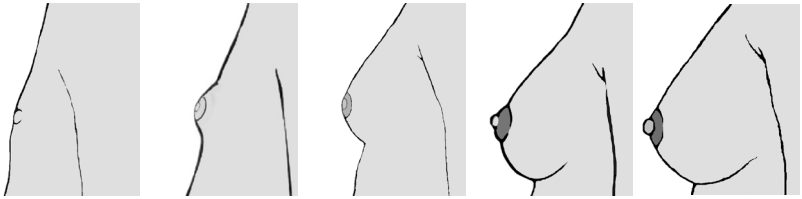

Figure 1. Tanner staging for breast growth, stages 1 to 5

Soon after breast budding starts, most girls develop coarse and dark pubic hair, as well as some hair under the arms. In addition, body odour starts to develop and acne, sometimes called pimples, may start to show. These changes of puberty are not controlled by estrogen. Instead, these changes are controlled by hormones called androgens. Androgens are made from two sources: the ovaries and the adrenal glands which are two small glands sitting above our kidneys. Androgen secretion from the adrenal glands is called adrenarche, and is normal in girls with TS.

Figure 2. Tanner staging for pubic hair growth, stages 1 to 5

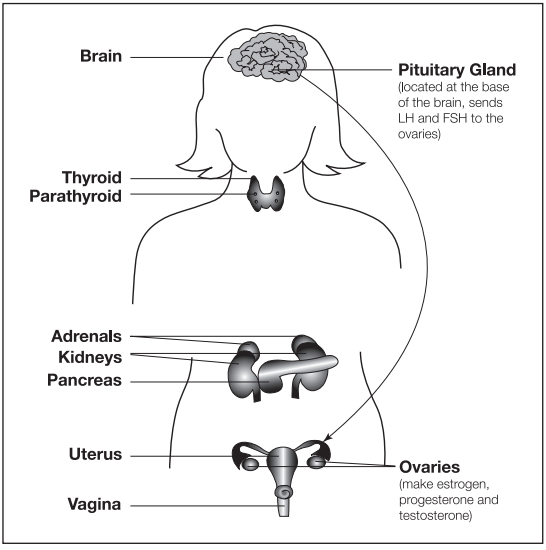

Figure 3. Hormones involved in regulation of puberty

The onset of menstrual cycles, known as menarche, usually begins about ~~2 to 2~~ and a half years after the onset of breast development. This occurs when the uterine lining has matured enough under the influence of estrogen. The average age of onset of menses in North America is around 12.6 years. Once the menses start, a young woman continues to produce adult levels of estrogen until she enters menopause. We will talk more about the benefits of estrogen during a woman's life later on in this chapter.

Most girls have their growth spurt in the year preceding the onset of menses. By the time they start menstruating, they have reached close to their final adult height. Most girls stop having bone growth within 18 to 24 months after the onset of menses.

What happens in puberty in girls with Turner Syndrome?

Ovarian development and function are regulated by genes on the X-chromosome. In a normal ovary, there are many immature eggs that are lost slowly over a woman's life span. This loss starts even before a baby girl is born, and it continues slowly over 30 to 50 years of life. When all the eggs are lost, a woman will enter menopause. This process of egg loss, which happens in all women, is accelerated in girls with TS. The abnormal X-chromosome in girls with TS affects the development and function of their ovaries. In a majority of girls, most of the eggs will be lost within a few years of birth. Your doctor may call this ovarian failure. This is the main reason why most girls with TS do not make sufficient estrogen to initiate breast development and progress through puberty.

However, there is a lot of individual variation in the rate of the loss of eggs. Studies in girls with TS showed that some degree of ovarian function persists in a significant number of girls. In as many as 20% of girls, the degree of estrogen secretion is sufficient to initiate breast development. This spontaneous onset of puberty in TS has been described in a variety of karyotypes. It is most common in girls with mosaic karyotype and it is rare in those who have 45,X karyotype. Some girls will continue to progress through the Tanner stages of puberty, with ongoing breast growth and eventual menses. A large Italian multi-centre study found menses occurring spontaneously at an average age of 13.2 years in approximately 16% of girls with TS. For a small percentage of these girls, menstruation will continue for many months and even years, but will end prematurely.

Most of these girls have mosaic karyotype. However, the majority of girls with TS do not enter into spontaneous puberty and will need estrogen therapy.

The function of the adrenal glands is not affected in TS. Therefore, girls with TS may have spontaneous development of pubic hair and hair under the arms, as well as body odour, as these changes are regulated by androgen hormones from the adrenal glands. However, because of the absence of ovarian androgen production, pubic and axillary hair may be somewhat sparse.

> *"I guess the feelings you would have when everybody else is growing up ahead of you, you're shy and awkward and left out of it. As a teenager, more comes into play, I wonder how come I'm not growing up as fast as the other kids. The other girls are interested in boys, you know, and will boys like me? Will they ask me out to the dance?"*
>
> *—Christine, age 44, speaking of the time before she learned she had TS. (Kagan-Krieger S, p.94) **

Why is it important to go through puberty and have adequate levels of estrogen throughout woman's adult life?

In addition to stimulating breast, uterine and vaginal growth during puberty, estrogen is extremely important for a variety of other organs in all women. Estrogen helps build stronger bones, thus minimizing the risk of osteoporosis and fractures later in life. Estrogen also improves fat and cholesterol metabolism. A lack of estrogen probably leads to an increased risk of earlier heart disease in women. Estrogen is also important for sexual functioning, as lack of estrogen can cause dryness and irritation of vagina. In addition, estrogen helps with our memory, it improves skin elasticity and reduces the risk of colon cancer.

There have been several studies demonstrating benefits of estrogen therapy specifically in girls and women with TS. Similar to the effects in the general population, estrogen promotes growth of breasts and uterus, as well as bone strength in girls with TS. In addition, estrogen may improve verbal and nonverbal memory, as well as nonverbal processing speed in these girls. In one study, adolescent girls with TS who were treated with estrogen were found to have an improved self-esteem. Estrogen has been found to contribute positively to the quality of life of young women with TS because it allows them to undergo physical changes during puberty similar to those of their peers.

Estrogen Treatment in Turner Syndrome

When should estrogen treatment be started?

Your ~~doctor~~ will be monitoring you for the onset of spontaneous puberty by Tanner staging and by blood tests including the level of follicle stimulating hormone (FSH). FSH is produced in the pituitary gland in the brain and normally signals the ovary to make estrogen. An elevated level of FSH confirms ovarian failure and it informs d~~octor~~s that puberty will not start or progress spontaneously. If there is no evidence of spontaneous puberty by age 12 or 13 and FSH is elevated in the blood, estrogen therapy should be initiated. It is generally not recommended to delay estrogen initiation beyond 15 years of age. The exact timing will depend on several factors, including the bone age and the timing of growth hormone initiation. Earlier and continued use of growth hormone allows for earlier initiation of estrogen. Bone age is assessed by an X-ray of the left wrist. This test tells doctors about the maturity of bones and growth potential. Usually, doctors will consider starting estrogen therapy once the bone age is around 11 years. Your doctor and you will discuss the optimal time for starting estrogen therapy.

> *"I remember, after my diagnosis at age 13, waiting for a couple of years to begin hormone replacement until after my bones had fused, to give me the maximum chance to continue growing. My mother was more concerned about this delay than I was, and had me fitted with a slightly padded trainer bra. I was a little embarrassed, but did realize that my friends had started to develop by then. I just felt my turn would come."*
>
> —Mary

What are the side effects of estrogen therapy?

It is important to remember that the goal of estrogen therapy in TS is to replace estrogen at physiologic levels that the ovaries should normally be producing. At these physiologic doses, side effects are uncommon and nearly always harmless. They may include irregular bleeding, fluid retention, and nausea. Oral estrogens may also affect the function of growth hormone (GH), thus decreasing some of the benefit of the growth hormone therapy. This alteration in GH function probably happens in the liver where both estrogen and growth hormone are metabolized. The good news is that newer forms of estrogen therapy do not have this negative effect on growth hormone. We will discuss these in the next section.

Methods of Giving Estrogen

When estrogen therapy is needed to induce puberty, the form, dose and timing of estrogen should reflect the process of normal puberty. There are many available forms of estrogen and your doctor will help you choose the best option for you – see Table 1. Oral estrogens in the form of pills have been most often used in the past. However, both estrogen patches, which are absorbed through the skin, and intramuscular estrogen injections have been studied and used more recently in research protocols. Transdermal patches and intramuscular injections may provide more physiologic forms of estrogen therapy, as they are absorbed directly into the blood stream without being altered in the digestive tract. One main benefit of these newer forms of estrogen therapy is that they may ultimately improve final height outcome with growth hormone therapy.

Initially, a very low dose of estrogen is given, with gradually increasing doses over the next 2 to 4 years. This gradual increase in the dose will allow for appropriate growth of breasts and uterus. It is generally advised that to allow for normal uterine and breast development, the addition of progesterone should be delayed until approximately 2 years after starting estrogen or until breakthrough bleeding occurs. It is for this reason that oral contraceptives are not used to achieve pubertal development. This breakthrough bleeding signals that the uterine lining has matured under the influence of estrogen and is starting to shed. Progesterone will enhance shedding and enable menses to occur at a regular interval. Progesterone also protects the endometrium from hyperplasia, an overgrowth under the influence of estrogen. Progesterone and estrogen are involved together in controlling the normal menstrual cycle. Your ~~doctor~~ will add progesterone for the first 10 to 14 days of the menstrual cycle, mimicking the normal menstrual cycle. Another way of administering estrogen and progestin is in the form of a variety of birth control pills. Your ~~doctor~~ and you will discuss the best way for you – see Table 1.

Estrogen and progesterone treatment should be continued at least until women are in their fifties, which is the usual age of menopause. If estrogen is stopped prior to this time, the risk of osteoporosis and spontaneous fractures is high in women with TS. The use of estrogen hormone after the age of menopause is currently controversial. We advise you to discuss with your doctor the possible benefits and risks of using estrogen after the age of 50 years.

"Taking my pills has been a fact of life, and I have felt like a fairly normal, though somewhat short, woman. Now in my 50s, I am at the stage of starting to reduce the dosage of estrogen, and I was surprised at my emotional reaction to this phase. This is a change mimicking normal menopause, and I associated it with aging and with giving up something I felt had always let me 'fit in'. I'm not going to miss the routine of having a period but it is a change in my life that has caught me a bit by surprise – perhaps that's the same for every woman at this age."

—Mary

Table 1. Available Forms of Hormone Replacement Therapy

1. Oral Estrogen

Brand Name	Active Ingredient	Initial Dosage
Estrace	Micronized estradiol	0.5 mg
Ogen	Estropipate	0.3 mg
Premarin	Conjugated equine estrogen	0.3 mg
C.E.S.	Conjugated estrogen	0.5 mg

2. Transdermal Estrogen Patch

Brand Name	Active Ingredient	Initial Dosage
Estradot	Estradiol	25 µg patch twice per week

3. Oral Progesterone

Brand Name	Active Ingredient	Dosage
Provera	Medroxyprogesterone acetate	5 mg day 1-14 of cycle or 2.5 mg daily
Prometrium	Micronized progesterone	200 mg day 1-14 of cycle or 100 mg daily

4. Oral Combined Hormone Therapy

A variety of oral contraceptive pills with both estrogen and progesterone	Available for use after puberty initiation

Key Points

- Many girls with TS have ovarian failure and do not enter or progress through spontaneous puberty.
- Girls with mosaic karyotype are more likely to develop puberty and to menstruate spontaneously.

- Estrogen therapy should be initiated if no spontaneous puberty occurs by the age of 12 or 13, and if the blood test confirms ovarian failure. The optimal time of estrogen initiation depends on a variety of factors that your doctor will discuss with you.
- Estrogen has many confirmed benefits in girls with TS.
- There is a variety of ways of administering estrogen. Your doctor will discuss the best form of estrogen therapy for you.

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* Susan Kagan-Krieger, "The struggle to understand oneself as a woman: Stress, coping and the psychological development of women with Turner Syndrome" (EdD dissertation, University of Toronto, 1998).

Chapter 5

You've Got That Loving Feeling: Sexuality

Part I: Adolescent Sexuality

Cathleen M. Steinegger, MD, FRCPC and Debra K. Katzman, MD, FRCPC

The developmental tasks of adolescence evolve gradually as part of a continuum of physical, cognitive, social and emotional changes that extend from childhood through to adulthood. The initiation and completion of these tasks vary widely among individuals. What it means to achieve a given developmental task will depend on an individual's culture, health, family and personal values and abilities. Although the developmental tasks facing adolescents are challenging, the majority of teenagers navigate them successfully. The developmental tasks of adolescence include:[1]

- **Identity development:** discovering and understanding oneself as an individual.
- **Attaining independence:** becoming a self-governing individual in both their own and others eyes by becoming less dependent on their parents.
- **Intimacy:** forming close and caring relationships with other people.
- **Achievement:** being a successful and competent member of society.
- **Sexuality:** refers to the evolution of sexual feelings, behaviours, fantasies, body image, self-esteem, personality, affiliations, sexual orientation, gender identity, relationships, values and attitudes.

Artist: Brooke, age 14. Self-portrait

Sexuality and the Adolescent

Sexuality is a natural, healthy part of life and one of the most fundamental aspects of who we are as human beings. Sexuality is influenced by a young girl's culture, ethnicity, socioeconomic status, religion, hormonal and physical changes. Sexual development is closely connected to the tasks of adolescent development. The onset of pubertal development marks the onset of significant changes in the experience of sexuality. Adolescent sexual development is divided into three stages: [2]

1. Early adolescence, from approximately 10 to 13 years old, is characterized by the onset of pubertal development. The onset of puberty causes the adolescent girl to look and feel different and prompts society to respond to her in a different way. Many young girls will have the onset of their menstrual period, known as menarche, signifying reproductive capacity. This is a time when young girls show concern and curiosity about their changing body. They have sexual thoughts and attractions. This is also a time when there is an increase in self-exploration including masturbation, a normal sexual behaviour. Some teens may also experiment with sexual experiences that are most often non-physical, including those with members of the same sex.
2. Middle adolescence occurs at approximately 14 to 16 years old and is characterized by pubertal changes that are almost complete. Girls establish longer-term relationships and begin to understand that intimacy involves more than sexual activity. However, many adolescents do not fully appreciate the adverse consequences of sexual behaviour. Dating and non-coital sexual activities are common. This is a time when sexual experimentation, including those with members of the same sex occurs.
3. Late adolescence, is from approximately 17 to 19 years old, and is characterized by the completion of pubertal development. Sexual behaviours become more expressive. This is a time when young woman develop intimate relationships with greater commitment and mutuality. Young women begin to consider the qualities, sexual and otherwise, that would be desirable in a potential spouse or life-partner.

Sexuality and the Adolescent with Turner Syndrome

Part of growing up is having sexual feelings and attractions. These feelings and thoughts can sometimes be intense, confusing and disturbing. As such, most adolescent girls have many questions about their sexual thoughts, feelings and concerns. They are trying to figure out who they are and who they're becoming, if they are growing and developing like their peers, and whether their sexual thoughts and feelings are "normal". Young women with TS are likely to have the same concerns, perhaps with additional worries about how the TS will affect their ability to function as sexual human beings. Adolescent data on sexuality is readily available. However, there is very little information on sexual behaviour and sexuality in young women with TS.

Individuals with TS are known to have their first sexual experience later, to be less likely to establish a steady relationship with a partner, and to be less sexually active than women from the general population.[3-5] One study reported that 30% of women with TS had sexual intercourse by the age of 20 years compared to 85% of the general population at the same age.[4] The reasons for this delay are probably the result of a number of factors including the underlying genetic or hormonal influences on behaviour compounded by the short stature, infertility, and possible physical differences associated with TS. Later age at pubertal development is associated with older age at first kiss, older age at first date and older age at first sexual intercourse.[4] Social relationships can be a challenge for girls with TS[6] and this may have an impact on the timing of dating and sexual behaviours. Health concerns, whether from TS or another condition, can delay sexuality by keeping an adolescent out of developmentally appropriate social activities, delaying physical development, making the adolescent self-conscious about their body, or causing overprotectiveness by caregivers. For instance, girls with TS and cardiac involvement begin dating much later. In addition, researchers observed an association between low self-esteem, hearing problems and limited sexual experience.[4]

Although 90% of girls with TS have ovarian failure, spontaneous puberty occurs in up to 30% of girls with TS,[7,8] and 2 to 5% of women become pregnant spontaneously.[9] Sexually active young girls with TS should discuss contraceptive needs with their physician. All teens should receive counselling regarding safe sexual practices and the prevention of sexually transmitted infections.

Some girls with TS may struggle with issues of poor self-image. This may in part be related to the associated short stature and delay in sexual maturation. Research has shown that puberty should be induced at a physiologically appropriate age in girls with TS to optimize psychosocial well-being, self-esteem and normal development of sexuality.[4]

> *"During my life I have never been one of the 'popular' girls. I don't dwell on it because I love my small group of friends. I had a boyfriend in grade 8, and even though I don't now, I remind myself that I want a quality guy and not just any old loser. I am even glad to be 'unpopular' sometimes because it means I get invited to less crazy parties and have less chance of doing something stupid that I will later regret."*
>
> —Larissa, age 15

Girls with TS are born with female external genitalia. However, most individuals with a single X-chromosome (45,X karyotype) do not develop normal functioning ovaries. Although gender identity is usually female, individuals with an 45,X karyotype may experience psychological stress because of their infertility, their appearance, and, in some, the awareness of their genetic profile, which may make them feel inadequate or incomplete as females. This, in turn, may cause some young people to question their gender role.[10] The adolescent with TS may need reassurance that she can expect to have healthy, normal relationships. How she chooses to express her sexuality has more to do with who she is as an individual than the fact that she has TS. The opportunity to speak with women who have TS that have successfully navigated adolescence and relationships may be reassuring.

Him

He was a normal boy
When he moved in seventh grade.
He started at his new school
With no fears in his mind.

His optimism was no short of wrong,
For when he met his peers,
They were the opposite of him.
He sure did not fit in.

In a world where guys
Like hockey and skateboarding
He liked Harry Potter books
And flirting with the chics.

They taunted his accent,
Though I thought it was cute.
They mercilessly insulted
And branded him a loser.

He asked my friend to dance,
She instantly said no,
He hung out with my friends,
But received bruises on his shins.

So when the next year came,
And we really got along,
We bonded instantly.
My friends knew it all along.

For in the beginning of December
He asked me out on a date.
I was simply sent to heaven
In that dark theatre with him.

I thought everything was perfect,
On our first and second date.
His crazy side was revealed
And I could not help but embrace it.

We both love Harry Potter,
And our conversations were so deep.
He told me I was beautiful,
I was living in a dream.

So when he took me out,
On Valentine's Day night
With my hair straightened
He made me feel so perfect.

He played gently with my hair,
And further caressed me with a kiss.
The movie was terrific,
/It was Pink Panther that we saw/

But what made the night so special,
Was that I was with him.

—Larissa, age 13

Talking to Adolescents About Sexuality

Almost all teens have questions about physical maturation and sexual health. Parents, physicians, and the adolescents themselves are often uncomfortable and unskilled in discussing sexuality. Here are a few tips to help you get started.

Admit Your Discomfort

Adolescents will sense your discomfort and may incorrectly interpret it to mean you are discussing an embarrassing or shameful topic. Being honest about your own feelings will help build trust.

Practice

If discussing sexuality makes you uncomfortable, practice with a friend, partner, or in front of a mirror.

Minimize Joking

Although often used to ease tension, beware of using jokes to avoid a serious discussion.

Know Your Resources, Know Your Facts

There are many excellent books and websites about teen sexuality. Your family physician, pediatrician or TS health care providers will also be able to help. Websites for adolescents and parents include *http://www.chebucto.ns.ca/Health/TeenHealth* and *http://www.goaskalice.columbia.edu* for general information on adolescent sexuality, and *http://www.turner-syndrome-us.org* and *http://www.turnersyndrome.ca* for information specific to TS. In many communities, resources such as youth groups composed of teens who are facing similar issues can provide opportunities for people to talk to others who understand.

Confidentiality

Part of adolescent maturation is developing an individual identity where everything is no longer shared with family. Respecting confidentiality and privacy will help build rapport and encourage teens to talk about the difficult feelings that go with their developing sexuality.

Respect

Respect the cultural values and beliefs of the adolescent and her family.

Promoting Healthy Psychosexual Development in Adolescents

Educate About Sexual Health

Sexual health education should begin in childhood, regardless of the developmental stage or limitations. Keep in mind that girls with TS may mature more slowly than their peers, and therefore developmentally appropriate sex education should be provided. Young people should be asked about or given an opportunity to discuss issues related to sexual feelings and behaviours well before they initiate sexual activity. All adolescents should be taught the basics about reproductive health, avoiding an unintended pregnancy with effective contraception or abstinence, and the prevention of sexually transmitted infections. In addition to these issues, girls with TS may need to talk about issues that are specifically relevant to their situation including infertility, body image and gender identity.

Promote Healthy and Safe Relationships

Adolescents should be counselled that healthy sexual relationships should be both honest and pleasurable. All young women should be comfortable saying "no" to sexual activity until they feel physically, emotionally and cognitively mature to enter into relationships that are consensual and non-exploitative.

Promote a Healthy Body Image

Most adolescent girls struggle with their body image. For those with TS, this may be compounded by physical differences including short stature and delayed pubertal development. These physical differences may cause a girl with TS to be more self-conscious in relation to beginning a sexual relationship.

Teach adolescents to be savvy about the media's influence on standards of beauty. Avoid negative talk about bodies – including your own – if they don't conform to these impossible beauty ideals. Websites like *http://www.bodypositive.com* and *http://www.bodyimagehealth.org* promote body satisfaction for every shape and size.

Foster Social Skills

Social skills are difficult to teach directly. However, you can lead by example in social situations. Help adolescents find opportunities to interact with peers through group activities, special interest classes such as sports, music or art, and community events.

Offer Confidential, Accessible and Affordable Sexual Health Services for Teenagers

All adolescents deserve services that offer healthy sexual development.

Help to Plan for the Future

Carefully plan for the transition from the pediatric to adult health care system in order to meet the specific medical, psychosocial, sexual, educational and vocational needs of young women with TS. This is best accomplished by an expert multidisciplinary group of health care providers and community support groups.

Know Your Adolescent

As children become adolescents and young adults, it is normal for them to spend more and more time with their peers instead of with their family. However, they still need parental guidance, support, and monitoring. In general, teens with family involvement and with whom there is closeness and open communication, will be less likely to engage in many risk-taking behaviours.[11] Schedule time for family meals and activities. Know their friends, where they hang out, and level of adult supervision.

Key Points

1. Adolescents all have the same developmental tasks, but the timing and meaning of the tasks vary widely between individuals.

2. All adolescents are sexual beings and need to be educated about sexual health.

3. Adolescents with TS may experience their sexuality at a different rate than other teens, but will have similar questions, concerns, and educational needs.

4. Adolescents with TS have specific medical and psychosocial needs that may influence their sexual development.

5. Parental involvement in their adolescent's life is vital, including discussing sexuality in an open, honest way.

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Part II: Adult Sexuality

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Sexuality is a part of all women's lives and women continue to grow and change sexually throughout their lives. This applies to women with TS; however they tend to achieve their sexual milestones at a somewhat later date than their same age and sex non-TS peers. Women with TS are completely female and tend to self identify as female and have the capacity to fully experience physical excitement and pleasure and being an active partner in a loving and intimate sexual relationship. Having the opportunity and freedom to choose how to, or how not to express one's sexuality is indeed a very

important and significant women's sexual health issue. Sexuality is a topic that has not been addressed too often in the literature on TS. This section will try to give young and mature women with TS a picture of what sexuality can imply in one person's life along with some specificity of TS. As you read along, you will find that many ideas and tips can be helpful to both those with and without TS.

Sexual health is influenced by a complex interplay of factors ranging from sexual behaviour and attitudes and societal factors to biological risk and genetic predispositions. The World Health Organization has partially defined sexual health as "a state of physical, emotional, mental and social well-being in relation to sexuality". This definition specifically intertwines the interrelated nature of the physical, mental and social dimensions of sexuality and perhaps most importantly the idea of sexual well-being. Sexuality is an important determinant of self-esteem and social adjustment. Sexual health means understanding your body, knowing and appreciating how it works. Women who understand and appreciate their bodies and themselves as individuals can make better choices about their sexuality and their sexual relationships.

An individual's sexual development occurs over a lifetime. Sexual health is composed of two sets of interrelated factors: the biological factors and the psychosexual factors. Biologically the body needs to be healthy in order to allow optimal sexual function. There are four body systems of importance:

1. The hormonal system is where estrogen hormones are responsible for the full maturity of the genitals, and their elasticity and lubrication during intercourse. For women with TS it is important to have an appropriate and physiological amount of natural or exogenous estrogen as part of their ovarian hormone replacement therapy.
2. The vascular system makes oxygenation and increased blood-flow of the genitals possible during arousal periods and helps to ensure enhanced elasticity during intercourse.
3. The muscular system provides the muscular tension and rhythmic contractions necessary to obtain orgasm. An orgasm is a muscular spasm! Orgasm encompasses rhythmic muscle contractions accompanied by pleasurable and often intense sensations.

4. Last but not least, the nervous system, including the brain, which allows us to feel, interpret and experience touch and sensations. The nervous system is also responsible for our emotional responses and for the release of endorphins, which are the "feel-good" hormones. These four physical aspects are the basis of sexual health.

Understanding the Cycle of Sexual Response

In 1966, Master and Johnson described the 4 sequential stages of the sexual response in men and women as excitement, plateau, orgasm and then finally resolution phase.

It is important to note that orgasm doesn't always follow arousal and excitement and may not be necessary for you to enjoy good sex. Not everyone goes through this cycle in the same way or each time. There is a wide range and variety of what is considered "normal" during sexual arousal and expression. Ultimately, "normal" can only be determined by you.

For women who experience discomfort or lack of lubrication during intercourse experimentation with various positions may be necessary to achieve comfort, satisfaction and preferences. Fortunately, the use of estrogen therapy increases vaginal lubrication for women with TS which aids intercourse and decreases discomfort. For women who experience issues with lubrication or just want additional lubrication during the arousal phase, the use of a water soluble lubricant is recommended, not a petroleum-based product.

A proposed method to increase circulation, strength and sensation in the pelvic or genital area, is to perform Kegel—pronounced "KAY gul"—exercises. These exercises were developed to help women with problems controlling urination by strengthening and enhancing their voluntary control of the pubococcygeus (PC), or pelvic muscles. These muscles make up the pelvic floor and form a sling of muscle stretching from the tailbone to the pubic bone that holds the pelvic organs, namely the uterus, bladder, small intestine and rectum, in place. Instructions on how to perform Kegel exercises are available on many websites on the internet.

A Few Words About Cystitis

Inflammation and infection of your bladder, called cystitis, frequently affects sexually active women but may also occur in those who are not sexually active or in young girls for different reasons. Cystitis occurs when the normally sterile lower urinary tract consisting of the urethra and bladder, becomes infected by bacteria and is irritated and inflamed. Females are prone to the development of cystitis because of their relatively short urethra that enables bacteria to enter the bladder.

Sexual intercourse increases the risk of cystitis because bacteria can be introduced into the bladder through the urethra during sexual activity. Common signs and symptoms of cystitis include lower pelvis pressure or pain, painful urination, frequent or urgent need to urinate during the day and night, cloudy or strong smelling urine. The concern for women with TS with cystitis is that there is an increased risk of spreading infection to the kidneys. For women with kidney issues or abnormalities, this could pose health risks and require rapid identification of infection and prompt treatment.

Women can do many simple things to reduce their risk of cystitis. First, urinate regularly and frequently as this prevents a build up of stagnant urine. Second, urinate immediately after sexual activity to flush bacteria away from the urethra. Third, drink plenty of fluids. Maintain good genital hygiene by washing regularly with mild soap and rinsing well. Finally, when toileting, always wipe from front to back—away from the vagina toward the anus—to prevent contamination.

Sexual Changes Associated with Menopause

During middle age and beyond, the body undergoes changes that may affect feelings of desirability and sexuality. Interestingly, men and women may view ageing and their sexuality quite differently. As men approach their mid-fifties they may fear the loss of their sexual capacity but not their attractiveness. Think of all the medication commercials aimed at males to enhance sexual function! Meanwhile, women generally fear loss of their attractiveness which accounts for the prevalence and acceptance of plastic surgery procedures during female middle-age, and not their sexuality. Most non-TS women

will experience menopause around 50 years of age, however it can be quite normal to experience it anytime after 40 years or so. Menopause generally occurs when a woman's body stops releasing eggs, her menstrual cycle ceases and estrogen production wanes and ultimately ceases. For most women with TS, menopause will occur when they stop taking their estrogen therapy. For women with TS, they have the advantage of determining, along with their health care provider, the best time for them to stop estrogen. Some of the physical, hormonal and sexual changes commonly associated with menopause may include slower sexual arousal, reduced intensity of orgasm, less lubrication produced during arousal and sexual activity, as well as an increase in discomfort during intercourse due to the vaginal wall thinning. "Hot flashes" are also described, although may not be as common in women with TS. Hot flashes are periods of intermittent intense warmth, perspiration and flushing which can last anywhere from seconds to minutes. They are believed to be triggered when falling estrogen levels send a signal to the brain to trigger dilation of blood vessels close to the skin's surface producing heat, flushing and perspiration. Many women who do go through menopause may experience insomnia, mood changes, weakening of pelvic floor muscles, as well as headaches, weight gain, and changes in sexual interest. Those with TS may experience these symptoms to varying degrees. While many women may experience a reduced interest in sex, others may have an increase in interest and sexual desire.

Talk to your Health Care Provider

If you are having difficulties engaging in sexual activity, speak with your health care provider (HCP). Common problems, as mentioned above, include painful intercourse and vaginal dryness. These symptoms could mean that your hormonal medications need some adjusting. But it could also mean that you are not aroused enough when you have intercourse. It is beneficial to talk about it to your doctor or HCP to help to identify the problem. If you find that you have issues with your libido which is your sexual drive or desire, then you may wish to talk with your HCP about your androgen levels, which are male hormones such as testosterone, that may be low in women with TS. Testosterone biologically influences libido in both men and women. In women, testosterone is pro-

duced in the ovaries and adrenal glands. While the relationship between sexual interest and testosterone levels are not that well understood we know that women are very sensitive to the effects of testosterone and the use of some androgen preparations may be of some use to some women. Remember, illness and sex do not pair up well together. If you are going through a health change, medical procedure or a change in medication, sexual desire may wane for a time. This lack of desire is normal. Your body and mind are preoccupied by something important.

Learning About Your Sexual Self

Women with TS tend to be less sexually active than non-TS women and tend to have their first sexual encounter experience later. 

Being sexual is far more than engaging in physical activity or a matter of physiology. Being sexual is about who we are, what we feel, value, know, think, and what we desire. Being aware of your own sexual needs and preferences is critical to enhancing and experiencing your own sexuality.

> *"I think it all has to do with the woman and the way she feels about herself. If she feels sexy then she will be sexy. If she feels desirable then she will be desirable, but if she doesn't feel like that, it won't work for her. If she doesn't feel beautiful then she won't be beautiful. [What about you?] I guess I do feel sexy so I act like that, so I have no problem with that."*
>
> —Karen, age 28
> (Kagan-Krieger S, p.133) *

Due to gender-role stereotypes and negative learning, experience and inexperience about sexuality, women may lose sight of their own sexual needs. Sexuality of an individual is largely determined by family, community, and social values and is very much influenced, often simultaneously, by gender, marital status, culture, religion, education, health and economic factors. These then influence our desires, intimate encounters and motivations associated with sexual activity, practice and behaviour.

Learn about your sexual self and ask yourself what it means for you to be intimate and have sex. What is important for you to have in place before you will proceed and engage in a sexual relationship or experience? Recognise that it is healthy and normal not to be doing things that are uncomfortable and that it is always okay to wait

and give yourself time or permission to decide. Conversely, you do not have to participate in an activity again if you found it unpleasant or unrewarding.

The human body can experience physical pleasure in a multitude of ways including hugging, kissing, touching, to even the highs experienced with exercise or eating a favourite meal or snack. Sexual pleasure can also be experienced in a multitude of ways including touching, caressing, kissing, hugging, masturbation, sex, sexual thoughts, fantasies or desires.

> *"I think there are times when I have sexual feelings but I tend to kind of suppress them or not to react to them and not kind of go with them and not encourage them because they feel so foreign. I don't know how much hormones play a part in how you feel sexual."*
>
> —Rita, age 42
> (Kagan-Krieger S, p.153) *

Using self-stimulation, called masturbation, to learn about and achieve sexual pleasure can enhance self-appreciation, improve body image and increase your understanding about the types of touch and sexual touch your body prefers. While some women do not believe in or enjoy masturbation, it can be very useful to learn how one's body responds to touch and may assist in relaxing and enjoying sex when they have not previously.

What is Good Sex?

You will know that you are enjoying "good sex" when you feel good about yourself, your partner, your relationship and what you're doing. Explore your needs as a couple for conditions necessary for good sex. While this may seem odd it is not unusual to require certain conditions for any activity. Take for example, a good start to a day. Some of us may need to have a certain number of hours of sleep, be awakened by suitable music, have a long hot shower and a good strong coffee before we can face the day and declare a good start. Learning about and coming to know what your internal and external conditions for "good sex" are, will likely increase sexual arousal. Are you feeling intimate? Are you anxiety free? Are you feeling positive? Are you feeling mentally and physically alert? Aroused? Do you need privacy? A romantic setting? Think about what you like and what you might like or love to try. Give yourself permission to ex-

plore and decide on what are your requirements for "good sex" are – for now – and set out to prepare and educate yourself and share with your partner. This dialogue will assist you to have consistent and good intimate experiences with your partner.

The Nature of Desire

Sexual desire is highly individual and variable and its origin remains largely a mystery. According to researcher Stephen Levine (1987), we can divide sexual desire into the three components of sexual drive, sexual wishes and sexual motivation. Sexual drive is rooted in our brain's neuroendocrine system and is considered biological. An individual's sexual drive may be high, moderate or low. Sexual wishes and motivations are closely related. A sexual wish is a desire or a "wanting" – or "not wanting" – to be sexual. Sexual motivation depends on sexual identity (sexual orientation and gender identity), the quality of non-sexual relationships (past experiences with parents that may involve positive or negative issues surrounding love, trust and intimacy), and transference of past experiences to current relationships that can impact sexual desire positively or negatively.

Sexual Fantasies

Sexual and erotic fantasies are likely the most universal of all sexual behaviours. Sexual fantasies have a number of important functions which include defining and directing our erotic goals, enabling us to anticipate or plan sexual situations that may or will arise, to provide an escape from everyday experiences and provide novelty and excitement into existing relationships. These fantasies have an expressive function, just as our nightly dreams do, and may offer clues about one's interests, attractions, anxieties, pleasures and fears.

Sex and the Media

Media images of sexuality permeate all areas of our life. We, as a society, are consumed and driven by sex, romance and popularity. The media messages we are bombarded with on a daily basis, reinforce the thinking that certain products or experiences will guarantee popularity, happiness, sex, sexuality, the right partner, and so on. Most images of women in the mass media are not natural and real, and have been romantically or sexually staged, airbrushed, cropped, and perfected. Thinking, "That's how I should be", can cause anxiety

for most women and can lead to unrealistic expectations for both men and women alike. When a company wants to sell their product, their tactics are to first, present something as a problem, then increase the level of anxiety related to what has now become a big problem and finally offer, or sell, a solution. Consequently, women, both TS and non-TS alike, may feel like we can't measure up to the women depicted in magazines and on television. It is important to acknowledge the effect that the media has on our collective conscience, and to understand that this portrayal of "sex" in the media is narrowly defined.

About Healthy Relationships

According to *www.SexualityandU.ca*, a healthy relationship has the five main characteristics of: **S**afety, **H**onesty, **A**cceptance, **R**espect and **E**njoyment or **S.H.A.R.E.**

In a healthy relationship you feel **safe** and are not worried about or engaged in physical or emotional harm from, or toward your partner. You can try new things, you are supported to take on challenges, you can change your mind without fearing a negative reaction from your partner, and you can refuse to participate in anything that you do not feel comfortable with.

Honesty in a relationship allows you to express your thoughts without fear of ridicule or condemnation. You can resolve disagreements by being open and honest.

In a healthy relationship you will **accept** and appreciate your, and your partner's differences and unique qualities without needing to change or fix them. You will support and be supported in your ongoing development and pursuit of interests, hobbies, education, spirituality and occupational work and advancements.

Respecting yourself and your partner is perhaps the most important of all these qualities as it is the characteristic that allows all the other traits of a healthy sexual relationship to exist and flourish. You and your partner are happy when good things happen to the other. You understand that you are two unique individuals that have a right to separate ideas and opinions. Coming to a consensus or compromise on how to approach a problem in an agreeable and respectful way is a sign of a respectful relationship. Sometimes you may resolve to agree to disagree.

Finally, a healthy sexual relationship is about **enjoy**ing each other. You feel happy, energized, proud, stimulated, comforted, supported and centered when you are together. You can have fun, laugh and play together.

An abusive relationship is the opposite of a healthy relationship. Signs of an abusive relationship include lack of mutual respect and support and can involve intimidation, controlling behaviours and fear. Some signs of an abusive relationship are jealous questioning, belittling, insulting comments, name-calling, force, coercion and intimidation, and ultimately physical violence. Should you suspect that you are in an abusive relationship, there is help and you need not stay. Your HCP, local or regional sexual health clinic or public health office can provide assistance and counselling. Staying in an abusive relationship will damage your self-esteem and health more so than being alone and ultimately it will prevent you from experiencing a healthy relationship.

In conclusion, our sexual health is affected by biologic, hormonal and psychosocial factors, and these change throughout life. Understanding these individual factors and reflecting upon our personal preferences and interpersonal relationships can help us to achieve a state of optimal sexual health.

Key Points

- Sexuality is a part of all women's lives.
- Women continue to grow and change sexually throughout their lives.
- Women think about sex, desire sex, act sexy and have sex.
- Sexual health means understanding your body, knowing and appreciating how it works.
- Do Kegel exercises regularly to strengthen pelvic muscles.
- Figure out what are your requirements for "good sex".
- Avoid cystitis.
- Any discomfort associated with intercourse should be explored with your health care provider.
- Nurture sexual desire, fantasies and your intimate relationships.
- Ensure that you are in a healthy sexual relationship (S.H.A.R.E.)

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* Susan Kagan-Krieger, "The struggle to understand oneself as a woman: Stress, coping and the psychological development of women with Turner Syndrome" (EdD dissertation, University of Toronto, 1998).

Chapter 6

All Kinds of Families: Infertility and Pregnancy Issues

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Artist: Julia, age 8

Infertility—decreased ability or inability to become pregnant—is experienced by the majority of women with Turner Syndrome (TS). During interviews of a sample of women, infertility was described as the most concerning aspect of having TS.[1] Spontaneous pregnancies have occurred in only a small proportion of affected women. Assisted Reproductive Technology (ART) has advanced dramatically over the

years, such that carrying a pregnancy, usually with a donor egg, is now a possibility for many women with TS. Nonetheless, specific considerations must be taken into account when considering the use of ART, and specifically in TS, that may increase the risk of pregnancy. In this chapter, medical issues related to infertility, ART and pregnancy are discussed. Of course, most women with TS will have had to grapple with the probability of their infertility long before they actually plan to start a family. To begin this chapter, we outline some of the challenges in discussing infertility with your daughter, and provide some strategies to create a comfortable and open dialogue about this issue.

How to Talk to Your Daughter About Infertility

Many parents may feel uncomfortable talking about sexual issues with their children. It can be difficult to speak with your daughter about the possibility of infertility. Your relationship with your child is an emotional one, and you may feel a sense of sadness or loss on her behalf as well as on your own. Explore your feelings around this issue. If you feel uncomfortable or unsure as to how to proceed, it may be necessary to first discuss this more with others you trust; for example your health care provider, family members or a TS support group. You may find guidance on what was helpful from parents who have already been there. A support group may also be helpful in dealing with your own feelings around your daughter's infertility. Parents may grieve this anticipated loss of choice for their child and ultimately the loss of their own biologic grandchildren. It is important for parents to have their own sources of emotional support when dealing with these difficult issues.

> *"I found out the name of the condition I was diagnosed with when I was 21. I had gone to Europe that summer and didn't take my 'pills' – estrogen. I thought it was a pain in the neck. Needless to say I didn't menstruate.*
>
> *I finally put two and two together. If I wasn't menstruating did that mean I couldn't have children? My endocrinologist confirmed this. He just blurted out, 'We can simulate a period but not an egg.' Then he left the room. Can you imagine, I was 21, just being told what I thought was some devastating news and being left alone without further explanation or support."*
>
> —Susan

Infertility may be the most difficult characteristic of TS to disclose. Researchers interviewing 97 girls and women with TS found that 30 subjects had all or part of their diagnosis withheld from them; half of these were told every aspect of their diagnosis except for infertility. Some girls and women who had this secret kept from them felt angry and upset upon disclosure, and a few felt their family members had betrayed them.[2] While it may be tempting to deliberately keep certain information a secret in an attempt to "protect" your daughter from the truth, early and full disclosure has advantages. Gradual open disclosure allows her time to process this information gradually, in steps appropriate to her age and emotional maturity. It can avoid the unfortunate, but unfortunately not uncommon, "crisis" experience of learning about TS and infertility suddenly and unexpectedly as an adolescent or young woman. According to Sutton et al., girls with TS who are left unaware of their infertility may have a harder time coping with this information when it is eventually disclosed. Open discussions help to de-stigmatize TS and infertility. It also supports girls in creating a positive self-image and hopes for a future that will likely not include biological motherhood by using her own eggs, but may involve alternative options. Through honest and early disclosure, parents can ensure that their daughter receives this information in a loving, helpful, encouraging and optimistic approach.

It is important to keep the discussion simple and appropriate for your daughter's age and development. Talking about complicated issues with children is an ongoing process. As your child continues to grow she will be able to understand more complex concepts, and over the years your shared conversations about infertility will become more sophisticated and in-depth. Start as simple as possible, and let your daughter guide the conversation. Do not feel that you need to fit and fill in all the details into the first conversation as this may be overwhelming. The important thing is to provide your daughter with age-appropriate, accurate information. Try to anticipate the type of questions she may ask, and reflect in advance how you will answer. Don't worry about knowing all the answers to your daughter's questions; what you know is a lot less important than how you respond. If she catches you off guard, it is fine to state that you do not know how to answer, but that you will think about it, look it up, or speak to an expert and get back to her to discuss it

further. There will be many opportunities to elaborate as your child continues to grow and develop the ability to understand complex and abstract ideas. You may be surprised that your daughter is not necessarily affected by this information at a young age, as the prospect of motherhood is quite distant and not necessarily relevant at her developmental age. However, grief and angst may come during later-teens or adulthood when infertility and its effect on relationships, life plans and decisions may be more significant.

Use opportunities when they present, or select storybooks, that highlight a wide variety of families and different ways to be a parent. The traditional definition of family—a married man and woman living together with one or more children—is no longer the norm in Canadian society, even though it remains the norm in popular culture and the media. In fact, only 44% of Canadian families fit this traditional family mold.[3] Talk to your daughter about how families come in all shapes and sizes. Young children have difficulty with abstract ideas, so real life examples of friends, family, or classmates work best. Introducing your daughter to families with adopted children, children from previous relationships or those with no children will help her to view these families as normal, real and tangible possibilities for her future.

Not all girls with TS are diagnosed at a young age. Many will be diagnosed around the age of puberty, and a rare few may not discover they have TS until they have difficulty in getting pregnant. If your older daughter has been diagnosed with TS, you will likely not have the luxury of slowly explaining infertility to her over time. Still, the key points are the same; be honest, have conversations appropriate to your child's developmental level, and emphasize that you are willing and happy to answer any questions your child may have – now, or in the future.

> *"Since the beginning of our relationship, my husband and I knew that having kids would be part of our lives. After having studied the many various scientific methods (insemination and others), we decided to embark on the adventure of international adoption.*
>
> *In January of 2004, we registered with an adoption agency that specializes in finding families for children in Colombia. Creating our adoption file was more difficult than we expected (the documents required were very precise and numerous). The waiting was painful, we were so anxious*

to start a family. After 2 years and 9 months, on July 27, 2006, we finally got the call. It was the real deal; a beautiful little 7-month-old princess was about to join our family. We had to prepare the last documents and all of our heavy suitcases. We left on September 16, 2006 to meet our little girl, and on September 18, 2006, we held our beautiful daughter, Camilia, in our arms for the first time. This little girl filled a gap in our lives. We had no idea of the happiness our new job as parents would bring."

—France

The Medical Facts: Infertility

The Female Reproductive System

The female reproductive system is composed of the vagina, uterus which is also known as the womb, and includes the cervix, two fallopian tubes and two ovaries – see Figure 3, Chapter 4. The ovary is responsible for the production of the female sex hormones estrogen and progesterone, and both the storage and maturation of ova, which are oocytes or eggs. These are then released, usually one each month into the fallopian tubes to reach the uterus. Pregnancy occurs when a woman's egg is fertilized by a male sperm and forms an embryo. If this embryo attaches to the endometrium, or lining of the uterus, a fetus then develops.

Ovaries in Turner Syndrome

When the ovary first develops in a female fetus with TS, it has the same number of immature eggs and hormone producing cells as an unaffected fetus. Over time, there is atresia or the spontaneous loss of cells in the ovary. Fibrous scar-like tissue replaces the cells. In women without TS, all the cells are usually not lost until approximately 45 to 55 years of age – the time of menopause. In TS, this process of atresia is accelerated so that all cells, including eggs, may be lost by the time of birth or during childhood.[4, 5] In at least 70% of girls with TS, puberty does not start spontaneously and they cannot become pregnant with their own eggs.

Even if menstrual cycles continue spontaneously throughout puberty or into adult life, indicating that eggs are still likely to be present, ultimately 90% of women have premature, or early, ovarian failure, at which time hormone replacement will become necessary. This means that there is a shortened time span to achieve pregnancy spontaneously. Women with certain TS karyotypes are more likely

to have continued ovarian function. These include mosaicism, especially if the majority of cells are normal, and deletions of only the short arm of the X-chromosome (Xp).

Fallopian Tubes, Uterus and Vagina in Turner Syndrome

The vagina is formed normally in women with TS. They can have intercourse, or "sex", in the same manner as women without TS. The fallopian tubes are also normal and the uterus is present. Some studies have shown that women with TS, who required estrogen to commence or continue puberty, had a smaller uterine size in length, thickness and volume, with a failure to attain a normal mature shape. The thickness of the endometrium was also decreased.[6,7] This may decrease the success of fertility treatments, as discussed later in this chapter. However, in some women, even with a 45,X non-mosaic karyotype and lack of spontaneous puberty, normal uterine size has been documented.[8] In recent years, hormone replacement therapy has been started at an earlier age and within the expected range of normal timing for puberty in females. It is possible that with timely commencement of estrogen and adequate dosing during puberty and young adulthood, that uterine growth and development may be less affected in future generations of women with TS.

Fertility Options

Most women with TS are infertile due to premature ovarian failure and cannot achieve a spontaneous pregnancy. It is estimated that only 2 to 5% of women with TS are able to become pregnant spontaneously. The likelihood would vary depending on an individual's karyotype as this influences whether ovarian function is preserved. Even if some eggs are still present, the number may be reduced compared to women the same age without TS.

Assisted Reproductive Technologies (ART) may be used to assist women attempting to become pregnant. In the case of women with premature ovarian failure, pregnancy may be able to be achieved with another woman's egg, called a donor oocyte.[9] *In-vitro* Fertilization (IVF) uses hormones to develop and mature the eggs before they are extracted and fertilized with sperm in the laboratory. The fertilized eggs are then allowed to grow until they have several cells, called an embryo, before they are transferred

back to a woman's uterus. Pregnancy is achieved when the embryo successfully implants into the uterine lining and continues to develop. Administration of hormones will be necessary in most cases to prepare the lining of the uterus to allow implantation to occur. Interestingly, success of ovum donation largely depends on the age of the ovum donor[10] making it as successful in both older and younger women with premature ovarian failure. In women with TS, it is advisable to limit the number of embryos transferred to avoid the additional medical risks associated with multiple gestations. Embryos may also be frozen for use in the future. This is known as cryopreservation.[11]

Progress is occurring with other experimental techniques that may soon offer additional options for women at risk of early loss of ovarian function. These include oocyte cryopreservation, which is the freezing of unfertilized eggs, both autologous – one's own eggs, and directed allograft – another woman's eggs, in addition to cryopreservation of human ovarian tissue.[12]

Other Factors Affecting Fertility

There is an increased risk of chromosomal abnormalities of the egg of a woman with TS. This may increase the chances of failure of embryo implantation or miscarriage. A uterus with a decreased length and endometrial thickness may have a reduced blood supply. Such uterine factors, if they do not respond well to hormonal stimulation, may limit the success achieved, even with donor eggs.

Medical conditions, such as obesity, diabetes and thyroid disease, that are more common in women with TS may decrease egg release, called ovulation, and increase the risk of miscarriage. Other implications of such conditions during pregnancy are outlined later in this chapter.

Pregnancy

Outcomes of Pregnancies Achieved With a Woman's Own Egg

Although most pregnancies in women with TS have been achieved with a donor egg, there are a few reports of spontaneous pregnancies. One report published in 1998 described the outcomes of 160 spontaneous pregnancies in 74 women with TS: 58% live births, including one set of twins, 29% miscarriages, 7% stillbirths and

in 6% no specific information was available.[13] Of live babies, 66% were healthy. An abnormality was detected in the remaining 34%. Two-thirds of these had either TS or Trisomy 21, known as Down Syndrome. The other one-third had congenital abnormalities, or birth defects, not known to be caused by chromosomal abnormalities such as heart defects or cleft palate. This suggests that there is an increased risk of miscarriage, stillbirth, chromosomal abnormalities and birth defects. The authors estimated that the risk of Down Syndrome was 26 times higher than the general population and the risk of TS was 30 times higher than the general population. This report could only describe the results of cases that have been published in the literature, and so it likely does not include all pregnancies that have occurred.

Genetic counselling and prenatal diagnostic techniques such as blood tests, ultrasonography, amniocentesis and chorionic villous sampling, are available to provide women with additional information about their pregnancies. Women who undergo IVF may also choose Pre-implantation Genetic Diagnosis (PGD) to screen the embryos before they are placed into the uterus.

Special Considerations in All Pregnant Women with Turner Syndrome

Medical Team

Pregnant women with TS should be cared for by a multidisciplinary team in a tertiary care hospital that may be comprised of specialists in various fields such as an obstetrician for potentially complicated pregnancies, a cardiologist for the heart, an endocrinologist for diabetes and hormone disorders, a geneticist and other allied health care workers to provide social work, psychology and nutritional counselling.

The Heart and Blood Vessels

Pregnancy stresses the cardiovascular system, which is the heart and blood vessels. Changes include increased circulating blood volume that results in an increase of up to 50% of the amount of blood that the heart needs to pump around the body, called cardiac output. Other stressors include an increase in cardiac output with uterine contractions during labour and straining during the second stage of labour or the "pushing stage". Cardiovascular stres-

sors continue for several weeks after the delivery. The specialist doctors should discuss the woman's individual heart condition with her and counsel her about the potential risks of pregnancy and precautions that may be recommended to minimize the risk. If the risks are thought to be high, a woman may be advised against proceeding with a pregnancy.

Women with TS are at increased risk of high blood pressure that may develop or worsen during pregnancy. This may be due to constriction in the large blood vessel leaving the heart, known as coarctation of the aorta, or abnormalities of the kidneys or blood vessels within the kidneys. Coarctation of the aorta is more common in women with TS – approximately 11%. Women with TS should have their blood pressure checked regularly throughout life and treated, if necessary, with antihypertensive medication. This is especially important during pregnancy as uncontrolled high blood pressure may lead to health concerns in the mother such as stroke, kidney damage or seizures and the baby may have poor fetal growth or be stillborn.

Approximately one third of women with TS have a heart problem. The most common abnormality is a bicuspid aortic valve, in which there are two rather than three leaflets or "cusps". Risks to the health of the mother and fetus may result from the development of aortic stenosis, or narrowing of this valve, or if there are associated complications such as impaired functioning of the heart muscle.

Women with TS are also are at increased risk of aortic dilatation (widening) and dissection (splitting), especially if there is associated hypertension or a bicuspid aortic valve. The risk of aortic dissection may be 2% or higher in pregnant women with TS. This has been the cause of sudden death in both pregnant and non-pregnant women. The risk of death during pregnancy may be up to 100-fold higher in TS than in unaffected women.[16]

Cardiology consultation and careful screening for heart abnormalities is imperative before attempting pregnancy. The tests will include a chest x-ray, echocardiogram, which is an ultrasound of heart and aorta, and a Magnetic Resonance Imaging (MRI) of the aorta. Ongoing careful surveillance using regular echocardiograms, throughout the pregnancy is also essential – even if there are no ini-

tial cardiac abnormalities. Specific management may include treatment of hypertension, epidural anaesthesia during an attempted vaginal delivery to minimize pain and stress or a planned caesarian delivery prior to the onset of labour.[16]

Preventative antibiotic therapy such as Spontaneous Bacterial Endocarditis Prophylaxis or "SBE Prophylaxis", may be advised prior to undergoing procedures, or delivery, in some women to reduce the risk of bacteria that may be in the woman's bloodstream from causing an infection of the abnormal heart valve. This is particularly important if there are any complications or existing signs of infection.

Hypothyroidism

In early pregnancy, fetal brain development depends on adequate amounts of thyroid hormone crossing the placenta from the mother. For women with TS, it is important to have their thyroid function tested prior to pregnancy and started on treatment if necessary. Thyroid function will also have to be rechecked regularly because the dose may need to be increased during pregnancy. Repeat testing in women with hypothyroidism is generally performed approximately 4 weeks after delivery of the baby, as a decrease in thyroid pill dose is usually required.

Hyperthyroidism

For those with autoimmune hyperthyroidism, or Grave's disease, leading to an overactive thyroid gland, treatment with anti-thyroid medication such as propylthiouracil (PTU) is used. Close monitoring of thyroid function tests and the well-being of the mother and fetus are required throughout the pregnancy with adjustment of the medication dose as needed. Babies born to mothers with Grave's disease require close follow-up by a paediatrician in the first weeks of life to monitor thyroid function. This is because the antibodies in the mother's blood stream, which cause the thyroid gland to be overactive, can cross the placenta and cause temporary thyroid function abnormalities in the baby.

Diabetes Mellitus

Type 2 and Type 1 Diabetes

There is an increased risk of diabetes mellitus resulting in high blood glucose levels in women with TS. This is usually type 2 diabetes

which is associated with insulin resistance which is a decreased action of the hormone insulin that controls blood glucose levels. There may also be a tendency to develop type 1 diabetes as it is an autoimmune condition like thyroid disease.

A test to diagnose diabetes should be performed before a planned pregnancy. This may include a fasting blood glucose test or an Oral Glucose Tolerance Test (OGTT), or both. In this test, a blood glucose level is also measured 2 hours after drinking a special glucose-containing drink. Optimizing blood glucose control in the 3 months before becoming pregnant and throughout pregnancy significantly reduces: the risk of miscarriage; birth defects of the heart and kidneys; spine abnormalities; excessive growth of the baby which increases the need for delivery by caesarean section; and problems for the baby in the newborn period such as low blood glucose levels and breathing difficulties. Screening for diabetes complications for the eyes and kidneys should occur before and during pregnancy. An increased dose of folic acid supplementation is recommended if mothers have diabetes.

Gestational Diabetes

There is also an increased risk of gestational diabetes which is diabetes that develops during pregnancy. This may be diagnosed by an Oral Glucose Tolerance Test (OGTT) that should be performed during pregnancy. Women with gestational diabetes are more likely to develop diabetes in the future, after the delivery.

Regular review by a diabetes specialist is important to monitor blood glucose levels and adjust treatment such as doses of insulin. An obstetrician also needs to carefully monitor fetal growth and other possible complications in pregnancy.

Metabolic Syndrome

The risk of hypertension during pregnancy is further elevated in the presence of obesity and diabetes. Both TS and type 2 diabetes are associated with adverse levels of blood cholesterol. Certain medications used to lower cholesterol levels will need to be stopped during pregnancy.

Kidneys and Urinary Tract

Pregnant women are at increased risk of urinary tract infections such as bladder infections, or cystitis, and kidney infections known as pyelonephritis. If not treated, urinary tract infections could cause a serious infection of the bloodstream and increase the risk of an early onset of labour and delivery. This risk of urinary tract infections is further increased if there are malformations of the kidneys or urine collecting systems. Such malformations are more common in women with TS. It is recommended that all women with TS have an ultrasound test to detect any abnormalities, if this has not been done previously.

Sometimes large numbers of bacteria are present in the urine but do not cause the person to feel unwell. This is known as "asymptomatic bacteriuria". Women with TS, particularly those who have known underlying abnormalities of the kidney and urine collection system, should have regular testing of their urine in pregnancy and undergo antibiotic treatment when necessary.

Some antibiotics have the potential side-effect of affecting hearing. Women with TS are at increased risk of hearing loss due to decreased functioning of the nerves that carry the signals from the ears to the brain, known as sensorineural hearing loss. Care should be taken to either avoid antibiotics that are ototoxic or have close monitoring of the medication levels in the blood if that particular antibiotic is used. In women with a high risk of repeated urinary tract infections, continuous low-dose antibiotics throughout the pregnancy may be recommended.

Stature and Bones

Short stature is a frequent feature of TS. There may also be differences in the size, shape and alignment of the bones, including a narrow pelvis, or hip bones. This may increase the risk of cephalopelvic disproportion, a situation where the baby's head is too large compared to the mother's pelvis to be delivered through the vagina. Caesarean section may be required.

There is concern that women with TS are at increased risk of osteoporosis, or fragile bones. During pregnancy, especially during the last 3 months and while breastfeeding, a woman's calcium stores

may be depleted due to the high demand of providing calcium for the baby. It is especially important during these times to have adequate calcium intake, either from the diet or by taking supplements. The recommended calcium intake during pregnancy is 1200 to 1500 mg per day. Vitamin D is also important for bone health. It is formed by the skin after exposure to sunlight and small amounts are present in certain foods. The recommended vitamin D intake in pregnancy is at least ~~200~~ IU, or international units.

Celiac Disease

Celiac disease, an autoimmune condition affecting the lining of the small intestine, is more common in women with TS, affecting up to 5 to 10% of females. If untreated, celiac disease may lead to malabsorption of nutrients, vitamins and minerals. Adequate maternal nutrition is important to ensure optimal growth and development of the baby. Folate and iron are of particular significance during pregnancy.

Lymphatic System

It is common for women with TS to have a problem with the development of the lymphatic system. The lymphatic system is composed of vessels that drain body fluids back towards the heart. Abnormalities of lymphatic vessels may result in swelling, called lymphedema. This is most commonly seen in babies as swelling of the hands and feet at birth that usually disappears or improves in early childhood.

During pregnancy, the amount of fluid pumped throughout the body by the heart increases significantly. Most pregnant women experience some ankle swelling. Little is known about the effects of pregnancy on lymphedema in women with TS. However, it is possible that this extra demand of pregnancy may cause lymphedema to occur or re-occur if it was present previously. It may also result in an increase in lymphedema that is already present. This may be even more likely if women gain large amounts of weight during pregnancy.

Lymphedema may cause some discomfort but is not usually harmful. It would be expected to improve after pregnancy to a similar amount that was present before the pregnancy.

There are other causes of swelling of the legs and ankles during pregnancy that may be due to serious medical complications and require urgent treatment. These include deep venous thrombosis which are blood clots in leg veins and pre-eclampsia which is high blood pressure, protein in the urine and swelling of the face, hands and feet. It is important to seek medical advice if ankle or leg swelling occurs.

Uterus

If the uterus is small, this may increase the risk of poor growth of the baby, premature onset of labour as well as malpresentation of the baby such as breech position.

Delivery Method

Many factors previously discussed increase the chances of a woman with TS requiring an operative delivery such as a forceps delivery or caesarean section. These include: (1) maternal heart and blood vessel complications such as hypertension, aortic root dilatation and aortic stenosis; (2) cephalopelvic disproportion or large baby in relation to maternal pelvis due to maternal stature, bone structure or maternal diabetes; and (3) malpresentation of the fetus or breech position. A possible tendency for keloid scar formation which are scars raised above the skin surface, has been described in women with TS. This has not been specifically described in caesarean section scars, but has been noted in some women after the removal of skin lesions or after surgery to remove excess neck skin.

Lifestyle

Recreational drug use, cigarette smoking and alcohol ingestion are strongly discouraged in all pregnancies. This is particularly important in a pregnancy where there may be many other medical complications. A balanced, healthy diet is recommended. Extra nutrients and energy are required to meet the demands of the growing fetus and the changes in a women's body during pregnancy and breast-feeding. Folic acid supplementation is recommended. Other supplements such as iron, calcium and vitamin D may also be required in certain women.

"I think there is that element. 'Am I really a woman if I can't have a child?' But I've come to realize more as I have grown up and become more self-confident that it doesn't define you as a woman. Who you are currently defines you as a woman. Your strengths, your challenges, and how you handle them all define you as who you are, you know. In any case, one can't be defined by one's children. You have to be defined by yourself."

—Christine, age 44

Key Points

Infertility

- Infertility is experienced by the majority of women with TS.
- Women with TS have described infertility as the most concerning aspect of the syndrome.
- It is important to create an open dialogue, providing age-appropriate information about infertility to girls and young women with TS.
- There are many ways to "create" a family including adoption, use of a surrogate, and with assisted reproductive technology. Young women with TS should be fully aware of available options.
- Oocyte, or egg, donation has expanded the options for achieving pregnancy.
- In the future, options may be further expanded due to current experimental techniques such as oocyte cryopreservation, or egg-freezing.
- In the small proportion of women with preserved ovarian function, genetic counselling and prenatal diagnosis to assess for fetal abnormalities is recommended.

Pregnancy

- Medical issues that may occur in women with TS need to be considered prior to, and during pregnancy.
- The risk of aortic dissection which may cause death is increased in women with TS and further increased during pregnancy.
- Cardiology consultation and careful screening is essential before any planned attempt at pregnancy.
- If pregnancy is attempted, careful cardiac surveillance and management throughout the pregnancy is required, even in the case of a normal echocardiogram.

- It is important that a pregnancy is closely monitored by a group of specialized doctors and allied health care providers in a tertiary care hospital.

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American Society for Reproductive Medicine: *http://www.asrm.org*

Centers for Disease Control and Prevention – Assisted Reproductive Technology: *http://www.cdc.gov/art*

Turner Syndrome Society of the United States: *http://www.turner-syndrome-us.org*

Turner Syndrome Society of Canada: *http://www.turnersyndrome.ca*

Chapter 7

The "Hard" Facts: Bones and Teeth

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Bone Abnormalities

Turner Syndrome (TS) may be associated with abnormalities in the structure and appearance of certain bones in the body. This is thought to be due to a problem with how the bones are formed. Typically, the legs are short, the upper part of the body is relatively longer than the lower half, and the hips tend to be wider. Overall, this leads to a stocky appearance. The chest is wide and squarely-shaped, and the nipples are spaced widely apart. There may also be curving of the spine, called scoliosis, especially during adolescence. The neck may be short because some of the bones of the upper spine are underdeveloped. These abnormalities of the spine may partly contribute to the short stature of people with TS.

Shortened fingers and toes are also commonly seen, but the hands and feet are still relatively large overall. The arms tend to turn out slightly at the elbows, called cubitus valgus, and similarly, the legs may have a "knock-knee" appearance, called genu valgum. The wrists may appear thickened because of a curve at the end of one of the forearm bones and crowding of the wrist bones. There may also be associated foot problems, such as short, broad feet and difficulty bending the toes, referred to as hyperextension.

Several common facial features of TS also are related to bone abnormalities. There is often a downward drooping of the outer corner of the eyes, and the ears may be positioned lower than usual. There are also differences in the bones of the mouth and jaw, which are discussed later in this chapter in the section on facial growth.

In general, these bony abnormalities do not cause pain or limit activity. However, it is still important to screen for them beginning in

infancy as treatment may be required. For example, referral to an orthopedic surgeon may be needed for treatment of scoliosis with braces or surgery. As well, it is important to examine the hips in the newborn period, as there is a higher risk of dislocation associated with TS. If this condition is not properly managed, it could lead to arthritis of the hips in adulthood.

If growth hormone treatment is given for short stature, regular screening examinations should be done by a member of your child's health care team to follow any changes in these bone problems. While growth hormone therapy may slightly improve overall body proportions, the rapid growth of certain bones that can sometimes occur with treatment, can worsen some of the other abnormalities, in particular scoliosis.

Fractures and Osteoporosis

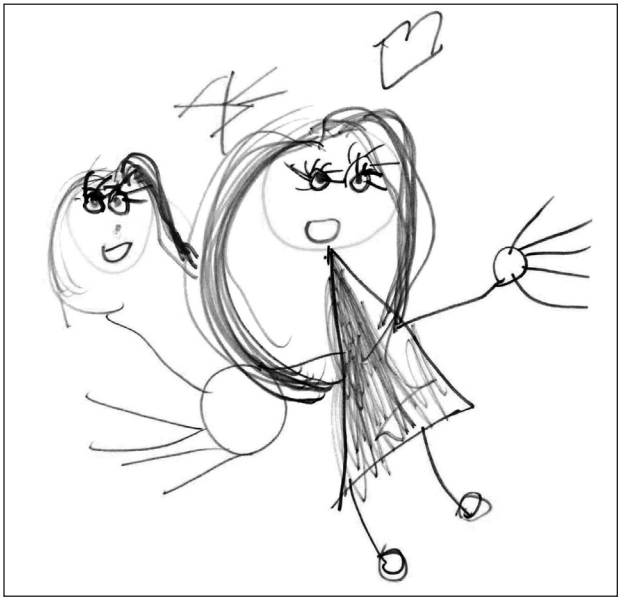
Some studies have shown that girls and women with TS have an increased risk of fracturing their bones, particularly the wrist. They also tend to experience their first broken bone at a younger age than females in the general population. This is felt to be partly due to the underlying bone problems already discussed, which may make the bones weaker and more likely to break. As well, some people with TS may have visual or hearing problems that affect their balance and make them more likely to fall. A history of fractures in a parent also raises the fracture risk. However, the most likely cause of the increased number of fractures is osteoporosis, or thinning of the bones.

Studies have shown that TS is associated with an increased risk of osteoporosis. It develops when there is not enough calcium in the bones. Calcium is a mineral that builds bone and keeps it strong. Without calcium, bones cannot reach their peak strength while they are growing during childhood and young adulthood. Bones continue to grow stronger until about the age of 30. If the bones do not reach their peak strength, they will be fragile and more likely to break, sometimes with little or no trauma. A special x-ray can be done to measure the peak strength of the bones or bone mineral density. This test should be arranged in early adulthood, however, if there are concerns about bone strength during childhood or adolescence, it may be done sooner. If the bone mineral density is

low, your health care provider will discuss whether treatment is required. If it is normal, regular follow-up testing will be done starting a few years after the first test.

In order to build strong bones that do not break easily, estrogen, a hormone made by the ovaries, is needed. Normally, estrogen levels rise as a female goes through puberty. In many girls with TS however, estrogen levels remain low throughout life. Often, estrogen replacement therapy is given to help puberty to progress and is continued during the reproductive years. Studies have shown that this treatment has the added benefit of improving bone mineral density and reducing the risk of fractures. Research has also shown that starting estrogen therapy at a younger age and treating for a longer period of time results in a greater gain in bone strength. An endocrinologist will discuss with you the best time to start estrogen replacement and also decide for how long it should be continued.

Many individuals with TS receive growth hormone therapy for short stature, and several studies have looked at its effect on bone density. Some of the studies have shown that growth hormone therapy before and during puberty is associated with an improved bone mineral density, however, these studies did not include untreated



Artist: Amira, age 6

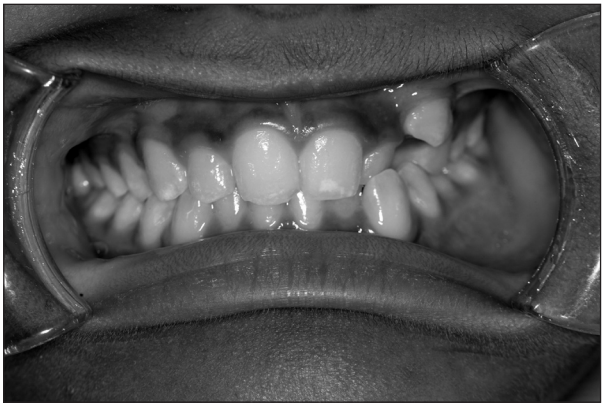
patients, so it is not known whether the improvement in bone density would have occurred even without growth hormone treatment. On the other hand, the most recent studies have shown that growth hormone treatment does not significantly improve bone mineral density in people with TS.

Estrogen therapy is not the only way to improve bone density. An adequate intake of calcium and vitamin D, either through the diet or with supplements, is also important. Your health care provider can determine if an individual is receiving enough of both. Weight-bearing exercises, such as running and tennis, also help to build strong bones. It is recommended that all females, not only those with TS, take part in thirty minutes of weight-bearing exercise daily. Finally, smoking and excessive alcohol intake should be avoided as these can contribute to low bone mineral density.

Dental Health

Facial Growth

Facial growth patterns vary in children with TS as they do in all populations. Children who have webbing of the neck usually have a small lower jaw and because of this, the upper and lower teeth will not come together properly. The roof of the mouth, called the palate, is often highly arched and causes crowding of the teeth. Orthodontic or sometimes surgical treatment will correct these problems. An orthodontist is a dental specialist who uses braces to move teeth and jaws into a proper alignment.



Dental crowding and malocclusion in a teen with TS prior to orthodontic treatment.

Teeth

In children with TS, the baby teeth may develop at a slightly younger age than usual, and permanent teeth may also appear earlier. This is not harmful. The teeth tend to be small and are sometimes abnormally shaped, with a thinner enamel covering. The roots of the teeth may also be shorter. On the favourable side however, those with TS tend to have fewer cavities than the general population.

It is common for adults with TS to develop an inflammation of the gums called gingivitis. If this is left untreated, pockets may form between the teeth and the gums that may collect bacteria, plaque, and bits of food and become infected. This can result in destruction of the bone supporting the tooth, which may result in tooth loss.

Due to the many dental issues that can arise in association with TS, your child should see a pediatric dentist by two years of age. If necessary, the dentist will refer her to an orthodontist generally at 7 to 8 years of age for evaluation. Regular dental follow-up should occur into adulthood to prevent and treat any dental problems.

Growth Hormone Therapy and Dental Health

There have been concerns that people with TS who receive growth hormone treatment for short stature may experience excessive growth of the facial bones and teeth, leading to further dental problems. However, most studies have shown that growth hormone therapy does not have a significant effect on the growth of the jaws and alignment of the teeth, particularly in older children. It should be noted that these studies involved only small groups of patients with TS and therefore the results might not apply to all patients. Because of this, it is important that every child receiving growth hormone therapy has regular follow-up with a dentist for the duration of treatment.

Studies have also shown that growth hormone treatment does not change how quickly the teeth grow and develop or cause any additional changes in the structure of the teeth. However, it is still suggested that any treatments to correct abnormalities in the facial bones or the way the teeth line up be delayed until growth hormone therapy has finished and all growth has stopped. Your child's health care team, which includes an orthodontist, will work togeth-

er to decide whether treatment is necessary and determine the best time for it to be done.

Ask your orthodontist or pediatric dentist about potential eligibility for orthodontic treatment coverage through various provincial programs, geared to provide assisted funding for children with clefts or syndromes, as TS may very well fit the inclusion criteria for approval.

Dental Procedures and Cardiac Health

If your child has a history of heart disease or abnormal heart valves you should inform the dentist and orthodontist before any procedure is performed. Children with certain heart conditions are at an increased risk of developing an infection, called infective endocarditis, of the lining of the heart or the heart valves during dental procedures, and antibiotics may need to be given to help prevent this from occurring.

Key Points

1. Although the bony abnormalities seen in people with TS usually do not cause pain or limit activity, they may cause cosmetic concerns and require treatment and therefore require close follow-up by the health care team.
2. There is an increased risk of osteoporosis associated with TS. Estrogen therapy and, to an extent, growth hormone therapy, can help build stronger bones that are less likely to break.
3. TS is associated with a number of dental issues, and each child requires at least an initial assessment by a dentist and possibly an orthodontist. Although growth hormone therapy does not significantly change the facial bones or the teeth, regular check-ups are recommended during the course of treatment.

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Chapter 8

Your Body's Thermostat: The Thyroid Gland

Robert Stein, MDCM, FRCPC

Normal Thyroid Gland Function

The thyroid gland is located in the front of the neck, just below the voice box and in front of the windpipe, or trachea (see Figure 1). It has two lobes that are connected by a narrow neck (isthmus).

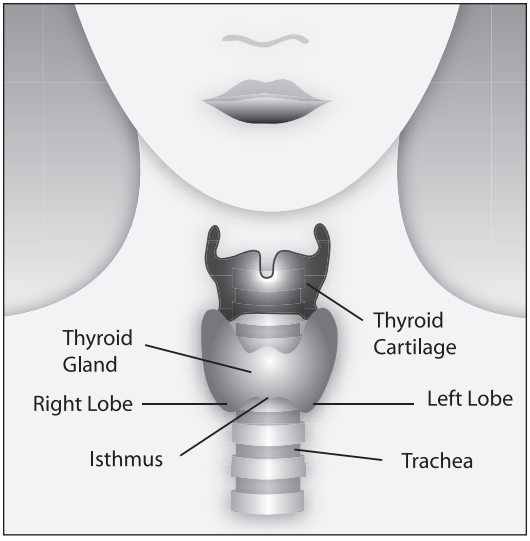

Figure 1

The function of the thyroid gland is to take up iodine from dietary sources in order to make thyroid hormones. The most important thyroid hormones are tetraiodothyronine (T4) and triiodothyronine (T3). Thyroid hormones have many important effects on the body's metabolism, as well as effects on normal growth and development. Thyroid hormone is important for the growth of the brain and nerves. It also helps to give us energy and helps to keep the body temperature healthy.

The thyroid gland is stimulated by hormones made in the brain. When thyroid hormone levels are low, the hypothalamus produces-Thyrotropin Releasing Hormone (TRH). TRH tells the pituitary gland to make Thyroid Stimulating Hormone (TSH). Higher levels of TSH cause the thyroid gland to produce more thyroid hormone (T3 and T4). It is important that all three glands work properly for there to be normal amounts of thyroid hormone in the blood –see Figure 2.

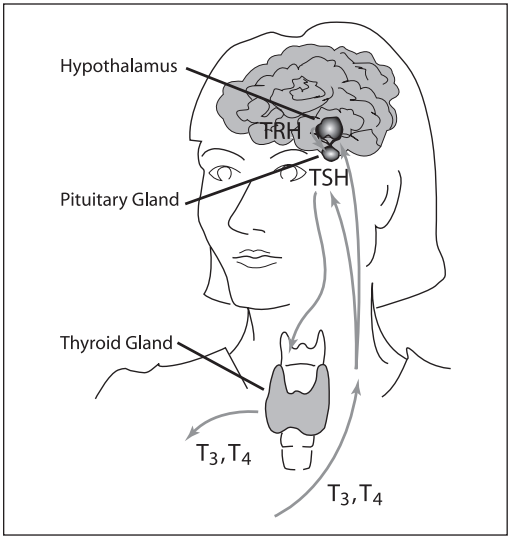

Figure 2

Thyroid disease generally results in the thyroid gland being under-active (hypothyroidism) or over-active (hyperthyroidism).

Hypothyroidism: The Under-Active Thyroid Gland

Acquired hypothyroidism refers to an under-active thyroid gland occurring in a person who is older than 1 month of age. Acquired hypothyroidism most commonly affects teenagers and adult women, with an incidence of approximately 2%. It is found in females ten times more frequently than in males. The most common cause of acquired hypothyroidism is an autoimmune thyroiditis (Hashimoto's thyroiditis). Autoimmune thyroiditis happens when the body's immune system attacks the thyroid gland and damages its ability to secrete thyroid hormone. This may occur alone as isolated hypothyroidism or along with other autoimmune diseases, such as type 1 diabetes mellitus, alopecia, Addison's disease, or rheumatoid ar-

thritis. Other causes of acquired hypothyroidism are rare and include iodine deficiency, surgical removal or irradiation of the thyroid gland, transient thyroiditis, or defects of the hypothalamus or pituitary gland.

A person with hypothyroidism may notice less energy, slow growth, weight gain, muscle weakness, constipation, and cold and dry skin. The thyroid gland may also be larger than normal.

The diagnosis of acquired hypothyroidism is typically made based on a history of symptoms as described above. The diagnosis may be confirmed with a blood test. The blood test results would show a higher TSH level and low levels of the two thyroid hormones, T3 and T4. In autoimmune hypothyroidism, thyroid antibodies may also be found in the blood.

Hyperthyroidism: The Over-Active Thyroid Gland

Hyperthyroidism refers to an over-active thyroid gland. It is less common than hypothyroidism, with an incidence of 0.5 to 1% in the adult population. As with hypothyroidism, the most common cause of an over-active thyroid gland is due to an autoimmune disorder called Graves disease. This condition also happens more often in females than in males. Graves disease may or may not be associated with other autoimmune conditions. Other causes of hyperthyroidism are rare.

A person with hyperthyroidism may have tremors, a rapid heart rate and palpitations, weight loss, muscle weakness, heat intolerance and sweating, and difficulty sleeping. The thyroid gland may also be larger than normal.

The diagnosis of hyperthyroidism is typically made based on a history of symptoms as described above. The diagnosis may be confirmed with a blood test. The blood test results would show a low TSH level and higher levels of the two thyroid hormones, T3 and T4.

Thyroid Gland Dysfunction in Turner Syndrome

It is common for girls with Turner Syndrome (TS) to develop a problem with their thyroid gland at some point during their lifetime. Hypothyroidism is present in 5 to 40% of girls and women with TS, compared to 1 to 2% of the general population. Hyperthyroidism

occurs five times more frequently in TS compared to girls and women without TS.

Etiology

The main cause of thyroid gland dysfunction appears to be autoimmune. Thyroid antibodies are commonly found in the blood of girls and women with TS. Having these thyroid antibodies means she has a greater chance of having an under-active thyroid gland, or hypothyroidism.

Clinical Features

The most common symptom of hypothyroidism in girls and women with TS is a higher body mass index when compared to those without thyroid disease. Most individuals with TS do not notice any symptoms of an under-active thyroid gland at the time of diagnosis.

Timing of Thyroid Dysfunction

The chance of having an under-active thyroid gland increases with age. It is uncommon before 10 years of age, however some reports have documented hypothyroidism in children as young as 4 years of age. It most commonly develops during the teenage and adult years of life with 3 to 4% of girls with TS developing hypothyroidism every year. Of these girls, around 50% have thyroid antibodies in their blood. By the third decade of life, 30% of TS women have hypothyroidism.

Karyotype Effects

The effect of the individual's karyotype on thyroid autoimmunity and the development of thyroid disease has been studied. Most studies report that TS individuals with a karyotype of isochromosome Xq are more likely to have thyroid antibodies compared to those with other karyotypes of TS. This means that girls and women with the isochromosome Xq karyotype have a higher chance of developing thyroid disease.

Monitoring and Screening Guidelines

In summary, it is common for girls and women with TS to have thyroid antibodies in their blood, which makes them more likely to develop a problem with an under-active thyroid gland during child-

hood and as an adult. Although it is less common, an over-active thyroid gland (Graves disease) also occurs more often in girls with TS than in the general population. As well, some data suggests that women with the isochromosome Xq karyotype also have a greater chance of developing thyroid disease.

The recommended guidelines for screening patients with TS for thyroid disease suggests that screening begin at four years of age and that patients are screened on a yearly basis. Screening should include a blood test with a TSH and free T4 level. Individuals known to have circulating thyroid antibodies may need to have blood tests more often as they are at higher risk.

Treatment of Thyroid Disorders

Hypothyroidism is treated with a small pill of thyroid hormone taken daily. A blood test should be taken approximately 6 to 8 weeks after starting the pill, and again after any dose changes are made. The dose of thyroid hormone may change over time, and once thyroid levels are in the normal range on medication, a blood test should be checked every year.

Hyperthyroidism may be treated in several ways. A common method is treatment with anti-thyroid pills such as methimazole or propylthiouracil to decrease the amount of thyroid hormone produced by the thyroid gland. Blood tests may need to taken fairly regularly to adjust the medication and also to test for side effects of the medication. In some cases, the hyperthyroidism will relapse or even evolve into hypothyroidism necessitating treatment with a thyroid hormone pill. A second common treatment involves taking radioactive iodine given as a single dose by mouth. The radioactive iodine enters the thyroid gland and gradually destroys the overactive gland. The goal of this treatment is to cause hypothyroidism with eventual treatment with a thyroid hormone pill. Advantages of radioactive iodine include (1) permanent and rapid resolution of the hyperthyroidism and associated symptoms; (2) fewer blood tests and monitoring are needed, and (3) it avoids the need for anti-thyroid medications which may have side effects. Less commonly, surgery to remove the thyroid gland is required; however, this is rarely done as the potential side effects of surgery are significant.

Key Points

- Thyroid disease can affect the body's metabolism and normal growth. Treatment is simple and easily normalizes these body functions.
- Thyroid dysfunction, both under and over-active, is more common in women with TS compared to the general population
- The main cause of thyroid dysfunction in TS is autoimmune disease.
- Thyroid dysfunction can occur at any age, but increases in frequency in the teenage years and early adulthood.
- Females with the isochromosome Xq karyotype have a greater chance of developing thyroid disease.
- Screening for thyroid disease should begin at 4 years of age and occur yearly.
- Hypothyroidism can be treated with a small thyroid hormone pill. Hyperthyroidism is usually treated with radioactive iodine, medication to suppress the overactive thyroid, or ~~less commonly, surgery~~.

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Chapter 9

When Sugar is Not So Sweet: Diabetes and the Metabolic Syndrome

Shazhan Amed, MD, FRCPC and Jill Hamilton, MD, FRCPC

Turner Syndrome (TS) has been linked to the metabolic syndrome (MS), insulin resistance and the development of type 2 diabetes mellitus (T2DM). Women with TS are 4 times more likely to develop T2DM as compared to the general population and T2DM accounts for 25% of mortality in women with TS. Therefore, preventing T2DM in women with TS is essential and requires:

- the identification of individuals at high risk for developing T2DM;
- the adoption of a healthy, active lifestyle; and
- ongoing medical surveillance for the presence of MS and T2DM.

What is type 2 diabetes and the metabolic syndrome?

Diabetes mellitus is a disease characterized by high blood glucose (sugar) that leads to symptoms such as excessive urination and thirst, weight loss, and fatigue. There are several types of diabetes, the two most common being type 1 diabetes and type 2 diabetes. This chapter will focus on type 2 diabetes mellitus (T2DM). T2DM generally evolves slowly over time, and is linked to insulin resistance. Insulin is the hormone that normally helps to regulate blood sugar. Foods eaten, such as carbohydrate, protein and fat are broken down by the intestine and absorbed into the circulation. As blood sugar rises, insulin is secreted by the pancreas, an organ located in the middle of the abdomen. Insulin then acts to promote storage of sugar into muscle, fat and liver. Insulin resistance occurs when the body does not respond as well to insulin, and higher amounts must be secreted by the pancreas in order to control blood sugars. Over time, the pancreas "exhausts" and is unable to secrete enough insulin. This leads to elevation of blood sugar and symptoms of diabetes. In the general population, certain factors have been shown to

increase the risk for the development of T2DM – see Table 1. Women with TS, even without any of the above risk factors, are at increased risk for T2DM because of the presence of insulin resistance and abnormal insulin secretion from the pancreas that are thought to be part of the syndrome. So, the presence of any of the additional risk factors listed below would further increase the risk of developing T2DM in women with TS.

TABLE 1	TABLE 2
What increases my risk for T2DM? • Weight gain or obesity • Family members with T2DM • Belonging to a high risk ethnic group (e.g. Aboriginal, African, Hispanic, South-Asian) • Insulin resistance • Diabetes in your mother while she was pregnant with you	What are the symptoms of T2DM? • Excessive thirst • Excessive urination • Fatigue • Weight loss • Fungal (such as yeast) infections involving the genital area • Excessive hunger • Blurry vision

Metabolic syndrome (MS) is also known as Syndrome X, and insulin resistance syndrome. In this chapter, the term metabolic syndrome will be used. There are many different definitions of MS and the debate continues as to which definition is the correct one. The idea of the MS arose when physicians discovered that the factors that increase risk for T2DM are the same as those that increase risk for heart attacks and strokes. These factors include obesity, insulin resistance, abnormal cholesterol levels, and high blood pressure. Simply put, MS exists in individuals with a combination of these risk factors. The diagnosis of MS helps to identify people at high risk for the development of heart disease and T2DM. Furthermore, by identifying those "at risk", physicians and patients can initiate treatment that may help to prevent T2DM and heart disease.

Why do women with Turner Syndrome have an increased risk of type 2 diabetes?

We do not know entirely why this increased risk exists. Studies have shown abnormal insulin secretion from the pancreas and increased insulin resistance in children, adolescents, and women with TS. Other clinical aspects of TS can contribute to abnormal glucose metabolism such as obesity, growth hormone therapy, ovarian failure and estrogen replacement therapy. Therefore, it is difficult

to determine whether the insulin resistance is directly linked to the chromosomal abnormality or a result of the other clinical features of TS.

Higher rates of insulin resistance and T2DM in women with TS may be due to the loss of genes located on the X chromosome that are important in both insulin secretion and insulin sensitivity. Studies looking at the effect of karyotype on glucose metabolism have been conflicting.

The Metabolic Profile in Turner Syndrome

Impaired Glucose Tolerance and Type 2 Diabetes

Abnormal glucose metabolism in females with TS appears to occur at an early age. Studies have shown insulin resistance is present very early and impaired glucose tolerance has been described in girls as young as 5 years of age. These abnormalities persist into adulthood. Fifty percent of women with TS are insulin resistant. In a review of 326 women with TS, about 30% had abnormal blood glucose levels two hours after an oral glucose test drink. Women with TS at highest risk of developing T2DM are those with obesity or a strong family history of T2DM. Additionally, the presence of other features of the metabolic syndrome including high blood pressure and abnormal cholesterol levels increase the risk for T2DM.

Abnormal Cholesterol Profile

High cholesterol levels have been reported in girls with TS as young as 11 years of age and may affect up to 50% of women with TS. Adult women with TS have high levels of both cholesterol and triglycerides. Also, they have been reported to have smaller sized cholesterol particles which are more likely to cause coronary artery disease. High levels of triglycerides in women with TS may be directly linked to the presence of insulin resistance and obesity.

Obesity

Overweight and obesity are usually defined by body mass index calculated as weight in kilograms divided by height in meters squared. There are numerous BMI calculators on the internet that can be used to easily calculate BMI. In adults, a BMI of less than 19 kg/m^2 is considered "underweight"; 19 to 25 kg/m^2 as "healthy"; 25 to 29.9 kg/m^2 to be "overweight" and greater than 30 kg/m^2 is "obese". These are

only guidelines, and it is important to take into consideration other factors as well, such as degree of muscle, bone structure, female or male, and age. Athletes will have higher BMI due to the fact that muscle weighs more than fat. In particular, the BMI of children will vary depending on their age, so normative curves have been designed that are similar to height and weight charts, so that BMI can be plotted on a chart. In general, in children, a BMI greater than 85th percentile for age and sex is considered "overweight" and greater than 95th percentile obese.

HEIGHT \ WEIGHT	31,5kg 70lbs	36,0kg 80lbs	40,5kg 90lbs	45,0kg 100lbs	49,5kg 110lbs	54,0kg 120lbs	58,5kg 130lbs	63,0kg 140lbs	67,5kg 150lbs	72,0kg 160lbs	76,5kg 170lbs	81,0kg 180lbs	85,5kg 190lbs	90,0kg 200lbs
127cm 4'2"	19.5	22.0	25.0	27.9	30.7	33.5	36.3	39.1	42.0	44.6	47.4	50.2	53.0	55.8
130cm 4'3"	18.6	21.3	24.0	26.6	29.3	32.0	34.6	37.3	39.9	42.6	45.3	47.9	50.1	53.3
132cm 4'4"	18.1	20.7	23.2	25.8	28.4	31.0	33.6	36.2	38.7	41.3	43.9	46.5	49.1	51.7
135cm 4'5"	17.3	19.8	22.2	24.7	27.2	29.6	32.1	34.6	37.0	39.5	42.0	44.4	46.9	49.4
137cm 4'6"	16.8	19.2	21.6	24.0	26.3	28.8	31.2	33.6	36.0	38.4	40.8	43.2	45.6	48.0
140cm 4'7"	16.1	18.4	20.1	22.9	25.3	27.6	29.8	32.1	34.4	36.7	39.0	41.3	43.6	45.9
142cm 4'8"	15.6	17.9	20.1	22.3	24.5	26.8	29.0	31.2	33.5	35.7	37.9	40.1	42.4	44.6
145cm 4'9"	15.0	17.1	19.3	21.4	23.5	25.7	27.8	30.0	32.1	34.2	36.3	38.5	41.0	42.8
147cm 4'10"	14.6	16.7	18.7	20.8	22.9	25.0	29.0	29.2	31.2	33.3	35.4	37.5	40.0	41.6
150cm 4'11"	14.0	16.0	18.0	20.0	22.0	24.0	26.0	28.0	30.0	32.0	34.0	36.0	38.0	40.0
152cm 5'0"	13.6	15.6	17.5	19.5	21.4	23.4	25.3	27.3	29.2	31.2	33.1	35.1	37.0	39.0
155cm 5'1"	13.1	15.0	16.9	18.7	20.6	22.5	24.3	26.2	28.1	30.0	31.8	33.7	35.6	37.5
157cm 5'2"	12.8	14.6	16.4	18.3	20.0	21.9	23.7	25.6	27.4	29.2	31.0	32.9	34.7	36.5
160cm 5'3"	12.3	14.1	15.8	17.6	19.3	21.0	22.9	24.6	26.4	28.1	30.0	31.6	33.3	35.2
163cm 5'4"	11.9	13.5	15.2	16.9	18.6	20.3	22.0	23.7	25.4	27.1	29.0	30.5	32.2	33.9
165cm 5'5"	11.6	13.2	14.9	16.5	18.2	19.8	21.5	23.1	24.8	26.4	28.1	29.8	31.4	33.1
168cm 5'6"	11.2	12.8	14.3	15.9	17.5	19.1	20.7	22.3	23.9	25.5	27.1	28.7	30.3	31.9

Underweight | Healthy Weight | Overweight | Obese

Categorization of Body Mass Index in Adult Women

Overweight and obesity occurs at a greater rate in TS as compared to the general population. Studies using BMI as a measure of overweight have shown that children and adults with TS have greater BMI scores as compared to females without TS. Being overweight can increase the severity of other medical issues faced by women with TS including insulin resistance, high blood pressure, and elevated triglyceride levels. These factors increase the risk for T2DM and coronary artery disease.

Hypertension

Hypertension, or high blood pressure, is 3 times more common in women with TS and is present in roughly 7 to 17% of children with TS. Although coarctation of the aorta and kidney disease (discussed elsewhere in this book) cause elevated blood pressure in women with TS, hypertension also occurs in the absence of these conditions. Hypertension is a contributing factor to the increased cardiovascular mortality in women with TS and therefore, should be screened for and aggressively managed.

The Effect of Growth Hormone and Estrogen Therapy

Growth Hormone Therapy

Growth hormone therapy is commonly used in the care of children with TS and has been shown to effectively increase final adult height. Growth hormone (GH) is known to have a negative effect on glucose metabolism by inducing insulin resistance. Therefore, theoretically, GH therapy can accelerate the development of diabetes in those at risk. The effect of GH therapy on glucose metabolism and insulin resistance in girls with TS has been well studied.

In general, studies have shown no change or a slight increase in insulin resistance during GH therapy with the development of T2DM being a rare occurrence. A recent study by Mazzanti (2005) looked at 46 TS patients who received roughly 10 years of GH therapy. They reported a slight increase in insulin resistance during the first 4 years of GH treatment which improved after long term therapy of 7 to 8 years. Furthermore, after the GH was stopped, the degree of insulin resistance returned to levels present before GH treatment was started. Therefore, the slight increase in insulin resistance seen during GH therapy in patients with TS is reversible. It is important to note that the presence of obesity and abnormal levels of cholesterol, specifically triglycerides, will amplify the increase in insulin resistance associated with GH therapy.

Estrogen Replacement Therapy

The effect of estrogen replacement therapy on insulin resistance and other metabolic parameters is a topic of great controversy. Firstly, the effect of estrogen replacement therapy on insulin resistance in patients with TS is not clear. Studies have been conflict-

ing with some showing a decrease in insulin resistance and others showing an increase in insulin resistance after 6 months of estrogen therapy. Additionally, no difference has been shown between oral versus transdermal estrogen replacement. Further studies of longer duration are required to resolve this issue.

The effects of estrogen replacement on other features of the metabolic syndrome have also been studied. Estrogen therapy has been shown to improve the body composition of patients with TS. However, estrogen replacement has not been shown to have a significant effect on cholesterol levels. The effect on blood pressure is inconclusive with some studies showing an improvement and others showing no effect.

Screening Recommendations

Screening recommendations for T2DM and metabolic syndrome in girls and women with TS have varied over time. Table 3 outlines the most common recommendations. Generally, awareness of the risk factors for T2DM and the features of metabolic syndrome will help alert the physician, the individual and their family of the need to make lifestyle changes initiate medical therapy if necessary in the case of overweight and obesity, T2DM, high blood pressure or high cholesterol. More importantly, individual awareness of the increased risk for T2DM, high blood pressure and high cholesterol may be motivating to adopt a healthy diet and regular physical activity. In turn, it may prevent the development of T2DM and significantly decrease the risk of heart disease.

TABLE 3

Screening Recommendations in Children and Adults with TS

	Children and Adolescents	**Adults**
Obesity	• Measurement of height, weight and BMI* calculation at each clinic visit • Close monitoring for appropriate weight gain	• Measurement of weight and BMI* calculation at each clinic visit • Close monitoring for weight gain

*BMI = Body Mass Index

**OGTT = Oral Glucose Tolerance Test – blood glucose level measured 2 hours after a glucose drink

TABLE 3		
Screening Recommendations in Children and Adults with TS		
Type 2 Diabetes	• Fasting blood glucose measurement or OGTT** in children with risk factors for T2DM (e.g. obesity, high risk ethnic group, family members with T2DM)	• Yearly fasting blood glucose measurement • OGTT** in women with risk factors for T2DM (e.g. obesity, high risk ethnic group, family members with T2DM)
High Blood Pressure	• Blood pressure check at each clinic visit from initial diagnosis • If high blood pressure established, thorough work up to rule out renal or cardiovascular causes • Aggressive management of high blood pressure if present	• Blood pressure check at each clinic visit from initial diagnosis • If high blood pressure established, thorough work up to rule out renal or cardiovascular causes • Aggressive management of high blood pressure if present
High Cholesterol	• Fasting lipid profile at least once during adolescence • Earlier if other family members with high cholesterol, T2DM, or obesity	• Yearly fasting lipid profile
*BMI = Body Mass Index **OGTT = Oral Glucose Tolerance Test – blood glucose level measured 2 hours after a glucose drink		

Prevention

The prevention of metabolic syndrome and T2DM in girls and women with TS relies heavily on the prevention of overweight and obesity. Individuals with TS have an inherently greater risk for obesity, T2DM, high blood pressure and abnormally high cholesterol levels which all add to their increased risk for heart disease. The adoption of healthy eating habits, regular physical activity and maintenance of a healthy body weight is very helpful to prevent diabetes and heart disease.

The World Health Organization has declared obesity to be a global epidemic. Consequently, a great amount of research and effort has been put into identifying strategies to prevent obesity, both in children and adults. Although the perfect prevention scheme has not been identified, recommendations to prevent obesity in the general population exist and are applicable to girls and women with TS. Table 4 reviews issues and prevention strategies that can be reviewed with your physician at regular health visits. Table 5 lists some "tips" for parents of children with TS. There are plenty of additional resources for patients and parents addressing obesity prevention, some of which are listed at the end of this chapter.

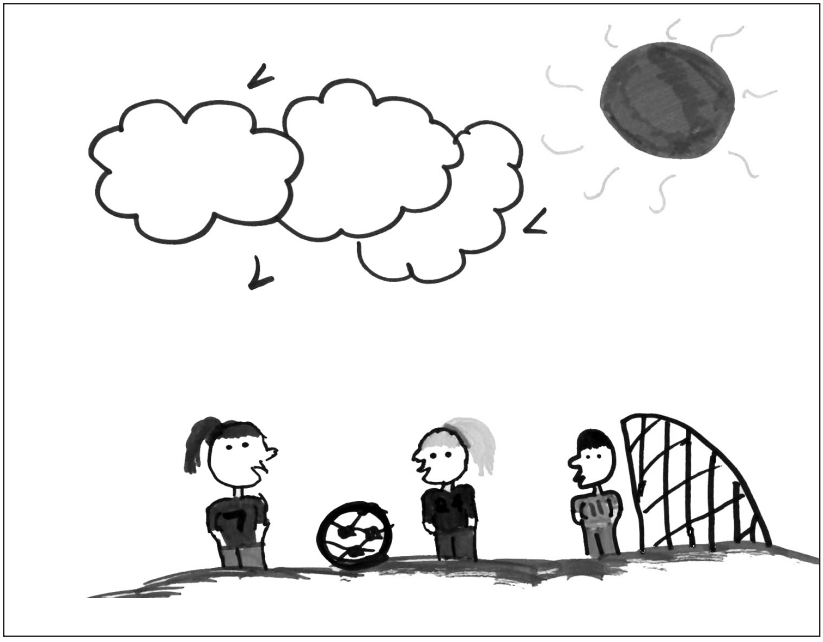

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TABLE 4
At each regular health care visit, your physician should:
1. Ask about nutritional intake and level of physical activity.
2. Promote increased intake of fibre, fruits, vegetables, and water and discourage the intake of high sugar and fat containing snacks, juices and soft drinks.
3. Encourage you or your child to incorporate physical activity into your daily life. An example of how do to this is outlined below.
a. A previously inactive child should start with 30 minutes per day of physical activity with at least 10 minutes involving vigorous-intensity exercise*. Eventually, children should participate in 90 minutes per day of total physical activity consisting of a wide variety of activities such as: sports, recreation, walking to and from school, chores, and physical education classes at school.
b. An adult should strive for at least 30 minutes of moderate-intensity exercise** for 5 or more days of the week OR 20 minutes of vigorous-intensity exercise for 3 or more days of the week.
4. Counsel you and your family to decrease sedentary activities such as watching television, playing video games, and sitting at the computer. Exposure to sedentary activities should be limited to 90 minutes per day.
* vigorous-intensity exercise – e.g. jogging, heavy yard work, high impact aerobic dancing, swimming laps, bicycling uphill
**moderate-intensity exercise – walking briskly, mowing the lawn, dancing, recreational swimming or bicycling

TABLE 5
Preventing Obesity in Your Child: Tips for Parents
1. Set a positive example by leading an active life yourself. Participate in activities that all members of the family can do together.
2. Enroll your children in age appropriate sports and recreational activities
3. Buy your children toys and equipment that require them to be active.
4. Take your children to places that require them to be active.
5. Make physical activity fun – this can include anything your child enjoys, structured or non-structured.
6. Make physical activity safe – always provide protective equipment (e.g. helmets, knee pads, wrist
7. Redu een time (television, computer, handheld games)

Summary

Children, adolescents and woman with TS are at increased risk for T2DM. This higher risk is due to the presence of insulin resistance and abnormal insulin secretion from the pancreas. Furthermore, girls and women with TS have higher rates of being overweight, having high blood pressure and high cholesterol levels. These features often appear together in the same individual and is called the

metabolic syndrome. The presence of the metabolic syndrome also increases the risk for the development of T2DM and heart disease.

Awareness of the risk factors for T2DM and metabolic syndrome, ongoing medical surveillance for their features and the early adoption of a healthy, active lifestyle are essential to prevent both T2DM and heart disease.

Key Points

- Insulin is an important hormone that helps to store sugar (glucose) in the body.
- When insulin doesn't work well, "resistance" occurs, and the pancreas must secrete more insulin to keep blood sugars in the normal range. Eventually, the pancreas cannot keep up with the demand, and blood sugars rise, leading to type 2 diabetes (T2DM).
- Women with TS have a higher risk for insulin resistance and T2DM. Other factors that increase risk for T2DM include: obesity; other family members with T2DM; belonging to a high risk ethnic group; and being born to a mother who had diabetes during pregnancy.
- Metabolic syndrome is diagnosed when an individual has a combination of: obesity; high blood pressure; glucose intolerance; and high cholesterol levels. Women with TS are at higher risk for metabolic syndrome.
- Metabolic syndrome increases the risk for both T2DM and heart disease.
- Growth hormone therapy in childhood and adolescence does not have a significant effect on insulin resistance and the risk for T2DM.
- The effect of estrogen replacement therapy on insulin resistance, cholesterol and blood pressure are not clear.
- Children, adolescents and adults with TS should be screened regularly for obesity, T2DM, high blood pressure and high cholesterol.
- Maintaining a healthy body weight is very important to prevent the metabolic syndrome, T2DM, and heart disease.

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Additional Resources About Healthy Active Living

1. The Childhood Obesity Foundation at *http://www.cofbc.ca/index.html*

2. Canada's Physical Activity Guide to Healthy Active Living at *http://www.phac-aspc.gc.ca/pau-uap/paguide/index.html*

3. Canadian Paediatric Society – Healthy Active Living for Children and Youth at *http://www.caringforkids.cps.ca/healthy/healthyactive.htm*

4. Heart and Stroke Foundation – Tips for Healthy Living at *http://ww2.heartandstroke.ca/Page.asp?PageID=35&CategoryID=3&Src=living*

Chapter 10

Gut Feelings: Gastrointestinal Tract, Liver and Kidneys

Samara Chitayat, MDCM and Karen McAssey, MD, FRCPC

This chapter will focus on several conditions that affect the gastrointestinal tract, liver, and kidneys. These conditions are:

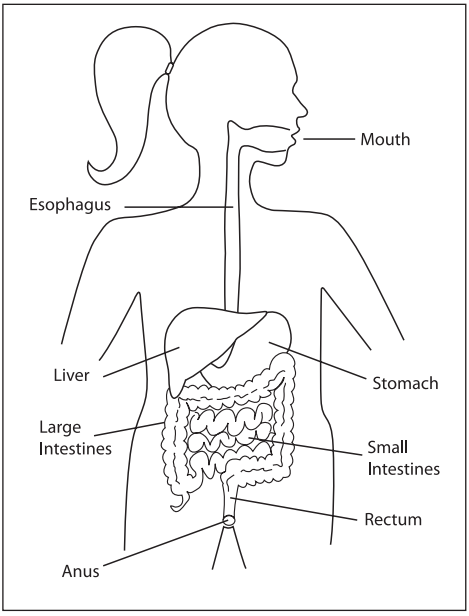
- Celiac disease
- Liver disease
- Kidney malformations

It is important for girls and women with Turner Syndrome (TS) to have a good understanding of these conditions, because they occur more commonly with TS than they do in the general population. If individuals are aware of symptoms related to these conditions, they can be brought to medical attention in a timely fashion. This may lead to an early diagnosis in those affected, therefore avoiding potential complications of the disease. Understanding why various medical tests are performed is important, because it is your body and your health!

Celiac Disease

What is the gastrointestinal tract and what does it do?

The gastrointestinal tract refers to the path leading from the mouth to the anus, whose function is to absorb nutrients from food, and excrete waste. Food enters your mouth, and travels down a tube called the "oesophagus" until it reaches the stomach. Your stomach is a muscular sac in the middle of your abdomen that helps to breakdown food. From your stomach, food travels down another tube that is divided into two parts. The first part of the tube is called "the small intestines." In the small intestines, nutrients from food are absorbed into the blood. The second part of the tube is called "the large intestines." In the large intestines, water is absorbed from food into your body. Once all of these steps are completed, stool is then passed through the rectum and out of the anus.



The Gastrointestinal Tract

What is celiac disease?

Celiac disease, sometimes called "celiac sprue" or "gluten sensitive enteropathy," is ~~a condition that affects~~ the small intestine~~s~~. Those who are affected have a permanent sensitivity to a protein called "gluten," which is found in foods such as wheat, barley, rye and oats.[1] Individuals with celiac disease must avoid these foods in order to prevent symptoms of ~~stomach~~ upset, as well as other unwanted affects on growth, bones, skin and mood.

How often does celiac disease occur in people who have Turner Syndrome?

Girls and women with TS are more likely to develop celiac disease than the general population. Approximately 4 to 6% of girls and women with TS develop celiac disease[2], compared to less than 1% of the general population.[3] Other conditions apart from TS that are associated with celiac disease include type 1 diabetes, certain thyroid diseases – diseases involving a small gland in the front of the neck that produces thyroid hormones – and Down Syndrome. First degree relatives of individuals with celiac disease are also more prone to this condition.[1]

What are symptoms of celiac disease?

Celiac disease may occur with a wide range of symptoms. Symptoms may vary from one individual to the next, as well as in one age group to another.

In infants and toddlers, symptoms may present between 6 and 24 months of age, once foods containing gluten are introduced into the diet. Symptoms in infants and toddlers may include the following:[1,4]

- Ongoing diarrhea
- Stomach bloating
- Poor appetite
- Vomiting
- Poor growth
- Weight loss or failure to gain weight appropriately for age
- Fussiness

At any age, the disease may present with: [1]

- Diarrhea and rarely, but sometimes, constipation
- Stomach bloating
- Nausea and vomiting
- Stomach pains
- Weight loss
- Decreased energy

In addition, celiac disease may affect body systems apart from the gastrointestinal system. These include:[1]

- Skin: rashes called Dermatitis Herpetiformis
- Bone: bone loss, tooth decay
- Hormones: poor growth, late puberty

How do we check for celiac disease?

Because of the increased chance of developing celiac disease, individuals with TS are tested for celiac disease every 2 to 5 years.[5] Testing begins after 4 years of age, once the individual has been on a diet that includes gluten.[5,1] This testing, or "screening," is per-

formed even though girls may be symptom-free at the time of testing. This is done to make sure that celiac disease is detected as early as possible and before bothersome symptoms develop or negative affects on the body take place. In addition, celiac disease should be suspected and tested for if any of the symptoms described earlier are present.

The screening process would begin with a visit to your health care provider (HCP). You will be asked some questions to see if you are experiencing any symptoms of celiac disease. Some questions might be: Are you having stomach pains lately? Have you been having diarrhea or constipation that is different from your usual? What has your energy level been like? Next, your height and weight will be measured to verify that there is appropriate development. Finally, you will be given a thorough physical exam to check for any signs of celiac disease. In particular, your abdomen, skin, and teeth would be examined.

The HCP would then take a blood sample. This test checks for an antibody to an enzyme made by the wall of the small intestine. Enzymes are molecules that help break down and digest foods that contain gluten. This enzyme is called Tissue Transglutaminase (TTG). High levels of TTG antibody may indicate celiac disease, and would require further investigation. Low levels of TTG antibody may require further testing in individuals with symptoms because this may represent an unusual presentation of celiac disease, or another problem with the gastrointestinal tract that needs further attention. As mentioned before, this test is performed every 2 to 5 years, starting at 4 years of age, and is only reliable if the person has been eating gluten in their diet during the previous year. If you suspect that you may have developed celiac disease, it would be wise to speak to your HCP right away before attempting a gluten-free diet in order to ensure that a correct diagnosis is made.

If your HCP thinks that you may have celiac disease, you may be sent to a specialist of the intestine, called a Gastroenterologist, who will confirm the diagnosis by examining a sample, called a biopsy, from the small intestine under a microscope. Certain changes seen in the wall of the small intestine will help confirm the diagnosis of celiac disease. Just like the TTG antibody blood test, biopsies must be done while not on a gluten-free diet.

What treatments are available for celiac disease?

The effective and only treatment available for celiac disease is a gluten-free diet.[6] The main sources of gluten in the diet, which must be eliminated, are:

- wheat
- rye
- barley
- oats

For some, this type of diet requires a major lifestyle change, since these foods are commonly eaten. Careful label reading, avoidance of certain foods, and replacing traditional breads, pastas, and cereals with gluten-free products, may be necessary. Speaking to a registered dietician is helpful in order to aid in meal planning and recipe suggestion. Speaking to other individuals with the condition and joining support groups such as the Canadian Celiac Association, is helpful as well. Follow-up with a gastroenterologist to monitor symptoms may also be needed.

The individual's response to gluten is quite variable: some people may feel very sick, while others may not feel sick at all. Despite this variability, it is important that those individuals who are diagnosed with celiac disease stay on a strict gluten-free diet to reduce the affects of long-term complications described below. A gluten-free diet will be necessary for life.

What are the long-term consequences of celiac disease?

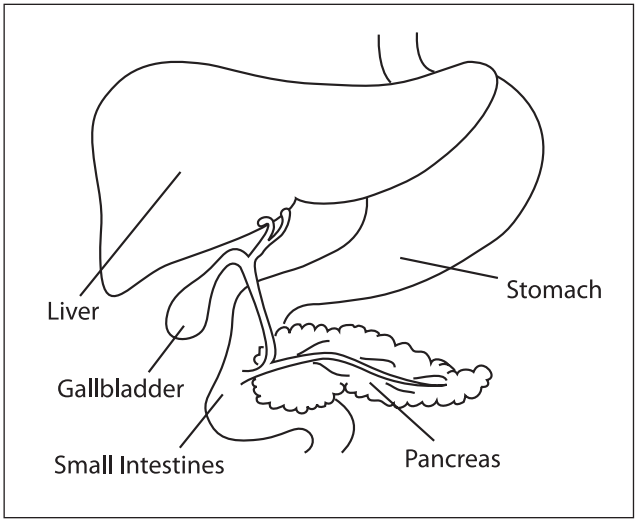
Celiac disease may lead to nutritional deficiencies, such as iron, folic acid, calcium, vitamin D, and vitamin B12. Bone loss, or osteoporosis, is common in celiac disease. Severe bone loss can cause bone pain, and make bone fracture more easily. Finally, symptoms described earlier may persist. All of these complications can be minimized by sticking to a gluten-free diet. People with celiac disease have an increased chance of developing gastrointestinal tract cancers. Though unproven, it is thought that this risk can be reduced by staying on a strict gluten-free diet, therefore eliminating ongoing inflammation of the intestines.[6]

Liver Disease

What is the liver and what does it do?

The liver is one of the largest organs in the body. It is dark red-brown in color, and is found in the upper right side of the abdomen. The liver helps us to:

- breakdown fat, as well as make fats
- store and release sugars
- make the building blocks of proteins
- make proteins that help the blood to clot
- clear the body of toxic substances
- store vitamins and minerals
- fight infection



The Liver

Turner Syndrome and Liver Function

Women with TS are six times more likely to develop liver disease compared to the general population.[7] This type of ongoing liver disease, called "cirrhosis," causes scarring of healthy parts of the liver, therefore preventing the liver from working as it should. This scarring may lead to increased blood levels of liver enzymes in some individuals with TS. In addition, it is important to know that some

girls and women with TS have elevated liver enzymes without having any damage to the liver.[8] Some studies have even shown an increase in liver enzymes in some girls with TS at a young age, but the long term significance of this is unclear. [9,10]

What are the causes of liver disease in women with Turner Syndrome?

Right now, the factors that lead to liver damage in women with TS are not precisely known.[11] Changes in the immune system leading to a process called "autoimmunity" may be involved. Autoimmunity occurs when immune cells, whose role is to fight infection, mistake your body's own cells as invaders and attack them. This "friendly fire" can involve almost any part of the body including the liver. Girls with TS are more susceptible to autoimmune conditions such as thyroid disease and celiac disease. Sometimes, these autoimmune conditions can be associated with higher levels of liver enzymes.

Other factors may also be involved in the development of liver disorders in TS. For example, fatty liver disease occurs when fat collects in the liver and causes cells to be damaged.[12] Some girls with TS are overweight and do not respond well to the hormone insulin. This is called insulin resistance. Obesity and insulin resistance increase the risk for fatty liver disease. In addition, some girls with TS have abnormalities in the formation of the blood vessels of the heart present at the time of birth. Similar abnormalities of the blood vessels of the liver may also be present at the time of birth, leading to liver damage.[13]

What are symptoms of liver disease?

Symptoms of liver disease may include:

- jaundice which is a yellow tint to the skin and eyes
- easy bruising or bleeding
- abdomen getting larger
- pain in the upper right side of the abdomen
- decreased energy
- nausea
- loss of appetite
- itchiness
- dark-colored urine – like cola, and light-colored stools – like clay

How do we check for liver disease?

Knowing that women with TS are at risk for liver disease, it has been recommended to check liver enzymes periodically, even if you are not having any symptoms.[14] In girls with TS, however, it is still uncertain when liver tests should be completed and how often. Some individuals may have liver enzyme levels that fluctuate over time, needing periodic follow-up.

Your HCP may screen for liver disease by performing a blood test which measures the level of liver enzymes in the blood. High levels of some or all of these enzymes may indicate that there is a problem with your liver. Other blood tests which help determine if the liver is working normally, include testing levels of: albumin which is a protein made by the liver; bilirubin which is a substance produced by the gallbladder which helps to absorb fats; clotting factors such as proteins made by the liver which help your blood to clot; and blood sugar.

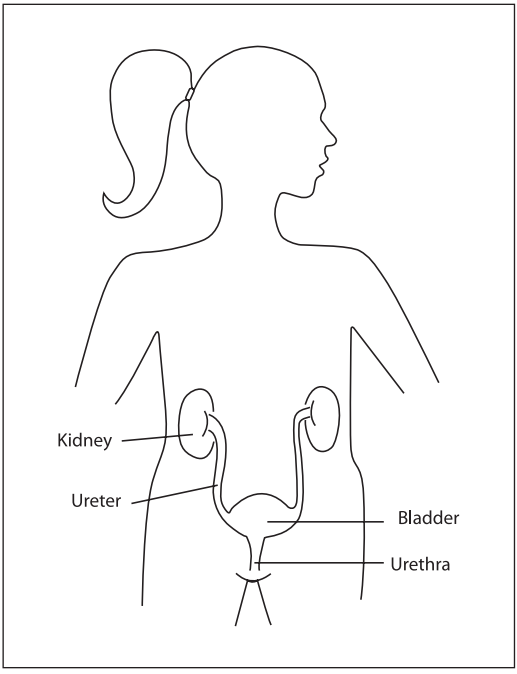
Your HCP may also send you for an ultrasound of your liver. An ultrasound is a painless procedure that takes approximately 20 minutes to complete. An ultrasound uses sound waves to take pictures of the liver.

Depending upon your symptoms, physical exam and test results, your HCP may also send you to see a gastroenterologist. If a liver problem is found, your health care team will find a treatment that is right for you.

Kidney Malformations

What are kidneys and what do they do?

Most healthy people have two kidneys. They are bean shaped organs that are positioned in the abdomen against the back, with one on either side. The main job of the kidneys is to take away waste from the blood, by making urine. Urine then passes from the kidneys through tubes called ureters until it reaches the bladder. The bladder is like a big sac that collects urine, until you need to urinate. The urine then passes out of the body through another tube called the urethra.



The Urinary Tract

Kidney Problems in Turner Syndrome

One third to one half of women with TS have some part of the kidneys or its associated structures – ureters, bladder, or urethra – shaped in an unusual way.[3] The most common types of these malformations include:[11]

- "horseshoe" kidneys where both kidneys are joined together in the shape of a "U"
- two sets of ureters that drain each kidney
- kidneys that are rotated in unusual ways or are placed higher or lower than expected
- a missing kidney
- a blockage somewhere along the path between the kidney and the bladder
- problems with the blood supply that flows to and from the kidneys

How do we check for kidney malformations?

We check for kidney malformations by performing an ultrasound of the kidneys at the time of diagnosis with TS. If abnormalities are found, further imaging and blood tests may be needed.[11,14] These tests are performed because some kidney malformations may lead to an increased chance of urinary tract infections, high blood pressure, and ongoing kidney problems. [14,15]

How do you know if you have a urinary tract infection or high blood pressure?

Signs of a urinary tract infection may include: burning on urination; increased frequency of voiding; having to void urgently; foul smelling urine; or cloudy urine. When infants and toddlers develop urinary tract infections, they may simply present with fever, irritability or vomiting. Urinary tract infections can be suspected based on symptoms, and confirmed by testing a sample of urine. Some HCPs may test for urinary tract infections at regular intervals in those girls and women with known kidney malformations, regardless of whether they are symptomatic. Repeated urinary tract infections may require a repeat ultrasound of the kidneys. High blood pressure, on the other hand, rarely presents with symptoms. For this reason, blood pressure readings are taken at each checkup.

Key Points

Celiac Disease

- Celiac disease is a condition that affects the small intestines; those affected have a permanent sensitivity to a protein called gluten.
- Girls and women with TS are more likely to develop celiac disease than the general population.
- Celiac disease may occur with a wide range of symptoms. Symptoms may vary from one individual to the next, as well as in one age group to another.
- Individuals with TS are tested for celiac disease every 2 to 5 years, with a blood test looking at an antibody to the enzyme TTG.
- The effective and only treatment available for celiac disease is a gluten-free diet. This involves the elimination of wheat, rye, barley and oats from the diet.

Liver Disease

- Women with TS are more likely to develop liver disease compared to the general population, however the factors that lead to liver damage are not precisely known.
- Your HCP may screen for liver disease by performing a blood test which measures the level of liver enzymes in the blood.

Kidney Malformations

- One third to one half of women with TS have some part of the kidneys or its associated structures shaped in an unusual way.
- We check for kidney malformations by performing an ultrasound of the kidneys at the time of diagnosis with TS.

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Chapter 11

The Right to Be Heard: Ear Health and Hearing

Johnna MacCormick, MD, FRCSC and Irena Hozjan, RN, BScN, MN

Hearing and other ear issues in Turner Syndrome (TS) have been receiving increased interest in the literature over recent years. External, or outer ear deformities, recurrent ear infections, and hearing loss all represent common ear problems of TS and illustrate the pervasive effect this genetic syndrome has on hearing and ear health. Young women with TS have a very high incidence of ear and hearing disorders and these problems have a major impact on speech and language development, learning, socialization and quality of life. For adult women with TS, some may develop significant sensorineural hearing loss in addition to a baseline conductive hearing loss over their lifetime. A survey of 143 females with TS revealed that hearing impairment rated as the fourth most serious problem associated with TS.[1] Eleven percent of adult women rated their hearing difficulties as severe, 15% as moderate and 49% as slight.[2]

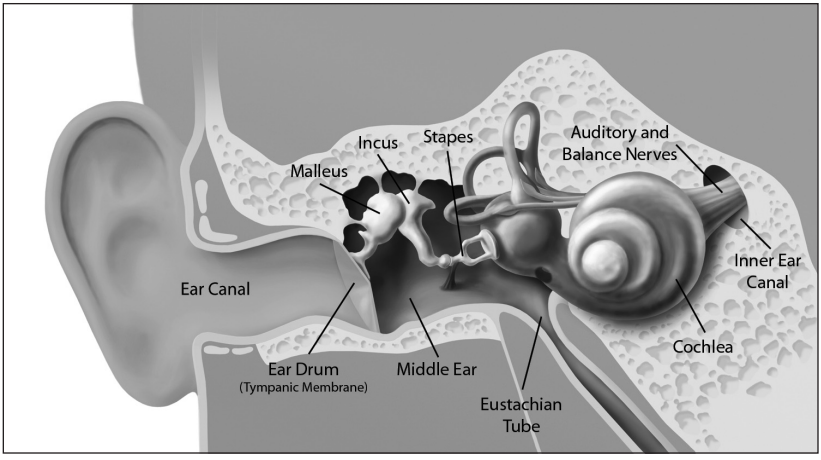

Illustration provided by Widex Canada Ltd.

The External Ear

The external, or outer ear includes the ear itself, called the pinna or auricle, and the ear canal, known as the external auditory canal. Outer ear abnormalities are relatively common in TS. The most characteristic finding in TS is low-set ears.[2,3,4] Cupped outer ears or pinnas are common, often causing protruding ears. One study shows more than half of individuals with TS have a low position of the outer ear which may be longer than normal,[5] and abnormally sloping.[6] The ear lobe may be smaller than average, although it is more commonly reported to be larger.

The external ear canal opening often appears to be flattened in a front-back direction[4] and a narrow and winding outer ear canal is commonly seen, which may make wax impaction more likely.[7]

Middle Ear

The middle ear includes the eardrum, or tympanic membrane, the three middle ear bones, called ossicles, with their associated muscles and tendons, and the eustachian tube. The middle ear space is the usually air-filled space behind the tympanic membrane.

Acute Otitis Media

At least three quarters of girls with TS have a history of recurrent middle ear infections, called acute otitis media, starting in early infancy or childhood. Of note, this is often the key historical finding that leads to the testing and diagnosis of TS in an otherwise short girl with no other signs of TS.

The first review of TS and ears was performed by Anderson, et al. in 1969. Seventy percent of 79 patients had a history of acute otitis media prior to the age of 10, with 8% persisting into and beyond puberty.[9] Other studies have confirmed these findings, with the incidence of acute otitis media found to be twice as high in TS girls as compared to unaffected girls.

Recurrent acute otitis media is defined as more than 4 episodes per year and is characterized by an inflamed and bulging tympanic membrane that is quite painful and is often associated with fever, malaise, and a pre-existing cold or flu-like illness. It is may also be associated with perforation of the tympanic membrane and drainage of blood or purulent which is a smelly, pus-like fluid.

In contrast, secretory, or serous otitis media, now called Otitis Media with Effusion (OME), refers to the chronic middle ear condition where non-infected fluid remains in the middle ear space without signs or symptoms of infection. Often this fluid may remain in the middle ear space for weeks to months following an acute otitis media infection impairing tympanic membrane and middle ear function. After its presence for 3 months, it is referred to as Chronic Otitis Media with Effusion (COME).

Due to an increase in acute otitis media and OME, a 2.5 times increased rate of insertion of ventilation tubes called grommets, is seen in girls with TS.[7] Ventilation tubes are used to allow the middle ear to effectively equalize middle ear fluid and prevent new fluid from building up behind the tympanic membrane.

Some additional middle ear findings in TS include marked tympanosclerosis, or myringosclerosis which is white scarring of the tympanic membrane, or eardrum; retraction of the eardrum, possibly even forming a pocket or sitting on the more interior middle ear bones, called incudostapediopexy; perforation or hole; and fluid.[3,7]

One serious complication of chronic middle ear disease is the development of a cholesteatoma. This is a slowly eroding and expanding skin cyst that can destroy the surrounding tissue and delicate bones of the middle ear. Cholesteatoma is a serious but treatable ear condition that can only be diagnosed by medical examination. Persistent earache, ear drainage, painful ear pressure, pain behind the ear, hearing loss, dizziness, or facial muscle weakness signals the need for evaluation by an otolaryngologist who is an Ear, Nose and Throat or ENT specialist.

Any chronic ear or middle ear conditions may cause hearing loss. Hearing loss affects normal development and social functioning of all who experience it.

Inner Ear

The inner ear contains both the organs of balance and hearing. The cochlea is fluid filled, resembles a snail's shell and is the part of the inner ear responsible for hearing.

The central auditory nervous system includes all the auditory interconnections between the auditory nerve and the auditory cortex in the brain.

Types of Hearing Loss

Hearing loss is categorized by where, or what part of, the auditory system is affected or damaged. The three basic types of hearing loss are conductive hearing loss, sensorineural hearing loss and mixed hearing loss. The degree of hearing loss refers to the severity of the loss.

Conductive Hearing Loss

Conductive hearing loss is common in TS. A conductive hearing loss results when something interferes with sound waves traveling through the outer and middle parts of the ear. It usually involves a reduction in the hearing level or in the ability to hear faint sounds because the tympanic membrane cannot receive or transmit sounds to the middle ear. Some causes of conductive hearing loss include complete blockage of the outer ear by wax called cerumen, or a foreign body; malformation of the outer ear, canal, or middle ear; infection (otitis media or otitis externa); or a collection of fluid in the middle ear. The latter is very common in young girls with TS and is particularly concerning as it is largely asymptomatic often resulting in a delayed diagnosis and treatment.

In a study of girls with TS aged 4 to 15 years, conductive hearing loss was found in 44%.[7] Of these girls, 83% suffered from recurrent middle ear problems. In girls without hearing loss, only 43% experienced recurrent ear problems. Most of the hearing losses are in the mild range.[7] Similar findings have been reported in adult women with TS.

The reason behind the higher incidence of middle ear infections in TS is likely multifactorial. In TS, a short and shallow cranial base along with a shorter, more horizontal eustachian tube predisposes to poor ventilation and drainage of the middle ear. One study of six 25-year-olds illustrates half of patients having a high arched palate.[5] A high arched palate may interfere with the ability of the muscles of the palate to open the eustachian tube to facilitate the equalizing of pressure. Large tonsils and adenoids are also noted in 38 to 48% of females with 30 to 40% of females requiring tonsillectomy or adenoidectomy.[5] Enlarged adenoids may cause obstruction at the opening of the eustachian tube, thereby preventing its opening. However removal of adenoids may exacerbate palatal dysfunc-

tion and negatively influence speech. Thus, surgery should be performed only when necessary for ear health or to improve breathing issues related to obstructive sleep apnea.

Hearing Assessments

The sounds that we hear can be measured by pitch, or frequency and loudness or intensity. We have the ability to hear sounds from very low in frequency such as 20 hertz (Hz) to as high as 20,000 Hz. In audiology the current practice is to measure hearing in the range of 250 to 8000 Hz which are the range of sounds found in normal speech. Intensity is measured in decibels (dB). Conversational speech occurs at approximately 50 dB.

An audiogram is a graph illustrating the faintest sound that an individual can hear known as their threshold, at various frequencies. It shows frequency along the horizontal axis and intensity along the vertical axis. An "O" is used to document right ear thresholds and an "X" is used to document left ear thresholds. When looking at a completed audiogram chart, any sound above the marked threshold line, towards the top of the chart, cannot usually be heard and any sound below the threshold line is audible. Thus the higher up the chart, in the 0 to 20 dB range the "O"s and "X"s are, the better your hearing.

How Hearing Loss is Categorized

Generally there are five broad categories used to represent the softest intensity that sound is perceived, or threshold, without a hearing aid.

Categories of Hearing Loss	**Degree of Hearing Loss**	**Effect of Hearing loss**
Normal range and no impairment	0 dB to 20 dB	No impairment
Mild	21 dB to 40 dB	May have trouble hearing faint or distant speech. Best experienced if you placed an index finger in each ear and had a normal conversation with someone.
Moderate	41 dB to 70 dB	Speech needs to be loud. Conversational speech in a quiet environment is very faint. The addition of background noise will make it inaudible. These children find it hard to understand speech in group situations.
Severe	71 dB to 90 dB	Can only hear loud voices one foot or less away or loud noises in the surrounding environment
Profound	91 dB or more	May be more aware of vibrations than sound.

For those that have hearing loss that crosses two levels of severity they are described in both categories, for example, mild-to-moderate or moderate-to-severe hearing loss.

Hearing loss is also referred to as either unilateral which involves only one ear, or bilateral, involving both ears. In a unilateral hearing loss, there is normal hearing in one ear and hearing loss in the other. These girls typically respond to normal conversation and environmental sounds and demonstrate normal speech and language development. However, they have problems determining where sound originates, referred to as sound localization, and may have difficulty hearing with increased background noise. The average age at which a child with unilateral hearing loss is identified is generally later than that of a child with a bilateral loss. Many of these children are not identified until they are in school. This underscores the importance of audiology assessment even when there are no overt signs of hearing loss.

Hearing Aids

Hearing aids merely amplify sound at frequencies that a person can hear. Sounds are made louder not clearer. Some sounds may actually be distorted. Although hearing aids are custom-fit to compensate for a particular amount of hearing loss they do not give an individual "normal" hearing. In fact, all sounds will be amplified as hearing aids cannot discriminate between speech and unwanted background noise.

An audiologist may prescribe hearing aids and will choose one based on the individual's hearing loss, lifestyle, educational environment and personal preferences.

All hearing aids consist of three main components: a microphone; an amplifier; and a receiver. The microphone receives the sound into the hearing aid, the amplifier makes it louder and the receiver directs the sound into the ear allowing sound to reach the eardrum via the earmold or earpiece. There are "on" and "off" switches, volume controls and a "T" switch that is used when on the telephone or when using a FM system, an assistive listening device used in classrooms.

The three general categories of hearing aids include:

- Custom hearing aids which include in-the-ear (ITE), in-the-canal (ITC) and completely in-the-canal (CIC) hearing aids.

- Behind-the-ear (BTE) hearing aids
- Body-worn hearing aids

The types of hearing aids prescribed or recommended will vary depending on the level of hearing loss, age, comfort, and preference. ITC hearing aids are housed entirely within the ear which may make them more cosmetically appealing compared to other hearing aids and are generally prescribed for mild, and at times moderate hearing losses.[12] ITE and CIC hearing aids are prescribed for mild, moderate and moderately severe hearing losses. BTE hearing aids consist of two parts – the actual hearing aid that fits snugly over and behind the individual's ear and the earmold which allows for sound to reach the eardrum. BTE hearing aids tend to be the most often used in children because the earmold material is soft and will not cause discomfort or injury to the ear during the active rough and tumble activities of childhood and it is compatible with various assistive listening devices available. Also, these soft ear molds are more easily replaced at less expense as a child grows. A sign that a child has outgrown their earmold or custom hearing aid is a squealing noise, known as feedback, coming from the hearing aid at its usual volume.[12]

From left to right, completely in-the-canal (CIC), in-the-canal (ITC), behind-the-ear (BTE), Power BTE, and Open Fit, a type of BTE, hearing aids, provided by Widex Canada Ltd.

"As my children were growing up, I used to joke that my hearing aid was a great parenting tool – I could turn it down when the noise level got out of hand, but more importantly I could turn it up when my kids had something to tell me.

I now wear two hearing aids and depend on them in much the same way I depend on my glasses for vision. It takes persistence to get a comfortable fit and the proper settings, but it is well worth the trips to the hearing aid clinic to get it right. It is frustrating sometimes since hearing aids can't

give the clarity of perfect hearing, especially in situations with a lot of background noise. I realize that I have to pay extra attention to people to make sure I get what they are saying – it helps if I can see their face (I probably lip read a bit without being aware of it) and take the time to repeat back what I think I have heard to make sure it is what was said!"

—Mary

Sensorineural Hearing Loss

A sensorineural hearing loss (SNHL) results from a problem in the innermost part of the ear, the cochlea, or in the transmission of impulses along the auditory nerve. Causes of SNHL include abnormal development of the inner part of the ear, genetic conditions, disease processes like meningitis and rubella, degenerative conditions, tumours and trauma. With a SNHL individuals may notice a decreased sensitivity to sound as well as a decrease in clarity of sound as well. With a SNHL, sound may travel to the inner ear however, the cochlea or auditory nerve may not transmit the impulse to the brain for interpretation even if sound is made sufficiently loud enough by use of amplification. There are no medical treatments for SNHLs and they are permanent. SNHL is prevalent in women with TS with a potential frequency of 50 to 75 percent depending on the study.[10,11] In women over 40 years of age, 27.3% which is approximately one third, wear hearing aids.[10] The later onset of a SNHL indicates or suggests that this is an acquired and perhaps a possible degenerative problem. Interestingly, development of a SNHL does not tend to correlate with a previous history of middle ear disease and hence the recommendation for ongoing audiological surveillance throughout life.

With SNHL there are two patterns of hearing loss generally seen.

1. Mid-Frequency Hearing Loss

Typically there is a unique dip in the hearing level in the mid-frequency range, most commonly at the 2 kHz region – see Figure 1 – which appears to be quite distinct for individuals with TS. This SNHL dip can be seen in ~~patients~~ as young as 6-years-old, and usually develops between the ages of 5 and 9.[10] This dip is more common in girls with 45,X karyotype.[7]

In a study of TS girls aged 4 to 15 years, 58% exhibit the classic dip in the mid-frequency range.[7] This is well tolerated as retention of high

and low frequencies allows for good speech discrimination. This dip tends to be bilateral and to worsen with age.[7]

The dip typically begins at a mild level, making it difficult to pick up on a regular screening audiogram. In adults, the majority of the mid-frequency losses are bilateral, with a wide range from mild, at 15 dB hearing level, to severe at 75 dB hearing level.[11]

The dip may be used to prognosticate future hearing. The dip often worsens with age, and if present may suggest an increased risk of the onset and progression of high-frequency hearing loss.[10]

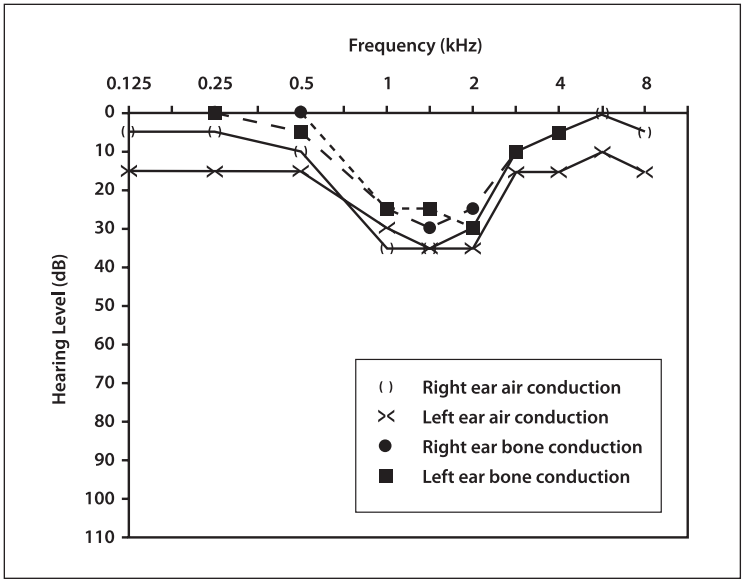

Figure 1. Audiogram showing the typical dip with the peak of 38dB in the 1.5 kHz frequency region in a 12-year-old girl with Turner Syndrome (karyotype 45,X). This girl has no subjective hearing problems. (Used by permission from A.E. Stenberg et al. Hearing Research 124 (1998) 85-90)

2. High-Frequency Hearing Loss

With increasing age, a high-frequency hearing loss may occur. It appears that women with TS have an early onset of presbycusis which is hearing loss due to the aging of the cochlea. Once this begins, it tends to deteriorate quickly.[10] A forty-year-old TS woman may be compared to the usual hearing level of a sixty-year-old unaffected female.[7] This type of hearing loss has more social implications as speech discrimination becomes more difficult. Speech discrimination describes how well you understand what you hear when

speech is loud enough to hear comfortably. Audiologists measure this in percent. For example if your speech discrimination scores are 100% then you understand everything you hear. If it is 80% you understand 4 out of every 5 words.

In some ~~patients~~ the high-frequency loss and mid-frequency dip are not mutually exclusive. Twenty-five percent of those with high-frequency loss also have a mid-frequency dip. In those with a mid-frequency dip, 11% have high-frequency loss.[11]

Mixed Hearing Loss

A mixed hearing loss is a combination of both a conductive and a sensorineural hearing loss. While the conductive component may often be treated with medication or surgery, as discussed earlier, no medical treatment is available for the sensorineural component.

This may be less common in adults with TS, as with eustachian tube maturation most of the middle ear problems resolve. Various studies report the incidence of mixed loss in adults with TS ranging from 11 to 26%.[4,9,10]

Karyotype Associations with Ear Anomalies, Disease and Hearing Loss

- Outer ear anomalies are seen more commonly with the karyotype 45,X
- The prevalence of otitis media is greater in karyotype 45,X and 46,X,i(Xq)
- Conductive hearing loss is more commonly seen in the 45,X karyotype. This hearing loss tends to be associated with a history of recurrent otitis media.
- The mid-frequency sensorineural dip is most frequently associated with karyotypes: 45,X/46,X,i(Xq); 45,X; 45,X/46,XX; and finally 45,X/46,XY. [4,10]
- The high-frequency SNHL is much more common with the karyotype 45,X.[4]
- The more severe the sensorineural hearing loss, the higher the proportion of 45,X cells,[8,11] That is, the more severe the degree of mosaicism.

How Hearing Loss Affects Speech and Language Development

The human ear is fully developed at birth and is able to respond to sounds that are quite faint or very loud. Even *in-utero* a fetus will respond to sound. Speech and language is learned from listening and interacting with others and the first 5 years are particularly critical for speech and language development. Hearing loss in childhood has potentially serious consequences for language development, acquisition, learning and socialization if it is not corrected or treated. The earlier a hearing loss occurs in a child's life the more serious and profound the effects on a child's development.

~~There~~ are numerous ways in which hearing loss affects children and their development. It causes delay in the development of receptive and expressive communication skills. Language deficits cause learning problems that impact academic achievements. Communication difficulties may lead to poor self-image and social isolation. Hearing loss may also have an impact on career choices and life plans.

For children with hearing loss, vocabulary develops more slowly and learning concrete words such as dog, hop, three and blue, are easier than more abstract words like before, after, soon, equal to, or envy. Words with multiple meanings such as rose, bat, bank, roll, or sink, may also be difficult to understand. This vocabulary gap widens with age between those children with and without hearing loss and unfortunately children with this loss tend not catch up without intervention.

Hearing loss affects sentence structure comprehension and production. Children with hearing loss tend to comprehend and use shorter and simpler sentences than children with normal hearing. Also, for those with hearing loss word endings such as *s* or *ed* may not be well heard and this may lead to misunderstandings and to misuse of verb tense, non-agreement of subject and verbs in their speech. Quiet speech sounds such as *s*, *sh*, *f*, *t* and *k* may be difficult to hear for children with hearing loss and may not be included in their own speech making it more difficult for them to be understood. Finally, a child with hearing loss may speak too loudly or not loudly enough, too high or low-pitched because she may not hear her own voice, and self-correct, when she speaks.

Hearing loss affects all levels of academic achievement and particularly reading and mathematical concepts. Children with mild to moderate hearing losses tend to experience lower grades than their normal-hearing peers unless active intervention and management is achieved. This academic achievement gap tends to widen between those with normal hearing and those with hearing loss as they progress through school.

Social problems tend to be more frequent in children with a mild to moderate hearing loss. Children with hearing losses have reported feeling isolated, without friends and unhappy in school. This is particularly significant for young girls and women with TS who may already have feelings of isolation, shyness, social anxiety and poor self-esteem without factoring in actual or evolving hearing loss.

Classroom Strategies

Communication, listening and learning for the child with a hearing loss can be extremely difficult. The child must concentrate intently and because of this may tire more easily than her normal-hearing peers.[12] Ultimately, lessons should be scheduled so that the student has time to rest and re-energize during the day. This would include periods of time in which the child is not required to focus her attention on listening.

For a student with a hearing loss, the classroom environment poses some challenges. Self-contained classrooms are preferred over those that are more open concept. Seating should be more toward the front in a traditional classroom arranged in rows to provide an unobstructed view of the teacher's face. If the student has a better ear, then this ear should be closest to and pointed toward the teacher. Next the student should be seated away from high traffic areas such as hallways, the entrance to classroom, a route to the pencil sharpener, or loud noise sources like fans or radiators. [12]

Students should be permitted to turn their chairs to view classmates during group discussions. If the class is arranged for learning centres or group discussions, then those with hearing loss may function better if seated at a round table than a rectangular table.[12] The round table will provide improved visual access to all members at the table.

Reducing unnecessary noises is conducive to both listening and learning for both the students with or without hearing loss.

> *I enjoyed figure skating for many years, but switched to hockey because it was getting progressively harder to follow the beat in the music. I do have a hearing loss and wear hearing aids everyday. This has presented challenges, but it has positive effects as well. One of my funniest elementary school memories is when my teacher forgot to turn her FM microphone off while having a personal conversation with another teacher in the hall. Our whole class heard her conversation! She was blushing pretty bad when she came back into the room and found out.*
>
> *—Larissa, age 15*

Normal Childhood Hearing Development

A Checklist from Birth to 5 Years

Birth to 6 months

- startles, cries, or awakens to loud sounds
- moves their heads, eyes, arms and legs in response to a noise or voice
- smiles when spoken to
- responds to music
- looks around to see where new sounds are coming from

7 months to 1 year

- turns or looks up when her name is called
- responds to the word "no"
- listens when spoken to
- knows common words like "cup", "shoe", "mom"
- responds to requests such as "want more", "come here"

1 to 2 years

- turns toward you when you call her name from behind
- follows simple commands
- tries to "talk" by pointing, reaching, and making noises
- knows sounds like a ringing telephone

2 to 3 years

- listens to a simple story
- follows two requests, such as "get the ball" and "put it on the table"
- tries to talk, even if you don't understand
- asks a lot of questions

3 to 4 years

- hears you when you call from another room
- listens to the television at the same volume as the rest of the family
- answers simple questions
- uses sentences with four or more words

4 to 5 years

- pays attention to a story and answers simple questions
- hears and understand most of what is said at home and at school
- talks easily with other children and adults

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Generally if your daughter is not achieving the above noted developmental milestones associated with appropriate hearing along with speech and language acquisition then it is important that she be assessed by an audiological professional. Some additional warning signs include:

- stops early babbling
- fluid draining from her ears
- pulls her ears with fever or crankiness
- has a lot of colds and ear infections
- does not respond when called
- speaks loudly, deeply, or highly pitched
- has trouble understanding a conversation in a crowded or noisy place

- frequently asks for words or phrases to be repeated
- does not understand someone unless the person is facing her
- turns up the volume of the television or radio, disturbing other listeners

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Summary

Due to the impact of ear disease on the quality of life and one's ability to interact in their external environment, early evaluation of ear health and hearing function is recommended as soon as the diagnosis of TS is made.[14] With the onset of SNHL occurring between ages 5 to 9, and the prevalence of middle ear disease causing conductive hearing loss, there may be significant impact on the acquisition of speech and language. Accordingly, starting at the time of diagnosis, girls with TS should have regular audiological monitoring on a yearly basis, and more frequently if recommended by their audiologist. Otolaryngology referrals should be considered when fluid causing hearing loss (OME) is present for more than 3 months, or if there is a history of recurrent acute otitis media.

Adult women with TS who have not had previous hearing issues should have an audiogram every 2 to 3 years or sooner if symptoms of hearing loss occur.[14]

Key Points

- Conductive hearing loss is common in TS.
- Following the initial diagnosis of TS, an audiology assessment is necessary.
- Otitis media (OM) should be managed aggressively.
- If there are any concerns about hearing, speech or language development an audiological assessment is necessary.
- A referral to an otolaryngologist (ENT specialist) should be initiated if OME is persistent or if there are repeated ear infections.
- The removal of adenoids may exacerbate palatal dysfunction in some with TS.

- TS women with a history of otitis media and hearing loss require a yearly audiology assessment.
- TS women with no history of hearing loss require surveillance every 2 to 3 years.

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Chapter 12

Seeing is Believing: Vision and the Eyes

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Abnormalities of the eyes and the visual system have not traditionally been considered important features of Turner Syndrome (TS). However, eye abnormalities in TS are not uncommon,[1] and early diagnosis is important in some cases to maximize the chance of successful treatment.[2] In this chapter, we will explore the most common eye abnormalities of TS, their diagnosis and treatment options.

Amblyopia

One of the most common, and arguably the most important, eye problems in TS is amblyopia.[1] The term amblyopia means reduced vision in a structurally normal eye.[2] Amblyopia is sometimes referred to as a "lazy eye" or a "weak eye". In amblyopia, however, the problem lies not in the eye but rather in the brain. Some of the brain cells that use information from the "lazy eye" are not formed properly. In addition, some brain cells that share information between the two eyes are not well-developed.[3]

Amblyopia has been reported to be very common in TS; a recent review suggested that more than one-quarter of persons with TS are affected.[1] It is, however, important to note that some subjects in these studies may have been evaluated specifically because an eye problem had already been noted.[4-7] As a result, amblyopia may actually be less common in TS than the studies suggest. This is consistent with our clinical experience. Amblyopia is present in about 1 to 4% of the general population.[2]

The two most common causes of amblyopia are strabismic amblyopia and ametropic amblyopia. Deprivational amblyopia, a third type of amblyopia, is much less common. These three types are explored in more detail below.

Strabismic Amblyopia

Strabismus means the eyes are misaligned, either some or all of the time.[8] Strabismic amblyopia refers to amblyopia that is associated with a misalignment of the eyes.[8] This misalignment is sometimes referred to as "eye turn" or a "squint".

Normally, a misalignment of the eyes causes double vision. However, when strabismus occurs in childhood, amblyopia acts like a defense mechanism against double vision – the brain concentrates on the information from one eye only, ignoring the other eye. As a result, the brain cells for the ignored eye fail to develop properly, reducing the vision in this eye.[3]

Fortunately, amblyopia is treatable. Strabismic amblyopia can be treated by patching the eye that is straight – see Figure 1 – to force the patient to only use the eye that would normally "turn". Another way of treating amblyopia is by using special eye drops to blur the vision of the better-seeing, straight eye.[2,8] With both treatments, the vision in the better-seeing eye is reduced, thus forcing the brain to use information from the amblyopic eye.

The timing of amblyopia diagnosis and treatment is particularly important.[2] Although some studies have shown that teenagers and even adults with amblyopia may improve the vision to some degree with treatment,[9] amblyopia becomes more difficult to treat with age.[2] Therefore, it is important that the diagnosis is made early, preferably before five years of age.[8]

Ametropic Amblyopia

In ametropic amblyopia, the image formed by the eye is out of focus. This usually occurs because the surface of the eye has an unusual shape, or because the eye is either shorter or longer than normal.[10] Ametropic amblyopia can affect one eye or both eyes. The end result is a blurry image that cannot be interpreted properly by the brain. As in strabismic amblyopia, some cells in the area of the brain that deals with vision fail to develop properly.[2] The two most common treatments for ametropic amblyopia are spectacles and patching of the better seeing eye.[8] Spectacles sharpen the image the eye sees, allowing the brain to process a higher quality image.

In both scenarios, the brain is forced to use visual information from the amblyopic eye, resulting in improved vision.[3]

Deprivational Amblyopia

The third, least common cause of amblyopia is deprivational amblyopia.[2] Deprivational amblyopia can be caused by anything that blocks light entering the eye. Examples include a droopy upper eyelid, known as "ptosis", a scar on the window of the eye, called the cornea, or an opacity of the lens in the eye, known as a "cataract". This type of amblyopia is not typical of TS.

Strabismus

Strabismus, or misalignment of the eyes, has already been discussed briefly above. Like amblyopia, it is reported to affect up to one-third of persons with TS.[1] Although in theory the eyes may be misaligned in any direction, in practice they are most commonly either turned in or turned out. When the eyes are turned in, the strabismus is called esotropia (Figure 1). When the eyes are turned out, the strabismus is referred to as exotropia (Figure 2).[8]

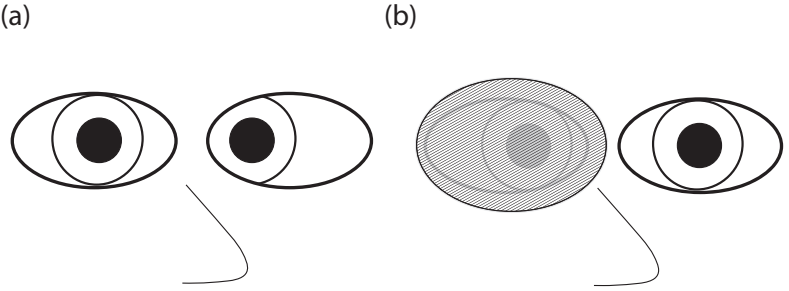

Figure 1. Esotropia and Patching

(a) In this case of esotropia, the left eye appears "turned in" while the right eye appears to be looking straight ahead. (b) The amblyopic left eye appears straight when a patch is placed over the right eye to treat the amblyopia.

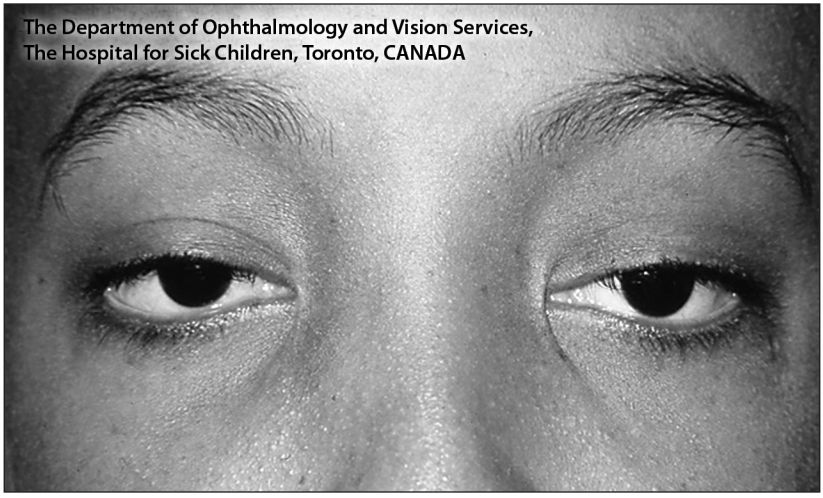

Figure 2. Exotropia and Upper Eyelid Ptosis. Note how the eyes appear "turned out" and the droopy appearance of the eyelids. (Photo courtesy of Dr. Alex V. Levin, MD.)

Strabismus is usually treated with spectacles, surgery, or both.[8] Some types of strabismus, particularly strabismus associated with esotropia and farsightedness, may be helped or even cured by spectacles.[8] Surgery for strabismus involves moving or shortening and sometimes both, the eye muscles that move the eye to weaken or strengthen their effect in a particular direction. It is important to note that strabismus surgery is a corrective, rather than cosmetic procedure.[11]

Ametropia

Ametropia refers to poor focusing of the images on the back of the eye, the retina, when it is in a relaxed state.[10] Too much focusing power results in myopia, or nearsightedness; while too little focusing power results in hyperopia, or farsightedness.[10] Normally infants are farsighted at birth. As an infant grows, the eye also grows and typically progresses from hyperopia to emmetropia, where the image on the retina is in perfect focus, or to myopia.[12] Hyperopia is present in about one-quarter of persons with TS, making it twice as common as myopia.[1] While myopia requires spectacle correction for clear distance vision, low levels of hyperopia may not require spectacle correction for distance vision, especially in young persons. However, hyperopic persons with TS may be more inclined to

require spectacle correction for near work, as some may have a reduced ability to focus on near objects.[1] In practice, ametropia rarely causes significant problems unless the spectacle prescription is very strong, or unless there is a significant difference in the prescription between the two eyes. Both these situations can result in amblyopia (described earlier), which must be treated to maximize vision.[2]

Near Vision Abnormalities

Persons with TS may have more difficulty with near visual tasks, such as reading, than the average person for a variety of reasons. First, as mentioned earlier, their ability to focus on near objects may be reduced.[1] This condition is known as accommodative insufficiency. It tends to be more troublesome for people who are farsighted, and may become obvious when large amounts of time are spent reading or doing computer work, such as upon entering university or college.[10] Symptoms may appear when reading for long periods, and include blurry vision, double vision, and headaches.[10] Treatment includes spectacles for near work, and taking brief, frequent breaks from reading or near work.[10]

Convergence insufficiency is another condition that may be more common in persons with TS than in the general population.[1] Under normal circumstances, the eyes must turn in to look at a near object. With convergence insufficiency, the eyes cannot turn in as much as they should to hold focus on a near object. The result is difficulty working at near, with symptoms similar to those caused by accommodative insufficiency. Spectacles that help relieve accommodative insufficiency may actually make convergence insufficiency worse.[10] Special eye muscle exercises prescribed by the eye doctor are often helpful in treating this problem.[10]

Nystagmus

Nystagmus is typically described as a shaking, jerking, or wobbling movement of the eyes. It has been reported to occur in 9% of persons with TS.[1] There are many types and causes of nystagmus.[13] Although nystagmus may occur without any obvious cause, it is sometimes a sign of serious eye or brain disease.[13] Anyone who is thought to have nystagmus should be examined by an ophthalmologist to first make sure that serious eye or brain diseases are ruled

out. When nystagmus is severe it may need treatment, including prescription of special glasses or surgery on the eye muscles.

Ptosis

Ptosis, pronounced "toe'-sis", refers to drooping of the upper eyelids, and has been reported to occur in about one-fifth of persons with TS – see Figure 2.[1] Ptosis has many possible causes, but when present from birth, it is usually caused by an abnormality of the muscle that raises the eyelid. In place of normal strong, elastic muscle tissue, the muscle fibers are replaced by a thin, fibrous band with little or no pulling power.[14] Depending on the severity, the drooping of the eyelids may range from barely noticeable to very obvious. It may affect one or both eyes. Some children will tilt their chin up to see under the droopy eyelids or raise their eyebrows to help lift up the eyelids. Ptosis can be particularly serious when it affects one eye more than the other, as the droopy eyelid may cause vision loss from deprivational amblyopia. Ptosis can usually be improved with surgery to raise the eyelids. Amblyopia treatment may also be necessary.[14]

Other External Eye Features

Epicanthus

A prominent fold of skin at the inner aspect of the eyes may be noted in about one-third of persons with TS, called epicanthus.[1] In the general population, epicanthus is very common in infants, and tends to decrease with time as the face grows.[15] Although a prominent epicanthus may cause the eyes to appear to be turned in, it is otherwise of no concern.[15]

Hypertelorism

Hypertelorism refers to a larger-than-normal distance between the inner walls of the two eye sockets, and is reported to occur in about 10% of persons with TS.[1] It does not have any direct effect on vision.

Downslanting Palpebral Fissures

Downslanting palpebral fissures simply refer to a downward slant of the eyelids in their outer aspect. It may occur in about 10% of persons with TS,[1] and does not pose any visual problems.

Colour Vision Problems

About 8% of persons with TS have some degree of red-green colourblindness[1] which is the same percentage of men affected in the general population.[16] This abnormality makes it difficult to distinguish reds from greens, although the severity of the problem is highly variable.[16] There is currently no treatment for this condition, but affected persons often can develop strategies for coping with their colour deficiency. Increased public awareness of colour vision deficiency is also slowly improving colour schemes in the media for those affected.[17]

Other Ocular Conditions

Many other eye conditions, including early cataracts and retinal detachment, or separation of the retina from the other layers lining the back of the eye, have been reported in persons affected by TS.[1,18,19] Although it is possible that TS is truly associated with these eye diseases, it is more likely that these conditions appear together with TS by chance alone.

Conclusions

Amblyopia and strabismus are the most important eye abnormalities commonly found in TS. Early diagnosis identifies ocular problems, can prevent progression of visual loss and increases the chance of treatment success. Fortunately, both conditions can be readily identified on routine screening examinations by a pediatrician or family physician through infancy and childhood.[20] Recent guidelines also suggest that infants with TS be evaluated by a pediatric ophthalmologist at 12 to18 months of age, and have routine eye examinations as recommended thereafter.[21]

Artist: Larissa

Key Points

- Amblyopia refers to a structurally normal eye that has reduced vision. It is a common and treatable cause of vision loss in TS.
- Strabismus is a misalignment of the eyes. It is common in TS, and is often associated with amblyopia.
- Patients with TS are more commonly farsighted than nearsighted, and may require spectacles for these or other eye abnormalities.
- Screening eye examinations in infancy and childhood are important for early identification of eye abnormalities, especially amblyopia and strabismus.

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Chapter 13

Lumps and Bumps and Other Swellings: Lymphatics and Skin Issues

Irena Hozjan, RN, BScN, MN and Jill Hamilton, MD, FRCPC

The Lymphatics

Lymph is a clear, watery, sometimes yellowish fluid derived from body tissues that contains white blood cells and circulates throughout a complex network of nodes, ducts, tissues, capillaries and vessels called the lymphatic system. The lymphatic system has three interrelated functions: (1) removal of excess fluids from body tissues; (2) absorption of fatty acids and subsequent transport of fat from the small intestine, to the circulatory system; and, (3) production and transport of immune cells such as white blood cells to protect the body against viruses and bacteria. The lymphatic system is a major part of the immune system.

Abnormal lymphatic development *in utero* seems to be responsible for the many physical traits and clinical manifestations of Turner Syndrome (TS), such as: a webbed neck; malformed ears; low hairline; shield chest; wide spaced nipples; lymphedema of hands and feet; and nail dysplasia, and tends to be more common in 45,X karyotypes than in mosaic[1].

During fetal development lymphatic tissues begin to develop by the end of the fifth week of embryonic life. Lymphatic vessels develop from lymph sacs that arise from developing veins. We develop 5 main lymphatic sacs, one on either side of the neck near the jugular veins, a single sac outside the abdominal or intestinal wall, and a pair near the back of the thigh and pelvis. In addition a structure in the lumbar region (lower back) develops called the cisterna chili. *In utero* ducts eventually develop and join these sacks to various veins that go on to form the complex interconnected circulation and drainage system of the lymphatic system. When communication between the developing lymphatic system is delayed, interrupted or absent, the jugular lymph sacs accumulate lymph

and enlarge forming a distended sac in the back and sides of the neck region. This is known as a cystic hygroma. Cystic hygromas are associated with generalized lymphedema due to small or absent peripheral lymphatic vessels. Severe cystic hygromas interfere in the appropriate development of the heart and lung tissues[2], structures and circulation *in utero* and likely accounts for the high miscarriage rate in 45,X embryos.

Due to this generalized or slowly resolving lymphedema during late gestation, a webbed neck from loose redundant skin occurs in approximately 25% of girls with born with TS[3]. This condition is secondary to lymphatic problems described above. Stretching of the thoracic cage as a result of this fetal edema may contribute to the shield like or broad chest and widely spaced nipples sometimes seen in girls with TS.

A low posterior hairline, or hair that extends onto the back of the neck, occurs in 40% of girls with TS. Bushy eyebrows and low-set ears are also associated with lymphedema. This develops secondarily to lymphedema and cell migration abnormalities. It is thought to be affected by stretching of the skin by the underlying cystic hygroma at around 10 to 12 weeks' gestation. At this time the hair follicles grow downward into the underlying tissues. The occurrence of bushy eyebrows and low-set ears in girls with TS has been attributed to the altered tension on the skin during this period of development.

Peripheral lymphedema tends to present on the tops of the hands and feet. It may be the initial presenting sign of TS and is found in approximately one-third of affected girls. At birth there may be a single crease across the ankle joint or on the palm called a palmer crease. This lymphedema tends to cause broadness of the affected hands or feet. Although lymphedema in girls with TS is occasionally severe or permanent, it tends to be transitory and improves with age particularly during infancy or early toddlerhood.[1] However lymphedema can potentially recur or occur at anytime in an individual's life particularly during puberty or with hormonal therapy such as growth hormone or ovarian hormones.[4]

Abnormal nail formation, or nail dysplasia, is found in approximately 70% of patients with TS. Peripheral lymphedema is most likely responsible for developmental abnormalities of the nails, which may

be small, narrow, thin, curved, and deeply inserted.[5] Nail dysplasia may be particularly marked in the feet, with some individuals having very small or a complete absence of toenails.

Treatment and Management of Lymphedema

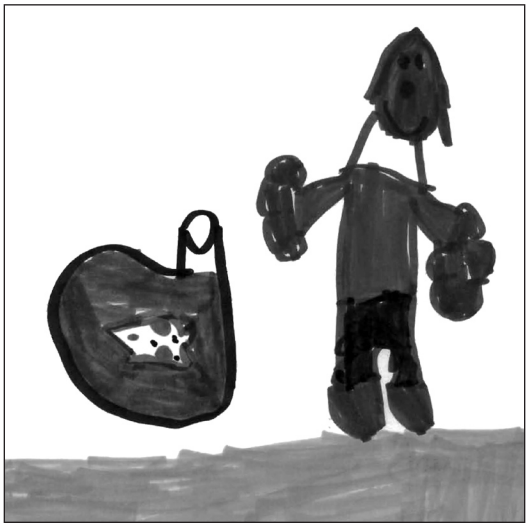
Lymphedema of the legs and feet tends to be the most common swelling problem noted by girls and women with TS. It is often described as "puffiness".

Simple lymphedema tends to be worse at the end of the day particularly when a lot of sitting, standing or walking has taken place. This type of lymphedema will improve with rest and elevation of the affected foot or feet.

Sometimes more aggressive therapy is required when prolonged swelling leads to pain, changes in skin quality, poor circulation or infections of the affected limb. Improving lymphatic flow is generally recommended by brisk walking or other exercise as well as manual massage starting from the toes and moving slowly up the foot, to the ankle, then calf and then knee. Sometimes custom-fitted compression stockings at night or elastic stockings during the day may be helpful to minimize the accumulation of lymph.[6] For more severe lymphedema, a four step intervention with attention to skin and nail care, comprehensive massage, compression bandaging and remedial exercise programming may be indicated.[4] This treatment should be carried out and supervised by a physiotherapist or physician. Some individuals may need to limit their salt intake to reduce their water retention and some may require medication for diuretic therapy to enhance fluid loss. However, long term diuretic use should be avoided because of limited benefit reported in the literature to date and potential problems associated with fluid and electrolyte imbalances.[4] Generally, vascular surgery should be avoided when possible. For more information, the National Lymphedema Network is a valuable resource.[7]

Girls with TS may have short broad feet that may prove difficult to buy and fit shoes properly. This makes them more susceptible to ingrown toenails and other toe, foot, nail, skin problems and infection. This can lead to increased risk of infection and cellulitis[8] especially when coupled with intermittent lymphedema. Intermittent lymphedema is one that comes and goes either periodically or

throughout each day. Good foot care and well-fitting shoes are important. Referral to a podiatrist for assessment or advise on nail-cutting, shoe-fitting and foot care is recommended for most girls and women with TS[8] and particularly those with ongoing issues or presence of lymphedema.



Artist: Katelynn, Age 7

Skin Issues

Dr. Henry Turner noted in his original article on TS that individuals with TS have a greater number of pigmented *nevi* known as moles, than what is seen in the general population. The cause of this increased number of *nevi* remains unknown. Some studies suggest that individuals with TS have at least 15 to 115 *nevi*. These *nevi* have generally been reported as benign melanocytic *nevi*.[9] In TS, as with the general population, *nevi* increase in number and size throughout childhood and particularly during adolescence.

While individuals with TS have an increase in the number of *nevi,* they do not have an increase in melanoma, a form of skin cancer, and this has led to theories that suggest there may be a protective tumour suppressive factor operating in TS.[10] However, some recent research has shown that increased numbers of melanocytic *nevi* are a risk factor for melanoma. Thus, it is important for any individual with a larger number of *nevi* to learn about the ABCDEs of mole

assessment[11] and have regular assessment of their *nevi* by their health care provider or dermatologist. Of note, studies have failed to confirm any pathologic or harmful impact of growth hormone or ovarian hormone replacement treatment on the number and density of melanocytic *nevi*.[12,13]

ABCDEs of Mole Assessment

A = **Asymmetry:** You should be able to imagine a line dissecting your mole or "spot" in half and creating 2 equal halves

B = **Border:** The border of a mole or spot should be consistently smooth not jagged.

C = **Colour:** A mole or lesion should have a uniform and solid colour.

D = **Diameter** or size across the middle of the spot: Most moles are less than 6mm, or ¼ inch, which is about the diameter of a pencil eraser.

E = **Enlargement:** Ordinarily moles do not change over time. A mole that suddenly grows rapidly in size or becomes elevated is suspicious.

Adapted from *http://www.cdc.gov/cancer/skin/pdf/skin95.pdf*

If your mole is asymmetric or has irregular borders or is not uniform in colour or has 2 or more colour traits or is larger than 6 mm or is enlarging then it should be assessed by a HCP and potentially biopsied.

Other warning signs include: a sore that does not heal; any change in sensation such as itchiness, tenderness, or pain; or any change in the surface of a mole such as scaliness, oozing or bleeding.

All skin requires protection. To protect against harmful ultraviolet A (UVA) and ultraviolet B (UVB) rays, sun screen with an adequate amount of Sun Protection Factor (SPF) such as 15 or greater rating is always recommended for everyday routine sun exposure and higher SPF, such as 30 or more, for more concentrated high or lengthy sun exposures. Also, avoidance of sunbathing, prolonged sun exposures and the wearing of protective clothing and hats is preferable.

Other skin conditions more commonly seen in TS are: (1) seborrheic dermatitis which is flaky, greasy, scaly skin noted most commonly on scalp, eyebrows, ear folds and skin folds; (2) blepharitis which is inflammation of the eyelids; (3) keratosis pilaris which is keratin accumulation within the hair follicles resulting in a raised rash or "rough bumps" usually found on the upper outer arms, thighs and cheeks; and (4) dry skin, dermatitis or eczema. Interestingly, a decrease in the prevalence of acne, or acne-prone skin, has also been noted with girls and women with TS.[1] These skin conditions are generally readily treatable by a health care provider or dermatologist with a variety of prescriptive and some over-the-counter solutions.

Keloids

Individuals with TS may have an increased risk of keloid scar formation called hypertrophic scarring, which is a form of exaggerated scarring. This has been noted in some case reports of poor healing or complications when a surgical approach such as plastic surgery or cardiac surgery, for correction or improvement of webbed neck, outstanding ears or other surgeries, have been completed. However, this may be more of a reflection of the sites of the surgery, being the head, neck, ears and upper chest, that may tend to scar more severely than other sites.[4] Careful discussion with a plastic surgeon about TS, cosmetic surgical correction and potential for scarring should be addressed and considered prior to any planned procedure.

Lymphedema, skin and nail issues may be common concerns facing individuals with TS. Observation and discussion of your specific issues should be addressed with your HCP to determine if any possible treatment or therapies may be of benefit.

Key Points

- Abnormal lymphatic development *in utero* seems to be responsible for the many physical traits of TS
- Lymphedema tends to present on the tops of the hands and feet. It may be the initial presenting sign of TS.
- Lymphedema tends to cause broadness of the affected hands or feet.

- Lymphedema can potentially recur or occur at anytime in an individuals life particularly during puberty or with hormonal therapy such as growth hormone or ovarian hormones.
- Referral to a podiatrist for assessment or advise on nail cutting, shoe fitting and foot care is recommended for most girls and women with TS.
- Learn about the ABCDEs of mole assessment.
- Protect you skin from harmful UVA and UVB rays.
- Individuals with TS may have an increased risk of hypertrophic scarring or keloid scar.

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Chapter 14

Reading, Writing, Arithmetic: Learning Issues Associated with Turner Syndrome

Clodagh O'Gorman, MB BCh BAO, MRCPI, MSc, Dianna Lanteigne and Joanne Rovet, PhD

Artist: Larissa - Age 7

Overview

In this chapter, we will discuss the cognitive strengths and deficits that can affect girls with Turner Syndrome (TS) as well as new insights into how abnormalities in brain structures and hormonal factors relate to the TS learning profile. The minds of girls with TS show unique functional and neurological patterns of differences. An aptitude in music and verbal areas, as well as difficulties in arithmetic and nonverbal areas, are typically seen in individuals with TS. However, commonly seen differences may not appear in all individuals. Some

individuals may be unaffected or able to overcome or compensate for limitations with learned strategies and techniques.[1] With a better understanding of the learning strengths and deficits associated with TS, everyone can be better prepared to offer the support that will lead to the success of individuals and their families.

Artist: Larissa - Age 7

General Academic Profile

Children with TS are at high risk for learning disabilities, particularly nonverbal learning disabilities and thus often require education tailored to their individual needs. Nearly half of girls with TS may have significant learning problems at school, primarily a major difficulty with arithmetic.[2] However, in 1993 less than half of these girls received special education.[3] The increased likelihood of low achievement in girls with TS suggests a lack of awareness in schools of the needs of girls with TS and that better identification and services need to be provided.[2]

Generally, individuals with TS score slightly lower than the average population on intelligence tests but their scores can range from very high IQ to very low IQ.[4] Intelligence tests usually consist of a number of different sub-tests which tap different abilities. Some of the sub-tests are categorized as measuring nonverbal or performance abilities while others are categorized as measuring verbal abilities. The first set of tasks provides a Performance IQ and the second, a Verbal IQ. Performance IQ focuses on visual tasks like perception of images and spatial reasoning, whereas Verbal IQ focuses on tasks like comprehension and vocabulary. Individuals with TS tend to have considerably lower Performance IQ scores relative to their Verbal IQ scores.[3] This uneven profile indicates that they may have difficulty with processing and understanding visual information, whereas verbal information processing is generally intact.

Academically, individuals with TS usually perform at par in reading and spelling and are often described as avid readers.[2] Some may also show a unique musical aptitude. Even girls with normal verbal abilities might have reduced fluency and articulation. In contrast, weak arithmetic skills and difficulty processing visuospatial information often poses unique challenges for girls with TS. Furthermore, selective attention and memory problems have also been observed[5] and are thought to play a role in the reduced performance of girls with TS as well.

Specific Deficits

Executive Function Deficits

The executive functions of the brain are functions that control and manage cognitive processes including conceptualization, planning, organization and fluent production. The executive system is like the "boss" of the brain because it co-ordinates and manages the rest of the brain. On tests of executive function, individuals with TS may show difficulty on tasks of planning, fluency and working memory, and focusing, whereas they perform normally on tasks involving switching focus from one task to another.[6]

Working memory is the ability to hold and manipulate information in the brain temporarily. Deficits in working memory often make it more difficult to solve complex problems with a number of steps because less information can be held at one time.

Planning is to think and prepare what you will do if a situation arises, or to envision the steps it would take to complete a concept.

Fluency is how well someone can communicate both when writing or speaking.

Attention Deficits

In general, girls with TS are attentive but may have a tendency to behave impulsively. A significant proportion of young girls with TS may appear hyperactive[7], and about 10 percent of adolescents have Attention Deficit Hyperactivity Disorder (ADHD).[8] On the other hand, during adolescence it is also common for girls with TS to become very inhibited and shy.[9]

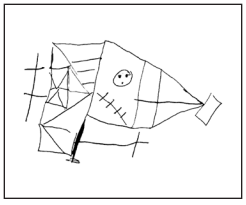
Arithmetic Difficulties

Girls with TS often show difficulty with mathematics, and by the time they reach sixth grade, many are performing two grades below their peers.[4] Their below-average performance is associated both with a delay in learning math facts and a deficit in knowing how to carry out math procedures.[1] Although children with TS are delayed in learning math facts, most eventually do catch up with their peers, and know their basic math facts unless put under time pressure.[1] However, the problem they experience with procedural knowledge, which makes carrying out a sequence of steps in math calculation very difficult, does not diminish with age. Common procedural errors include using the wrong operation, such as addition versus subtraction, and failing to separate intermediate steps.[1] Some studies indicate that in comparison to controls, children with TS exhibit more wrongly learned facts and wrong computations and make more alignment errors, which can be related to visuospatial ability, than their peers.[10]

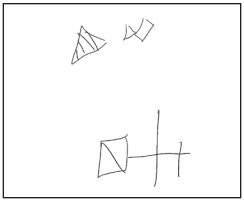
Additional arithmetic problems include difficulties with multi-digit addition and multiplication[1], most likely because as numbers increase there is greater strain on the working memory. However, difficulties with number comprehension, counting skills, number reading and writing, understanding quantities, geometry and dealing with symbols are not usually observed.[1] Not all girls with TS have a math learning disability and across time their math aptitude and abilities may change.[10]

Visuospatial Deficits

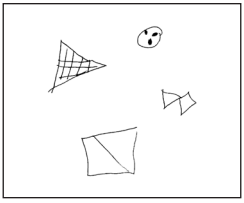
Some girls with TS have difficulty with spatial memory and copying designs. For example, when asked to copy a complicated design on a visual memory test, they may draw the design poorly, as well as forget the overall configuration, revealing their difficulty with part versus whole perception.[11]



Copying the Design



Immediate Recall



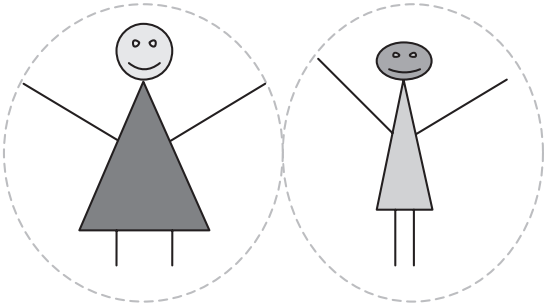
Delayed Recall

They also often have trouble with directional sense, knowing their right and left orientation, extra-personal space perception, spatial reasoning and visual sequencing.[12] Furthermore, visuospatial processing impairments are intensified when tasks require increased working memory.[12]

Directional Sense is being able to find your way around. For example, when shopping in a mall, directional sense would help you remember where your favourite stores are located, where you entered the mall, and where your car was parked in the parking lot.

Right and Left Orientation is knowing which way is right and which way is left. For example, when driving if you are following the directions to turn left and right you are using your left and right orientation to help you get to your destination.

Extra-Personal Space Perception is being able to judge the distance between you and other people or things. For example, when talking to a friend, both people use their extra-personal space perception to judge how far away they are from each other. This helps them maintain a comfortable distance between them. Girls with TS sometimes have difficulty judging the space between them and others. It is important to remember that everyone needs a different amount of personal space or "personal bubble" around them to feel comfortable. Be aware not to crowd another person's personal space because it may make them feel uncomfortable, invaded or intimidated. Every situation is different but generally staying at least one arms length away from someone when talking to them will prevent invasion of their personal space.



Spatial Reasoning is being able to interpret images, form mental images and visualize changing those images in your head. For

example, close your eyes and visualize the shape of an "S". Now visualize the "S" turning clockwise onto its side. What does it look like? To do this task you need to use spatial reasoning.

Visual Sequencing is seeing and remembering objects in order. For example, visual sequencing helps you remember the order of a series of pictures that were shown to you.

Hormonal Influences

This section reviews some of the recent research findings on hormonal influences on brain development and functioning. Some benefits of hormone therapies have been found for some individuals but due to the complex nature of hormones, it is best to speak to an endocrinologist for more information and specific advice.

Estrogen

Estrogen therapy appears to improve motor speed and cognitive performance but not visuospatial ability.[13] Spatial ability has not been related to hormonal deficiency, rather it appears to be caused by loss of genetic material on the X-chromosome.[2] Attention and executive functions may be mediated by estrogen treatment. Low-dose treatment to assist growth in younger girls may be related to improved memory ability.[14]

Growth Hormone

Growth hormone is sometimes given to girls with TS to increase height. Improved psychological well-being, a reduced number of internalizing emotional problems, and slightly improved arithmetic performance[15] have been reported in girls who are taking the therapy. The cognitive effects of growth hormone have not been thoroughly studied.

Androgen

Androgens are hormones that are predominantly responsible for the development of male characteristics but nevertheless are also important in aspects of female development. Initial studies suggest that androgen therapy might improve performance in some areas of memory.[16]

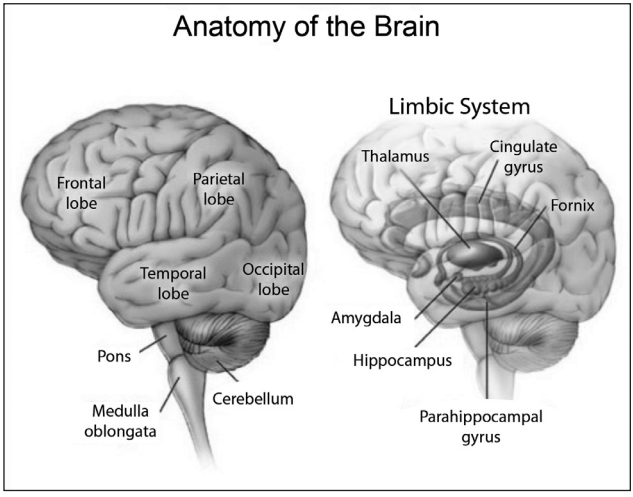
Investigating the Unique Turner Syndrome Brain

Early Research Findings

There is some evidence that brain development may be somewhat different in individuals with TS. Early studies using an electroencephalograph (EEG), a device that records electrical signals from the brain, showed neurodevelopmental abnormalities in certain specific areas of the brain in individuals with TS, for example the back of the right hemisphere which is the right side of the brain.[3] The right hemisphere is typically associated with nonverbal or visuospatial processing and the left hemisphere is associated with verbal processing. Thus, it is not surprising that abnormalities are seen in the right hemisphere because girls with TS tend to have difficulty with nonverbal processing. Also, adolescents with TS showed atypical hemispheric specialization. This means that girls with TS tend to use the left side of their brain more often on nonverbal tasks and the right side of their brain more often on verbal tasks than in girls who do not have TS.[17]

Recent Research Findings

As technology has improved over time researchers have been able to discover more specific differences in brain structures. Refer to the diagram below for the location of brain structures.



Medical illustration courtesy of Alzheimer's Disease Research, a program of the American Health Assistance Foundation.

Hippocampus is a small sea-horse shaped structure located deep within the brain. It is thought to act as the control centre for learning and remembering new information. Girls with TS have less than normal gray and white matter volume in the right hippocampus.[18] This likely relates to learning deficits.

Amygdala is a almond shaped structure in the limbic system that is thought to process and remember emotional reactions. Girls with TS have larger left-sided amygdalae than other girls.

Frontoparietal Region is near the top-middle of the brain that integrates sensory information and plays a role in determining the location of objects. Many studies show that there was impaired frontoparietal circuitry recruitment when processing visual information.[12] This means that when individuals with TS are engaging in a spatial task like remembering the location of a shape on a piece of paper, they were not able to engage the frontoparietal regions adequately. In contrast, when engaging in a verbal task, like remembering the word on a piece of paper, they performed normally. These studies often use functional magnetic resonance imaging (fMRI) which is a brain imaging technique that measures neuronal activity indirectly through the blood flow to certain areas of the brain. This technique is being used to study TS because it allows the researcher to investigate which areas of the brain are being used for various tasks.

Intraparietal Sulcus is a groove located in the parietal lobe that is thought to be critical for numerical representation. This region in the brains of girls with TS shows both structural and functional differences compared with peers.[19] Structurally, the intraparietal sulcus is shorter and less deep and shows abnormal features.[19] Functionally, when making an exact calculation, the intraparietal sulcus region shows increased activation as the size of numbers increase in people without TS[19], whereas in TS, the level of activation remained the same in the region regardless of number size.[18] The inactivation in this region suggests why it might be difficult for people with TS to do arithmetic with large numbers.

Differences in brain formation have been studied recently in girls with TS. They tend to have difficulties with global processing, "seeing the whole picture," while they have no problem with local processing, seeing individual features. For example, when asked to

describe a playground from a picture they might tell you wonderful details about the slide, the swings and the monkey bars but be unable to generate the over-arching concept that these features make up a playground. Visuospatial deficits in TS are associated with multiple brain regions including parietal eye fields, frontal eye fields, and parts of the prefrontal cortex, not just a single region.[20]

Neuroplasticity of the Brain

Contrary to what was thought in the past, the brain is not static, rather it is undergoing changes at all periods of life. This ability of the brain to change is called neuroplasticity. Therefore it might be possible to work to build up parts of the brain that are weak, similarly to how you would build your body at the gym with specially designed exercises.

Recommendations

The learning disability profile associated with TS is unique and requires special modifications or accommodations in education in many cases. In the education system, modifications and accommodations are two very different things. Modifications are expectations that change in different grade levels and the student must have an individualized education plan (IEP) created for this to be instituted. Accommodations are strategies to assist a child to be successful at the correct grade level. This encompasses such things as extra time for tests, use of a scribe, a fewer number of tasks to demonstrate competency, always having a calculator or using a computer to compose. Due to the variability in learning ability within TS, it is important for every individual to have their strengths, needs and learning style assessed and she should be monitored frequently. This section provides an overview of some of the common needs and recommendations that are beneficial to girls with TS.

At Home

First and foremost, parents must be encouraging and supportive in their daughter's learning experience. Use strengths and interests to motivate learning. If she enjoys reading, encourage her to continue, but also suggest that she tries writing stories, plays or keeping a journal. To use her verbal abilities, maybe have her read to younger children, enroll her in a local reading buddies program or tutor

English depending on her age. Allow her to interact with other children with TS and possibly attend TS camps to increase self-esteem and positive social interaction. Parents should also seek special assistance within the school system if necessary, and form an open line of communication with your daughter's teachers. Ensure that they are aware of your daughter's specific needs and progress.

Be aware of her areas of weakness at home. For example, if you give her a map to read, ensure that you supplement it with verbal directions.

Be active and aware. Become an active member of learning disabilities and TS support groups and continue to seek knowledge by attending conferences, talking with other parents and reading current material in print and on-line. Become involved in the schools by lobbying for learning aides—people that will provide educational assistance—and for additional resources for your daughter.

A parent's first priority should be parenting, not tutoring! While it is helpful when parents are actively involved in their child's learning, it is recommended that the primary teaching support is provided by someone other than the parent, such as a private tutor. This will help separate the role between support and comfort and the frustration that might be felt when learning. A tutor can help with learning strategies to remember important math skills and visual information and parents can provide the support and comfort.

At School

What is a Special Education Program?

A special education program is defined in the Education Act as an educational program that: is based on and modified by the results of continuous assessment and evaluation; and includes a plan called an Individual Education Plan (IEP). This is a legal document containing specific objectives and an outline of special education services that meet the needs of the exceptional student.

Ontario Ministry of Education

http://www.edu.gov.on.ca

General Recommendations

Have your daughter's specific learning needs assessed. An educational assessment can be performed through the school or a private psychologist. Once her specific learning style is assessed, you can discuss with school teachers and tutors exactly how to help your

daughter learn effectively. For example, if she has good oral attention and receptive language skills, she may learn better by verbal teaching strategies rather than by visual information.

Deliver information in small pieces. This is a preferred teaching method because then the working memory is not overwhelmed. Your daughter should be made aware that it is acceptable to ask questions and ask her to seek extra help if she needs it.

Reduce distractions and give frequent breaks to help keep attention. To deal with attention problems in class, it is best to try to reduce distractions and have her sit close to the teacher. Frequent breaks throughout the day may also help keep her attention. If inattention seems to be interfering consistently with learning, consider visiting a neuropsychiatrist or behavioural pediatrician.

Visuospatial Recommendations

Be aware of visual deficits when using visual aids and provide alternate learning approaches if necessary. When using visual representations, simplify them and supplement them with verbal description. Many girls with TS have difficulty in visual recall so they should be taught with verbal strategies rather than copying diagrams from a black board. This may pose difficulty in certain subjects in school that focus on complex visual configurations such as geography and science, so special accommodations should be considered. Teachers should be made aware of visual deficits if necessary so they can provide verbal descriptions and extra support to help the child comprehend.

Math Specific Recommendations

Obtain an assessment of specific needs and seek help outside of school. Math has been shown to give girls with TS great difficulty in school so an intervention and assessment of specific needs through the school and seeking private help is strongly recommended.

It is important to note that in Ontario, as in the rest of Canada, math is divided into the five areas, which include Number Sense and Numeration, Patterning and Algebra, Measurement, Geometry and Data Management. Girls with TS may have difficulties with some areas of math but are fully successful in others. For example,

geometry requires use of spatial sense and may pose greater challenges, whereas the ordered fashion of data management may appeal to their need for structure. The point is that saying girls with TS have trouble with mathematics may be too broad a statement and could potentially set the bar too low.

Train to remember math facts. Extensive training in retrieving relevant math facts automatically will help her carry out procedures because it will free up space in her working memory.

Break down a computation into a series of steps. Tasks should be broken down into sub-skills and the instructor must understand the prerequisites needed for each sub-skill. For example, you need to know how to subtract 3 numbers before you are taught how to borrow.

Tips for Teaching Math

Teach your daughter how to think of abstract problems in meaningful ways. Mnemonics and tricks for making facts and procedures easier are helpful. Once she demonstrates competence of simple computational math, provide a calculator for computational math involving multiple digits. This would be an example of an accommodation. Using graph paper when doing arithmetic problems will help them align the numbers properly. Teach her the key words in word problems that tell what kind of computation to do. Encourage her to verbalize each step and check over her work when she is done. Learning math with educational computer games can provide more motivation to do math, but make sure that it is at the appropriate level for her specific needs. Parents and tutors should work together to monitor learning progress. Parents should become knowledgeable about teaching math principles by reading parent guides that are readily available today.

Recommendation for Tests and Evaluations

Avoid her being tested on tasks that require visual memory such as the skills associated with mapping or timelines and zones in geography. Extra time should be given for tests and examinations if necessary. To reduce anxiety on timed tasks, practice doing problems with a time limit at home.

Beyond High School

Many girls with TS choose to attend post-secondary programs at colleges and universities and are successful. Most post-secondary institutions have learning disability associations that can help with academic concerns and social interactions as well as offering vital services like note-taking. Do not be afraid to seek extra support through the institution if it is needed.

If girls have a history of learning disabilities, they should register at college or university with the Office of Student Disabilities. This will ensure they get the proper compensations and extra help that they might need during their time at university. This office can help when taking exams and might be able to help get extra time or exams that are oriented to the needs of an individual. To get this help, however, either an assessment or documentation of previous learning problems is usually required. A letter from your psychologist, or pediatrician or endocrinologist might be sufficient.

A Final Note

While common themes are seen throughout the TS population there is also considerable variability among affected individuals. Thus, recommendations should be made specifically for each individual and her individual pattern of strengths and weaknesses. Teachers and parents need to be supportive and educated about the specific learning needs associated with TS and seek extra help for her in mathematics. Additionally, there should be compensations to supplement any weaknesses in visual information processing with verbal information in order to reduce frustration and lead to better educational outcomes. Research on TS will continue to provide more answers and applications with time. With the known challenges of mathematics and visuospatial abilities, parents, educators and women with TS can seek to improve educational supports so they can enhance their learning.

Key Points

- TS learning profile is usually characterized by a nonverbal learning disability, whereas verbal abilities are normal.
- Many girls have strong reading skills and are musically talented.
- Typically, girls with TS show difficulties in arithmetic and on visuospatial tasks.
- Some aspects of memory and attention may be compromised.
- The loss of X-chromosome material has been shown to exert a number of effects on brain development, including reduced size of some regions and enlargement of others.
- Brain development is also affected by reduced amount of hormones but hormone treatments can alleviate some of these effects.
- Understand your daughter's individual learning style. Engage educators to provide a learning environment to support her educational needs.

At School: 10 Tips When Teaching a Child With TS

- Try and ensure that the child is seated so that she is facing the teacher for the majority of the time.
- Make eye contact whenever possible.
- Use handouts, rather than the blackboard, when possible.
- Try and keep background noise to a minimum.
- When giving instruction start with the girl's name and finish with her name.
- Give full and detailed instructions and repeat if possible.
- Encourage the use of visual aids and colour to aid memory.
- Set realistic targets and award with lots of praise.
- If not reaching academic targets then praise helpfulness, for example.
- Listen to her concerns and treat her fairly.

Adapted and printed with permission from the United Kingdom Turner Syndrome Support Society publication "How to help your child survive and succeed at school".

At Home: 10 Tips for Parents

- Take time to help your daughter plan her day, especially if there is a change.
- State the obvious. Do not expect her to know what you want without saying it.
- Use her name at the beginning and end of a sentence when asking her to do something for you.
- Encourage the use of a diary, wall planner, calendar or notebook.
- Write a list if you want her to complete a few tasks.
- Give lots of praise and encouragement.
- Be firm and fair. Say yes and no. Some may find it difficult to respond to "in a minute" or "maybe".
- When asking her to get something for you, mention the colour and the name of the object – give more details.
- Do homework in short bursts with a break in between subjects.
- If possible allow them to complete one task before staring the next.

Adapted and printed with permission from the United Kingdom Turner Syndrome Support Society publication "How to help your child survive and succeed at school".

Special thanks to Kathy Anderson, RN, MSc, BEd, Teacher Librarian at the Hospital for Sick Children, Toronto District Elementary School, who reviewed and contributed valuable information about educational systems and curriculum.

Glossary

Alignment error is when you make a mistake when arranging numbers on a line.

Articulation is the degree to which one can communicate by pronunciation of words.

Attention is being able to focus your mental concentration on something.

Cognitive Activity is to consciously perform an intellectual activity. Examples of these activities include when you are thinking, remembering, visualizing or trying to figure out a problem.

Computations are the steps taken to calculate or figuring out a problem.

Fluency is how well someone can communicate both when writing and speaking.

Performance IQ measures visual ability using tasks that require perception of images and spatial reasoning.

Procedural Knowledge is the understanding and knowing how to apply steps to solve a problem.

Memory is remembering the past such as things learned and events in one's life.

Motor Speed is how quick you can move and react.

Multidigit Addition is the ability to add numbers that are more than one digit for example, 24+470=494.

Nonverbal Ability is how well one can understand and apply visual and spatial information. Examples include, being able to recognize where and what an object is, and visualizing objects changing position.

Verbal Ability is how well one can use and understand language. The level and ease at which someone can read, write and speak.

Verbal IQ measures language and speaking ability using tasks that require comprehension and vocabulary.

Visuospatial Information is what something looks like and where it is located. This information is used by the brain to recognize and integrate what is seen.

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Chapter 15

Why Me?
Supporting Social Skill Development

David Worling, PhD, R. Psych

Children with a diagnosis of TS often have a number of difficulties in psychosocial domains that include low self-esteem, learning disabilities, and social skills. While there is considerable variation among the psychosocial profiles of individuals with TS, they are generally seen to have problems with reading the intention of others, understanding subtleties of social language, and reading social cues. Additionally, many individuals with TS often present with a number of generalized and social anxiety features. This may translate into difficulty making and maintaining friendships which can lead to feelings of loneliness and a sense of isolation. This chapter will address some of the more common social difficulties that are characteristic of TS and outline some areas of potential intervention and support.

TS and Social Competence

"The single best childhood predictor of adult adaptation is not IQ, not school grades, and not classroom behaviour, but rather the adequacy with which the child gets along with other children".[1]

Artist: Larissa

Individuals with TS often have a number of social difficulties that relate to their neurological profiles[2] and processing difficulties. In particular, girls with TS have difficulty in interpreting social cues, which may render them vulnerable or easy targets for bul-

lying. In addition, their smaller size may make them appear younger, causing peers to "baby" or patronize them. These deficits in social skills are combined with a genuine interest in making and maintaining friendships. Without a clear understanding of their social difficulties, however, these girls often present with significantly lower self esteem and typically develop some social anxieties.[3] Helping individuals with TS to increase social understanding and comfort are seen to be critical to the overall health of this population.[4]

Individuals with TS require social interventions on a number of levels. Listed below are just a few of the areas of difficulties likely to be encountered in social contexts.

Empathy:

Ability to understand, and relate to, the feelings of others

Humour:

Understand and appreciate various forms of humour such as punch lines, slapstick, parody and sarcasm

Eye Contact:

Use eyes to read and communicate intention and emotions

Language Use:

Prosody: Flow and sound of the words

Volume: Change the volume or tone of voice as appropriate

Loquaciousness: "Too much talking" or chatter

Gestures:

Ability to read, understand and use hands and non-verbal communication to accentuate meaning of language

Proximity:

Understanding the need to assess the "correct" distance to the other person

Adaptation to Novel Situations:

Ability to generalize or transfer skills from one social situation to a slightly different one

Reciprocity:

Pragmatics: My turn to talk... then your turn... then my turn... , and so on

Interpret Meaning from Intent of Others:

Ability to understand some subtle cues through sarcasm, exaggeration and deceit

Theory of Mind:

Perspective-taking: Ability to put yourself "in the other person's shoes"

Accurate Reading of Facial Expressions:

Ability to understand the differences between a smirk, smile or neutral expression, grin for example

Difficulties with Teaching Social Skills

Given the vast number of potential areas with which TS individuals can display social difficulties it feels like a daunting task to initiate a program of change. The primary challenge of "teaching" social skills is that for most individuals, the difficulties listed above are typically learned through a slow, dynamic and almost unconscious process in early childhood. To introduce these concepts with a structured teaching approach seems to be counter-intuitive for most us. In addition, the sheer volume of individual skill sets involved in casual social interactions can be very difficult to break down into teachable lessons. If you consider reading facial cues, for example, teaching someone to distinguish between a sly, genuine, shy, or malicious grin is difficult for most children—if not, for most adults!

The second difficulty with teaching social skills to girls with TS is that while they recognize that they have social difficulties, it is very difficult for them to identify why they are having trouble. It is hard to make change to something if you're having trouble identifying the causes of their challenges!

The third challenge relates to the difficulty in finding age-appropriate materials for older children and teens. As mentioned above, many of the skills necessary for improved social understanding are often learned early in life and it can be tricky to find a system of delivery that isn't considered to be "babyish" or overly school-like for the older child.

The final challenge associated with teaching social understanding is that "social learning" is often lower on the curriculum of schools and mental health agencies. While social competence is seen to be crit-

ical to day-to-day functioning, it is rarely given a high priority within the curriculum.

There is still hope!

> *When our daughter Samantha was in grade 3 we first began to notice that she sometimes experienced difficulties in various social settings. In particular this was most evident when interacting with peers her own age or slightly older while at school. She experienced particular difficulty in reading non-verbal language such as facial expressions and body language. As a result of missing these cues she often took every spoken word literally and was oblivious to schoolyard sarcasm. This made her especially susceptible as a target for teasing or emotional bullying by her peers who were more astute in these matters.*
>
> *To compound matters further our daughter gravitated towards socializing with the younger children at her school where she sometimes took on an overly dominant or protective role over her junior peers. She now and then tended to get into their space and "mother" them, which tended to be misinterpreted by some members of the faculty at the school. Several teachers without an appreciation of TS sometimes punished her for the manner in which she interacted with these younger children.*
>
> —Lorianne, mother to Samantha, age 9

Types of Interventions

Fortunately, there are a number of interventions available for those with social skills deficits. The type of programming ranges from highly structured, manualized treatments to more casual parental and peer interventions. Listed below are some options to consider.

Adult-Mediated Individual Approaches

Board Games

A variety of games are available which centre on basic skill development and often focus on "what if...?"-type scenarios. With adult support, these games can work through potentially difficult situations in a non-threatening manner. Examples can be found at *http://www.adamlab.com/Social%20Skill%20Builder%20Board%20Games.htm*.

Play Therapy

A registered play therapist has the skills and training to help your child work through difficult social situations in a supportive play-based format. Specific anxieties and mood issues can be addressed in an effort to help ease social interactions.

Social Stories

These are designed to provide a social teaching format through stories and pictures. They allow for some positive comments and help the child work through social interactions. More information can be found at *http://www.thegraycenter.org*.

Peer-Mediated Interventions

Dyads and Triads

Setting up small group interactions with one or two peers who have well-developed social skills can be instructive and provide excellent adult-supported modeling situations. These small groups allow for direct feedback and instruction on skills such as turn-taking and sharing. Successful triads allow for the understanding of triangulation between friends.

Buddy System (Educational)

Schools will often pair a more socially mature student alongside those with social skills needs in an effort to increase social interactions and to broaden her social network.

Group

Therapeutic groups designed to address social skills deficits can be useful in providing each member with a sense of belonging and skill acquisition.

The method of delivery of social skills chosen will likely be influenced by a number of factors that include; timing and scheduling, availability of professionals, family resources, educational support, and motivation of the participant. There are some other factors to consider when choosing the appropriate intervention.

Individual social skills approaches are useful when:

- Supplementing a group program
- Social or general anxiety is too high to be in a group of peers
- Skill sets are seen to be transferable. That is, the skills that are taught can be applied to different situations or contexts.
- Helpful for children and youth with higher levels of insight and motivation
- No peer group available

Group programs are useful when the groups are well supervised and delivered in a safe and fun environment. They are often seen to be the most effective way to deliver social skills. Group treatments allow each child to experience adult-supervised direct feedback from her peers in a supportive manner. Group programs are almost always indicated unless the child's anxiety level is too high to participate in such a setting.

The social skill interventions listed above are considered to be clearly formatted and highly structured. There are also a number of less formal interventions that can be used alongside the structured ones, or in place of, if the other types are not available in your community. The interventions listed below are designed to be followed at home or school and are likely being informally followed, to some degree, by many of the families and schools.

General Recommendations

Continued Gentle "Forcing" of Social Contact with Known Peers

There is a need to gently "push" past the high degree of anxiety often associated with novel social situations. Continue parental and school "brokering" of social situations and friendships which means to continue to help with adult emotional support and direct guidance with play dates, parties and such.

Attaching Meaning to Emotion

Girls with TS often miss the slight gradations of expressed mood such as moving from slightly annoyed, to miffed, to super angry. Therefore, adults need to verbally express intent and reaction.

Use a 1 to 10 system to more clearly articulate mood, where 1 is very happy and 10 is explodingly angry. This will allow for processing of events such as, "I feel... when you... then you... and I was at an 8", or alternatively, it allows for opportunity to learn situational markers like, "I'm about a 4 right now, and do you remember how last time I went to a 7 when you continued!" Over time, a clearer understanding of emotions can emerge such as, "Oh, ya! This is what Dad looks like when he's an 8. Hmm, I need to stop and think".

Role-Plays

Provide a safe environment in which to practice, away from peers. This is best accomplished either right before the act or immediately

following. Role-plays should be judgment-free and neutral as much as possible so as to remove the sense of embarrassment or shame.

Exaggerate "poor choices" by modelling poor social choices. It allows the individual to see the outcome without being seen as mocking or making fun of her.

You will need to acclimatize her to accept constructive feedback. Not everyone is happy to receive criticism regarding their social choices so work slowly and help her understand that the intent behind your interventions is to help. Humour really helps!

Practice, Practice, Practice

All skills, including social ones, are better learned through rote and repetition. Poor choices will often be repeated, despite the best teaching, and the process of shaping the choice takes time and multiple opportunities. It's helpful to think of the social judgment errors as being neurologically based and linked to difficulties with processing.

Walk Through Social Experiences

Verbally mediate exposure prior to and following social situations. Walking your child through a potentially difficult social situation before she encounters it, and again afterwards, will reinforce the learning. Providing alternative ways to act in specific situations will allow for a broader range of responses. Help anticipate and predict the social difficulties in order to avoid the embarrassment and help her begin to predict them as well.

Video Interpretation with Scene Playback and Discussions

Watching a video together and deciphering the emotional content together can be very helpful. Just prior to, or following, an emotional scene of a movie, ask her to help identify the emotions, intent and the likely outcome. It is really important to have fun with this. Do not make it too much of a teaching scenario... or she may never watch videos with you again!

If you happen to have your camera out at a sporting or family event and you "catch" some social interactions that involve your child, it can be very instructive to go back over the event and help "dissect" the social event. For example, "I noticed you and your cousin were having some trouble yesterday. Let's take a look and see if

we can figure it out together." Again, it is critical to try and remain as judgment-free as possible and allow time for her to share her side of the story. Trying to have your child sequence the events and attribute meaning to them can be a very helpful skill to learn.

Drama

Drama programs offer an excellent way to enhance emotional expression. Dramatic representations of emotions allow for a clearer understanding of the mechanics behind facial expressions as well as clear and scripted dialogue to accompany it.

Dramatic programs provide scripts for acting or reacting to everyday social events. Although it is very difficult to do well, some improvisation practice will help to make spontaneous social reactions easier. The meaning behind the emotional reactions in drama programs is often overt and scripted and easy to follow.

Sports

Team sports are very useful for younger children as it allows for a fun and dynamic way to socialize. At a young age, most children are lacking the skills and are all there to have fun and play. As children get older, the skill levels of their peers increase alongside the social skill levels. Team sports can be difficult to maintain if your daughter's skills are seen to be significantly below that of her teammates. Individual sports that are social in nature are often encouraged at this point. Martial Arts, for example, can be a great benefit as they often involve highly scripted moves. Children are graded on their own performance, and involve a number of children of varying levels in the same class. Swimming, horseback riding, diving, skateboarding, gymnastics, golf, tennis and biking are examples of some other individual sports that may be considered.

While the emphasis of any sports program should be on skill development and exercise, the key ingredient will need to be fun! Make sure that the coach or instructor has an understanding of your child's difficulties and that the focus will include fun and social interaction.

"I think the other people in your life, they're the ones that help you cope with it [having TS]. If you have somebody in your family like a brother or sister always saying you can't play baseball, you're too short, or if you have a mom that's kind of cuddling you up and she won't let you go out and be independent, that will make it harder for you to cope. My mom didn't do that to me. I think if you have a family that lets you go out and experience life the way you should be and not trying to cuddle you and keep you as a baby (maybe because you look like a baby cause you're short), if they let you experience the life the way you should, then that will make it easier for you."

—Karen, age 28
(Kagan-Krieger S, p.187) *

Key Points

- Although the social skill difficulties encountered by girls with TS are neurologically based and likely to persist into adulthood, there are a number of effective and relatively simple interventions that can allow for change.
- Practice, practice, practice.
- Any social skill intervention should be fun and relatively non-intrusive to best predict success.
- Social skills are learned by rote and will require a number of repetitions and reminders.

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Chapter 16

You want me to do what? Taking on Adult Health Care Responsibilities and Transitioning Care

Irena Hozjan RN, BScN, MN

Most teens do not have a problem in asserting their independence when it comes to choosing their clothes, music, friends and expressing their opinions about family rules and values. However, taking responsibility for their own health care may not be high on their adolescent priority lists.

In practice, we have many adolescents that embrace and welcome the transition to adult health care and perhaps just as many that find it difficult to leave the familiarity and comfort that they have grown accustomed to with their parents and pediatric providers organizing their care.

There are many major differences between the pediatric and adult health care systems that adolescents and parents need to consider. In the pediatric setting, services are family-focused: children are seen with one or both parents; parents do most of the talking and listening; and parents take most of the responsibility for explaining to their child what the health care provider (HCP) said during the appointment. Parents tend to arrange all follow-up appointments, purchase and obtain all necessary medications, handle insurance information and ensure adequate preparation for medical procedures.[1]

In the adult health care setting, the individual is seen alone and family members are not usually invited to medical appointments. The individual is expected to book appointments, show up on time and with adequate documentation (health cards, insurance information) and preparation for medical procedures. She is expected to be a participating partner in her health care, arrive prepared with specific questions for the HCP and make decisions about treatment by herself. This can be problematic for some young women who still

require parental involvement because of the complexity or number of health issues that may be affecting them, their confidence to interact with others, their understanding of their health-related issues, or in their ability to make decisions and follow through with instructions or therapy.

Common concerns or fears often identified by both parents and teens in transitioning care are: inability to identify with a HCP who is familiar with them and their unique needs; concerns with developing rapport, trust and confidence with a new HCP[2]; adapting to new service delivery approaches and policies; and potential changes to health care coverage or insurance.

Transitions are part of normal, healthy development and occur across the life span. Health care transition has been defined as "the purposeful, planned movement of adolescents with chronic medical conditions from child-oriented to adult oriented health care.[3] The new emphasis in health care is to engage teens early on and develop their abilities to actively participate in their own care. Transition planning is a way to accomplish this.

> *"I am now a person that can stand up and it doesn't matter whether I have TS or not. I'm an adult person in my own right who takes life on its own terms and who will learn and I'm really happy about that. I feel really good about that. Because I feel I have not been bowled down by things. I have worked with them and overcome a lot of obstacles. I've learned that you don't have to be like someone else, you have to be like yourself."*
>
> —Christine, age 44, Geriatric Care Worker
> (Kagan-Krieger S, p.195) *

Adolescents with special health care needs often lag behind their peers in acquiring the life skills required to successfully manage their chronic condition. According to Whitehouse and Paone (1998) it is important to recognize that all teens regardless of their physical, cognitive or social circumstances, are confronted with similar tasks in reaching adulthood. These include:

- Development of self-esteem and a healthy identity
- Moving from parental control to autonomous behaviour and some level of independence
- Formation of a sexual identity

- Establishing meaningful social and peer relationships
- Seeking suitable education and employment

And for those with chronic health conditions:

- Looking after their own health care needs

Additionally, adolescents with chronic health conditions face the two simultaneous developmental and situational transitions of moving from adolescence to adulthood and from pediatric care to adult care along with potentially a third transition of relative health to illness.[4]

Achieving these developmental milestones and life tasks does not happen overnight. When it comes time to managing their health care, teens do not automatically become competent and fully independent on their 18th birthday. But where do we start? How do we as parents and HCPs know what we need to discuss or address? We can ask simple and direct questions that illuminate understanding or competence with certain desired skills or knowledge. A good example of such a tool is the *"How well do I manage my own health care?"* questionnaire developed by the Children's Hospital, Division of Adolescent and Young Adult Medicine, as part of Massachusetts Initiative for Youth with Disabilities. This questionnaire has been adapted to ascertain basic TS related health literacy and transition life skills. It can serve as a useful tool for families and HCPs to review what knowledge and active health care responsibilities and autonomous skills the child is already proficient in and identify areas that need to be addressed or practiced prior to transition.

How well do I manage my own health care? Please Circle Yes or No		
1. I know my height, weight, birthdate and social insurance number.	Yes	No
2. I know the name of my condition, can explain my special health care needs, and can talk and tell about my general health.	Yes	No
3. I know whom to call in the case of an emergency.	Yes	No
4. I ask questions during my medical appointments.	Yes	No
5. I respond to questions from my health care providers.	Yes	No
6. I know what kind of medical insurance I have.	Yes	No
7. I know the names of my medications and what they do.	Yes	No
8. I know how to get my prescriptions refilled.	Yes	No
9. I know where to find my medical records and health card.	Yes	No
10. I have discussed the use of tobacco, alcohol and drugs with my health care provider.	Yes	No
11. I have discussed my sexuality questions and issues with my parents or HCP.	Yes	No
12. I know how to protect myself from sexually transmitted diseases.	Yes	No
13. I know how and when to schedule an appointment (doctor, dentist, etc).	Yes	No
14. I keep a schedule of my medical appointments on a calendar.	Yes	No
15. I can get myself to my medical appointments.	Yes	No

Scoring

If you answered Yes to...

11-15 Statements: Super! You are already taking on adult responsibilities. You are ready to transition your health care and should speak with your health care providers about a transition plan.

6-10 Statements: You are on your way. You are actively taking on many responsibilities in your health care. Pick a few more responsibilities from the checklist to do for your next appointment. Also, start talking about transitions with your health care providers.

5 Statements or Fewer: Now is a good time to start taking on more responsibility in your health care. Pick one new responsibility from the checklist and practice it at your next appointment. If you need help, ask a friend, parent, nurse, social worker or doctor.

Adapted from: Children's Hospital, Division of Adolescent and Young Adult Medicine, as part of Massachusetts Initiative for Youth with Disabilities, a project of the Massachusetts Department of Public Health, as cited by Callahan, S. T., Winitzer, R. F., Kennan, P., 2001, "Transition from pediatric to adult-oriented health care: a challenge for patients with chronic diseases", Current Opinion in Pediatrics 13:310-6.

Ultimately, we all learn by observing and practicing how things are done ourselves. It is never too early or too late to start helping your daughter with the opportunities to learn the necessary health surveillance and maintenance skills through observation, participation

and networking. We can prepare our teens to meet the challenges of adult health care by using ordinary, every day teaching opportunities and lots of practice.

> *"Although it [TS] can be a painful aspect of who we are, but like I said it can also add a lot, and bring a lot of people into our lives who weren't there before. It can bring in a new acceptance of differences and a greater empathy. I think it also makes us stronger individuals…"*
>
> —Jennifer, age 23, University Student
> (Kagan-Krieger S, p.117) *

Helpful Tips to Consider

Consider your child's learning style. Some are verbal, some visual and some learn by listening or by touch or a combination of ways. We know that girls and young women with TS often learn best by practice. Try to teach and encourage anticipatory management and problem solving skills to your daughter and provide plenty of opportunity to practice. Listen to how your teen describes her special health care needs. This will serve as your starting point from which you will fill in the gaps to build knowledge and understanding. An excellent strategy is to ask your daughter what she might anticipate at her upcoming appointment with her doctor or HCP. Will she have to answer questions about her health? Has she been having any difficulty in school? Does she have any questions she would like addressed? Would she like to spend some time alone with her physician or HCP? Does she anticipate needing laboratory tests or x-rays? Does she need a refill for any of her prescription medications?

Have your daughter reflect on her health and any changes she has experienced or noticed such as recently being prescribed glasses or a hearing aid, feeling tired and lethargic, or weight changes. Has she been taking her medications regularly? Also, encourage her to reflect on her health behaviours such as physical activity and nutrition, academic accomplishments or difficulties, as well as extra-curricular activities like sports, hobbies or the theatre. This will begin to encourage and foster self-awareness and recognition of important personal and health facts that could be shared with her HCP.

Your teen may need help in knowing what to say in different situations, how much information to share and how to make the information appropriate to the situation. Giving your teen opportunities to practice using her own words in different situations may be help-

ful. For example, ask your daughter, "What if you are meeting a new doctor for the first time? What would you want to tell that person about yourself and your health?" Or, "What if you are seeing your doctor because you are having a problem or don't feel well. How would you communicate this?"

From an early age, encourage her to ask and answer questions with her health care providers (HCPs). You can help your teen to get used to this, at upcoming appointments without you immediately present. Generally, from around the age of 14 years most HCPs will spend some time alone with your daughter to facilitate her autonomy and comfort with sharing information and asking questions. Encourage her to arrange her follow-up appointments and to fill any necessary prescriptions.

Following health care appointments, have a debriefing session with your daughter. Ask her if she was happy with the appointment? Did it proceed the way she anticipated? Did she understand the discussions fully? Did she have any further questions or concerns? Did she understand the instructions she was given? Does she understand what signs or symptoms or health changes require advising an adult, parent or HCP?

Almost everyone benefits from having some sort of calendar to help them keep track of health surveillance, appointments and opportunities. This can certainly help young women with TS to have a "big picture" overview of the things that they need to do such as book an appointment, re-order prescription refills or supplies, and attend clinic appointments or support group activities. Encourage her to have, or keep the phone numbers of her HCPs and pharmacy readily available for her use. During the adult years timely health visits and follow-up tests are recommended at certain intervals as discussed in our previous chapters. At the end of this chapter is a chart that will provide an overview of these important health surveillance recommendations. At transition, review it with your daughter to anticipate and advocate for necessary assessments.

Every teen and adult needs a place to keep track of important information. A Health Card, TS Health Surveillance Passport, passport, Social Insurance Number, emergency numbers, health insurance, pharmacy and medication information, menstrual calendar are just some examples of important information. This information should

be kept available for general use, a handy reference and for emergency situations. It is good practice to have your teen take responsibility, with gentle reminders, to anticipate and bring necessary information to her appointments.

It is very important to remember that although your teen may have some special health needs, she is a typical teen, so do not forget to cover the same issues and concerns you would with any adolescent and ask your HCPs involved with your daughter to assist you with this. This becomes especially important when addressing sexuality, sexual activity and other potential risk taking behaviours (smoking, drugs and alcohol use). While it may be assumed that adolescents dealing with chronic health conditions are not engaged in risky health behaviours, the truth is that this is a myth. Numerous research studies have shown that adolescents with chronic conditions are just as likely to engage in the risk-taking behaviour of tobacco, alcohol and illegal drug use, as well as sexual activity, as their healthy counterparts and peers.[5] Interestingly, adolescents with chronic conditions are just as likely to be sexually active and as or less likely to use condoms than their peers.[6] All women should know how to protect themselves from pregnancy and sexually transmitted diseases.

Information and support organizations such as the TS Society of Canada, TS Society of the United States and the Magic Foundation provide a wealth of educational information, psychological and social supports and networking opportunities for those with TS. Early involvement in a TS support organization is strongly encouraged.[7] Do not underestimate the benefits of meeting other girls and families dealing with TS locally, nationally and internationally both for yourself, your daughter and others. Attending conferences and getting involved with your local TS Society Chapter provides a wonderful opportunity to experience and contribute to this valuable resource.

> *"TS should not stop you from doing anything you want to do. You have to find what you want to do in life and you have to go and do it. Nothing should hold you back, especially not TS. You yourself will hold you back. TS is not going to hold you back."*
>
> —Karen, age 28, works at a publishing company
> (Kagan-Krieger S, p.134) *

Find out the policies regarding age and service limits with your teen's pediatric HCPs. Age limits can be related to organizational mandates and policies as well as a HCP's expertise and comfort with providing medical services to various populations.

There continues to be some debate as to whether adult care and follow-up of women with TS should be supervised by an endocrinologist, reproductive endocrinologist, gynecologist or general practitioner. Any of these choices may be appropriate if the HCP has genuine interest and knowledge of TS and is willing to help coordinate the ongoing multi-disciplinary care required[8] and is geographically located in a convenient location to facilitate regular follow-up. In taking your daughter's history and preferences into consideration, your pediatric endocrinologist should be able to provide some recommendations and a referral to available and TS knowledgeable adult HCPs in your area or desired location.

Find out about your private health care insurance carrier's policy regarding age limit or conditions of coverage for dependent children 18 years of age and older. Loss of insurance coverage can be a significant issue if a young adult no longer qualifies as a dependent. Educate your daughter about her coverage. If possible, help her to become accustomed to filling out medication reimbursement forms and other insurance forms.

Up until the mid-1990s children under the age of 16 could not choose treatment options independently. However the minimum age for consent has been removed since the Advocacy Consent and Substitute Decisions Law Amendment Act became law in Ontario in March 1996 and the Health Care Consent Act (HCCA) replaced the Consent to Treatment Act. The importance of this is that the HCCA does not identify an age at which minors may exercise independent consent for health care because the capacity to exercise independent judgment for health care decisions varies according to the individual and complexity of the decision at hand.[9] These types of Health Care Consent Acts and legislations are found in other jurisdictions throughout Canada and the world. What does this mean? While parents have legal guardianship of their child until 18 years of age, a HCP must make a determination of capacity for a child just as they would for an adult. This includes fulfilling the 4 elements

of consent as outlined by the act which include: (1) consent must be related to treatment; (2) consent must be informed; (3) consent must be voluntary; and (4) consent must not be obtained through fraud or misrepresentation. This means that a child under the age of 16 could effectively give or withdraw consent for treatment or procedures provided they have capacity and fully understand the consequences of their decision.

Generally, this does not pose much of an issue in pediatric care when teens have capacity for consent and are considered active partners in their care, especially when their families and HCPs have used an open and honest approach to their care and health education. However problems can arise if a teen or young adult has limited capacity and this persists into adulthood (age 18 and up). It will then become necessary to explore a province's or state's legal requirements for limited guardianship or substitute decision maker status based on a young adult's unique needs. In Ontario, the Consent and Capacity Board is an independent body created by the provincial government under the HCCA to hear and determine issues and guardianship surrounding consent and capacity. For more information visit *http://www.ccboard.on.ca/scripts/english/aboutus/index.asp*.

The transition from pediatric to adult health care environments requires that adolescents, parents and HCPs work collaboratively together to ensure the best possible health outcomes and attainment of independent life skills that will help young women with TS effectively manage the transition between health care settings. The time is now. Start small, start slow but most of all start!

Key Points

Tips for Teens

- Learn about TS and how it affects you and your health.
- Ask questions of your parents and HCPs.
- Know the names of your medications and why you are taking them.
- Learn about health care issues for that which you would require urgent treatment.

- Get familiar with the names and types of specialists you will be meeting with regularly to manage your medical needs.
- Ask your parents if they have kept a file about you and your health and review it with them.
- Learn to make and keep track of appointments, your medications, and upcoming tests and test results.
- Ask questions about the advantages and possible risks of any treatments being offered or recommended.
- Talk with others who are going through what you are going through.
- Become actively involved in TS support organizations or support groups.

Tips for Parents

- Ask questions of your teen's understanding of TS and fill in the gaps.
- Begin discussions of transition at 14 to 15 years of age with both your teen and her HCP.
- Foster the development of an independent relationship between your teen and her HCP as this will provide a foundation for future relationships with adult HCPs.
- Assist and support your teen to take increasing independent responsibility for themselves and their health care.
- Discuss sexuality, safe sexual practices and address risk taking behaviours.
- Become actively involved in TS support organizations or support groups.
- Find out the policies regarding age and service limits with your teen's HCP.
- Find out about your health care insurer's policy regarding age limit or conditions of coverage after 18 years.
- Request referral to an adult HCP who is sensitive to and knowledgeable of the special health care needs of TS.

"As Tyra Banks so often says, 'So what!' So what if we have Turners and are shorter than our peers? So what if you're not that skinny blonde Barbie doll who's queen bee at school? Does it really matter? Should that stop you from following your dreams? Some people think I'm crazy wanting to go to medical school because of my hearing loss, but I am still going to do my best to get there because that is my dream. I've never let Turners stop me before, and I don't ever plan to."

—Larissa, age 15

Adult Health Surveillance in Turner Syndrome

At Transition know your:

Karyotype _____ Surgeries _____ Cardiac Status _____ SBE? _____

Allergies _____ _____ Hearing Status _____

_____ _____ Kidney Status _____

Medications: Thyroid _____ Estrogen/OCP _____ Other _____

Weight _____ Height _____ BMI _____ _____

All medical problems that presented and were managed in childhood should be actively followed in adult care.

	Transition	Yearly	1-2 years	2-3 years	3-5 years	Comments / Recommendations
Wellness and Mental Health	✓	✓				Psychological / social support and assessment of general well-being, body image, stress and coping.
Healthy Lifestyle and Behaviours	✓	✓				Review of diet, physical activity, risk-taking behaviours (smoking, alcohol, recreational drug use).
Sexuality, Sexual and Reproductive Health	✓	✓				Ovarian hormone replacement (OHR). Consistent estrogen replacement is required through to the normal age of menopause. Contraception, review of safe sex practices and prevention of sexually transmitted diseases (STDs). Reproductive health and fertility options. Breast and pelvic health review.

	Transition	Yearly	1-2 years	2-3 years	3-5 years	Comments / Recommendations
Physical Exam	✓	✓				
Breast and Pelvic (PAP) Examination			✓			Breast and pelvic examinations same for regular population.
Blood Pressure	✓	✓				Blood pressure monitoring should occur at least once per year and more often if borderline. Hypertension should be treated aggressively.
BMI (weight)	✓	✓				A BMI of less than 25 kg/m^2 is recommended.
Lymphedema	✓	✓				Referral to a podiatrist for advise on nail cutting, shoe fitting and foot care is recommended for women with lymphedema.
Mole Assessment	✓	✓				ABCDEs assessment of moles.
Screening blood work for the following conditions:						
Thyroid Disease (TSH, free T4 and anti-TPO antibodies)	✓	✓				Hypothyroidism is common in adult women with TS, particularly in their 3rd decade.
Diabetes Random / fasting blood glucose, urinalysis, and +/- OGTT	✓	✓				Diabetes is 2 to 4 times more common in those with TS and onset is earlier than in the general population. Signs and symptoms of diabetes are increased drinking (polydipsia) and urination (polyuria).
Kidney Health (BUN and creatinine)		✓				If there is a history of repeated bladder or kidney infections, yearly testing is indicated.
High Cholesterol Fasting lipids (cholesterol, LDL, HDL, triglycerides)		✓				If cholesterol levels are elevated aggressive management and change of lifestyle (improved nutritional intake, decreased portion sizes, weight loss and increased regular physical activity) is recommended.

	Transition	Yearly	1-2 years	2-3 years	3-5 years	Comments / Recommendations
Celiac Disease TTG, IgA antibodies				✓ (every 2 - 5 years)		Women with TS have increased risk for celiac disease. If anemic or low iron stores then repeat testing.
Cardiac Evaluation *		✓ (with heart abnormalities)			✓	Screening for aortic dilatation, and dissection. If no cardiac abnormalities rescreen every 3 to 5 years.
ECG		✓			✓	* A complete and thorough cardiac assessment including an ECG, ECHO or cardiac MRI is required if spontaneous or assisted pregnancy is being attempted or contemplated. Medical alert bracelet if aortic disease/dissection risk.
ECHO		✓			✓	
CT / MRI if necessary		✓			✓	
Need for precautionary antibiotics (SBE prophylaxis)		✓				Review need for precautionary antibiotic use prior to any invasive procedures (dental work, surgery, other testing).
Vision			✓			Regular eye examinations and referral to ophthalmologist as needed are recommended.
Hearing (audiology)		✓ (with hearing loss)		✓ (without documented hearing loss)		Hearing aids should be used as soon as they are recommended.
DXA (bone density study)	✓				✓	Screening for osteoporosis and low bone mineral density. Good dietary or supplementary intake of calcium and vitamin D is strongly recommended as is regular exercise and weight resistance activities.

Adapted from Recommendations from Bondy CA (for the Turner Syndrome Consensus Study Group). Care of Girls and Women with Turner Syndrome: A Guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab 2007;92(1): 10-25.

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* Susan Kagan-Krieger, "The struggle to understand oneself as a woman: Stress, coping and the psychological development of women with Turner Syndrome" (EdD dissertation, University of Toronto, 1998).

Resource List

Websites

Turner Syndrome

Turner Syndrome Society of Canada
www.turnersyndrome.ca

BC Turner Syndrome Network
www.bctsnetwork.com 

Turner Syndrome Society of the United States
www.turnersyndrome.org

Turner Syndrome Support Society UK
www.tss.org.uk

Turner Syndrome Society of Australia
www.turnersyndrome.org.au

Turner Syndrome Research Today: Symptoms, Causes, Chromosomes, Prognosis…
http://turnersyndrome.researchtoday.net

Free monthly on-line journal that collates and summarizes the latest research journal articles on Turner Syndrome. Articles summarized are from medical journals and are usually highly technical and directed at a scientific audience. Abstracts are free; however there is a charge for full articles.

Other Health-Related Websites

Canadian Diabetes Association
www.diabetes.ca

Canadian Hard of Hearing Association
www.chha.ca

Canadian Hearing Society
www.chs.ca

Canadian National Institute for the Blind
www.cnib.ca

Canadian Liver Foundation
www.liver.ca

Kidney Foundation of Canada
www.kidney.ca

Canadian Society of Intestinal Research
www.badgut.com

Heart and Stroke Foundation of Canada
www.heartandstroke.ca

PediHeart
www.pediheart.org

International Society of Adult Congenital Cardiac Disease: Especially for Patients
www.isaccd.org/patients/index.php

The Learning Disabilities Association of Canada
www.ldac-taac.ca

Osteoporosis Society of Canada
www.osteoporosis.ca

Canadian Orthopaedic Foundation
www.canorth.org

Thyroid Foundation of Canada
www.thyroid.ca

Canadian Institute of Child Health
www.cich.ca

Canada's Physical Activity Guide to Healthy Active Living
www.phac-aspc.gc.ca/pau-uap/paguide/index.html

Canadian Paediatric Society – Healthy Active Living for Children and Youth
www.caringforkids.cps.ca/healthy/healthyactive.htm

About Kids Health
www.aboutkidshealth.ca

Nonverbal Learning Disorders Websites

Nonverbal Learning Disorders Association
www.nlda.org

NLD on the Web
www.nldontheweb.org

Maple Leaf Center
www.mapleleafcenter.com

Adoption Websites

Adoption Council of Canada
www.adoption.ca

Adoption Resource Central: extensive list of resources about different methods of adoption
www.familyhelper.net/arc

Books

Turner Syndrome

All About Me: Growing up with Turner Syndrome & Nonverbal Learning Disabilities (Softcover) by Kayli Gizel, Jim Boughton (Illustrator). Kayli's personal account of her experience growing up with Turner Syndrome would be a useful read for persons who seek to understand the difficulties that those with this syndrome, as well as NLD, have to face. Kayli is a vivacious and delightful girl whose personality sings across the page. She has shown remarkable ability to absorb information, gain personal insight, and communicate both

information and reflections to the reader. Available from the Maple Leaf Center at *www.mapleleafcenter.com*.

Nonverbal Learning Disorders

A wide choice of books on Nonverbal Learning Disorders is available from the Maple Leaf Center at *www.mapleleafcenter.com*.

All Kinds of Minds by Dr. Mel Levine, written for children and young adults, provides a positive way of understanding what it means to have a learning disability. Written in a way that makes children feel good about their individual learning styles, the book is generally available in libraries, bookstores and on-line booksellers.

Star Shaped Pegs, Square Holes by Kathy Allen, M.A. This book was written for middle or high school students to use with their parents in adjunct with professional guidance in treating nonverbal learning difficulties. It focuses on many of the "life skills" aspects of NLD, like social interaction, small motor skills, organization and anxiety. It is available from Goodenough Books at 925-443-4354.

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