Growth and Growth Disorders

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GROWTH AND GROWTH DISORDERS – SERIES NO: 1
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CGF INFORMATION BOOKLETS
The following are also available:

No. Title

1. Growth and Growth Disorders
2. Growth Hormone Deficiency
   (Puberty and the Growth Hormone Deficient Child now incorporated in 2 above)
4. Premature Sexual Maturation
5. Emergency Information Pack for Children with Cortisol and GH Deficiencies and those Experiencing Recurrent Hypoglycaemia
6. Congenital Adrenal Hyperplasia
7. Growth Hormone Deficiency in Adults
8. Turner Syndrome
9. The Turner Woman
10. Constitutional Delay of Growth & Puberty
11. Multiple Pituitary Hormone Deficiency
12. Diabetes Insipidus
13. Craniopharyngioma
14. Intrauterine Growth Retardation
15. Thyroid Disorders

NB: To order a single copy, send an A5 SAE envelope to the Child Growth Foundation: For multiple copies obtain quote from the CGF

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INTRODUCTION

This booklet is the first in a series produced by the Child Growth Foundation (CGF), the UK's national charity seeking to ensure that the growth of all children is regularly assessed and that children who seem not to grow enough or grow too much are immediately referred for appropriate medical attention.

The booklet summarises for the health professional the panorama of growth disorders, some of which may be described in greater detail later in subsequent booklets in the series. The CGF acts as a resource for all patient support groups and it may be able to assist you to refer your patient to an appropriate clinic. Every child with a growth condition should be under the care of a physician with a specific knowledge of the subject. CGF would also be happy to respond to any other question that you may have concerning child growth.

Tragically, growth disorders are often diagnosed too late for optimal care and treatment. In 1996 the Department of Health specifically advised providers and purchasers of child health surveillance to review their growth monitoring policies in the light of a growing number of legal actions taken against health authorities for the late diagnoses of physical impairments [1]. Even worse, some conditions e.g. the Turner Syndrome, are still being diagnosed in adulthood when growth hormone treatment is no longer possible.

In order to identify children with growth-related abnormalities, early concerted efforts were made in the final years of the twentieth century to set a universal policy for growth assessment in the twenty first century. A paper by Professor David Hall (President of the Royal College of Paediatrics & Child Health [2000-2003]) sums it up and was published in the Millennium Edition of *Archives of Disease in Childhood* (January 2000). The protocol, rubber stamped by the Chief Medical Officer's National Screening Committee, is likely to remain unchanged for several years. It is also published in full in *Health for all Children, Edition 4*, the gold standard for UK child health surveillance.

For the sake of convenience the masculine gender has been used throughout this booklet unless the condition is specific to girls/women.

> The growth curves illustrated in this booklet are *representative* of the curves for each of the conditions featured. The curves for the children who may be causing you concern may climb/fall from different centile positions on the chart and may be more/less severe in their shift.

The series is supported by an educational grant by Serono Ltd and written in collaboration with a member of the associations for growth specialists, the British Society for Paediatric Endocrinology and Diabetes (BSPED).

The CGF has produced a training booklet for professionals, *Growth Assessment in the Community,* (2).

(1) Child Health in the Community: A Guide to Good Practice: *NHSE:* September 1996.

(2) Growth Assessment in the Community: *CGF* February 2001.

CENTILE CHARTS AND GROWTH ASSESSMENT EQUIPMENT

The Child Growth Foundation's 9-centile cross-sectional reference growth charts should be the only charts used for the assessment of height and weight in the United Kingdom. They have been endorsed by the Department of Health and the Royal College of Paediatrics and Child Health [RCPCH] ([1, 2, 3]). The charts differ significantly from previously published longitudinal charts, which may still be in circulation. Though these charts may be useful for the assessment of height at puberty they should never be used for general growth assessment where both height and weight are a factor. The cross-sectional charts are updated whenever new data demands or at routine 5 year intervals.

Because linear growth is the best long-term indicator of a child's health or wellbeing, the illustrations in this booklet will emphasise length/height to describe normal and abnormal growth. Weight measurement, however, is the principal indicator of good health in the child's first year of life with a length measurement ideally being taken at intervals. It is crucial that head circumference measurements are taken during the early months until the practitioner is assured that the head is growing normally. The CGF designs, manufactures and markets all the equipment necessary to assess growth in either the hospital or community environment.

In the UK a Personal Child Health Record [PCHR] should be issued to every new-born at birth and should contain a set of A5-size growth charts identical to those on the following pages. The PCHR is designed to be the child's principal professional health record and held on its behalf by a parent or guardian. Since families as well as health professionals are encouraged to complete the Record, the growth section illustrates how children may be accurately measured at home.

These UK reference charts should also be used for plotting the growth of ethnic community children. They may be genetically taller or shorter than caucasian [white] children, but their growth will always follow the same pattern ([4]).

*Charts in other formats - and covering specialist growth areas - are available for professional use: contact the Foundation for details.

(1) Cross-sectional stature and weight reference curves for the UK, 1990 (JV Freeman et al) *Arch Dis. Child* 1995: 73: 17-24
(2) Child Health in the Community: A guide to Good Practice: *NHSE:* September 1996
(3) Growth reference charts for use in the UK: www.rcpch.ac.uk
(4) Growth charts for ethnic populations in the UK (S Chinn et al) *Lancet*, March 23rd 1996: 347: 839-840

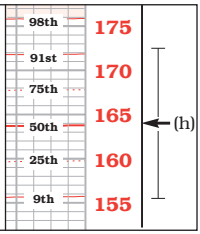
The chart opposite shows normal growth and how it should be plotted. The curve is seen flowing parallel to one of the centile lines within the child's Target Centile Range (TCR) - represented by the shaded area. Raw Growth data should always be recorded on/collated with the chart. Every health professional working with children should have: training in plotting and interpreting growth data, be supplied with the correct equipment for recording it and understand the criteria for referring children with abnormally slow/excessive growth.

THE INFLUENCE OF FAMILY HEIGHT ON STATURE

Many normal short and tall children are wrongly referred to specialists for investigation simply because their genetic height potential has not been calculated. More seriously, abnormally growing children are not referred for the same reason. Each child's potential height – otherwise known as the Mid Parental Height/Centile or Target Centile Range (MPH, MPC or TCR - see below) – will be one of the first calculations made by an endocrine specialist at the beginning of any consultation. For instance, the height of a girl with Turner Syndrome will invariably fall outside her TCR and every girl who appears to be short for her age should have her karyotype checked. The CGF seeks to ensure that, whenever possible, the heights of both natural parents are recorded with the child's birth records so that mid-parental height can be calculated. **NB: The MPH calculation is not appropriate if either parent is not of normal stature.**

The calculation of MPH is not difficult. The table and illustrations below show how to work out a girl's adult height potential. The chart shows that she is following her genetic pattern, her curve is bordering the 50th centile and she is destined to reach 164cm as an adult - **Mid-Parental Height (MPH).** The 50th centile is her **Mid-Parental Centile (MPC).** Even if her curve was not *on* the 50th centile, she would still be growing normally if her growth kept between 91st - 9th centile (MPH ± 8.5cm) and parallel to one of the printed centile lines. This range of growth is called her **Target Centile Range (TCR).**

CALCULATION	ILLUSTRATION
(a) = father's height	(a) 186cm
(b) = mother's height	(b) 156cm
(c) = sum of (a) and (b)	(c) 342cm
(d) = (c) ÷ 2	(d) 171cm
(e) = (d) – 7cm (MPH)	(e) 164cm
(f) = MPC - nearest centile to (e)	(f) 50th centile
(g) = TCR (mid-parental height ±8.5cm)	(g) 9th - 91st centile



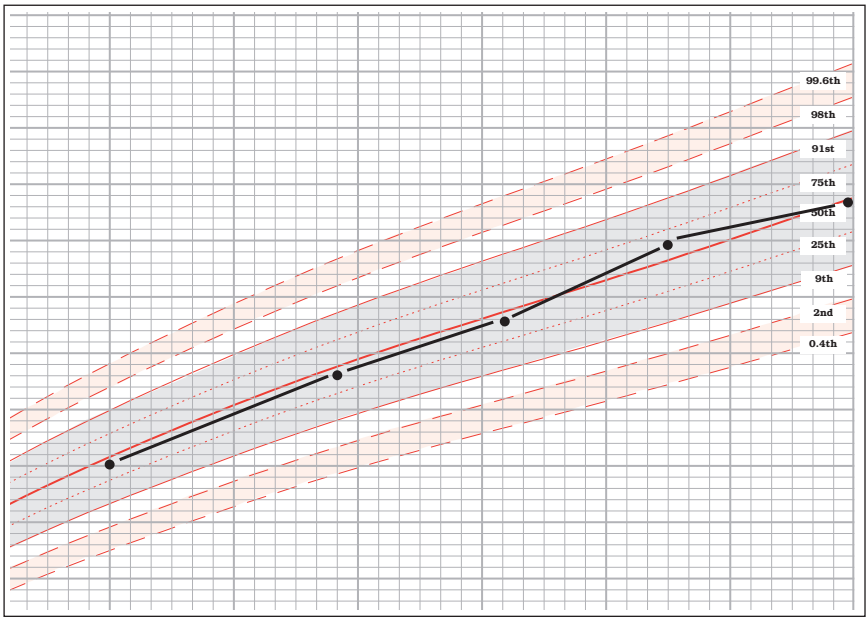


Figure 1: Normal growth plotted on 9-centile chart

GROWTH ASSESSMENT / GROWTH DISORDERS (CGF recommendations)

Measure Every Child	• Weight:- birth, 2, 4, 6, 8, 12, 16 weeks, 6-8 months, 1 year. • Length:- 10 days and 3 monthly up to year 1. • Height:- yearly from 18 months, school entry and routine checks at school. • Head Circumference:- 36 hours, 10 days and 8 weeks and as indicated.

If there is any concern about growth, measurements should be taken more frequently.

Record child's measurement and plot on 9-centile growth charts

Measure real father and mother and calculate/plot mid parental centile [MPC] and target height range [TCR]

Is this child small/tall but appropriate for parental heights?	**YES ➜**	**Normal short/tall stature**
Is child inappropriately short/tall for parental heights? **Is child growing at an inappropriate growth rate?**	**YES ➜**	**Refer to local paediatrician for further assessment as shown below**

Referral criteria

Review:	**Birthweight and all available growth information**
Examine:	**Height, weight, body proportions, BMI, dysmorphic features, pubertal status**
Consider Investigations:	**Bone age, blood tests, chromosome assessment (karyotype), simple biochemistry, hormone levels, brain scan**
If concerns are still unresolved:	**Review assessment after 6 months. Consider referral to growth specialist for final diagnosis**

Possible diagnoses

SHORT & TALL STATURE

● **Small for chronological age**	**GROWTH DELAY**
● **Abnormal karyotype**	**CHROMOSOME ABNORMALITIES** Turner Syndrome Down's Syndrome
● **Low birthweight, thin, dysmorphic, possible asymmetry**	**INTRAUTERINE GROWTH RETARDATION (IUGR)** Including Russell Silver Syndrome
● **Dysmorphic, cardiac problems**	**NOONAN SYNDROME**
● **Abnormal hypopituitary function**	**ENDOCRINE DISORDERS** Growth hormone insufficiency Panhypopituitarism Hypothyroidism Cushing's Syndrome Premature sexual maturation Environmental growth failure
● **Dysmorphic**	**BONE DYSPLASIAS** Achondroplasia Hypochondroplasia
● **Chronic ill health**	**CHRONIC DISEASES** Congenital heart disease Renal failure Coeliac/Crohn's disease Cystic Fibrosis Asthma/eczema

● **Inappropriate tall stature**	**SYNDROMES** Marfan Sotos Klinefelter's **ENDOCRINE** Precocious puberty

NORMAL GENETIC SHORT/TALL STATURE

All children who are considered short/tall should be assessed for their MPC and TCR (see page 5). If their height is within normal limits for their parents and they are growing at a normal rate, they are normal, whatever their position within the population standards.

There is no effective treatment for genetic short stature. The availability of biosynthetic growth hormone has allowed increased interest in the use of this substance for the treatment of children who are very short. This is still in the stage of clinical trials but available evidence suggests that final stature will not be altered significantly. While it is clear that even in children with normal growth hormone secretion, a short-term acceleration in growth may be achieved during growth hormone therapy, there is no certainty at this time that the long-term final height prognosis is altered. Further careful studies, extending over a number of years, will be necessary to show this. However, in the USA, there is a much more liberal treatment regimen for children with genetic short stature. Although this probably represents a very heterogenous group of children, growth hormone is now licensed for use in this indication.

CONSTITUTIONAL DELAY/ADVANCEMENT OF GROWTH AND PUBERTY

Constitutional delay of growth in puberty (CGDP) frequently causes concern and seems to be more prevelant in boys than girls. It is often first noticed when the boy seems to have stopped growing, has younger siblings catching up or even being taller than him, or has classmates leaving him behind. Growth delay of up to two years is not uncommon and a small number of children are delayed three, or even four years. Frequently one of the parents, an aunt or an uncle, brother or sister, will have had growth delay. A mother will often be able to establish that she was 15 or more years old at menarche instead of the more usual 12 to 14 years: it may be more difficult to establish a father's pubertal delay owing to the lack of a fixed event such as menarche.

Once growth delay has been established any boy or girl can be absolutely reassured that puberty occurs in the end and that they will develop quite normally in every way. They can be reassured with a full demonstration of facts, figures, charts and predictions. Children find the information that they are simply taking after their mothers or fathers reassuring if not particularly welcome. What reassurance does not do is remove the very real physical handicap associated with being small and, worse, remaining pre-pubertal with a peer group of adolescents.

If reassurance does not completely satisfy the patient then there are, at present, two options for treatment. When the anxiety only concerns height, the first line of treatment is the mild anabolic steroid, oxandrolone. This makes no difference to final height but it does initiate the growth spurt a little earlier than would occur with no treatment. If a boy is also concerned about his lack of pubertal development then testosterone, the male sex hormone, can be used. In girls, low dose oestrogen can be used. It should be emphasised that these forms of therapy require careful monitoring by specialists experienced in the treatment of growth problems.

Constitutional advanced growth is the converse of growth delay but rarely presents as a clinical problem – however, see page 15.

Further reading: **CGF booklets – see page 1**
Further contact: **Child Growth Foundation**

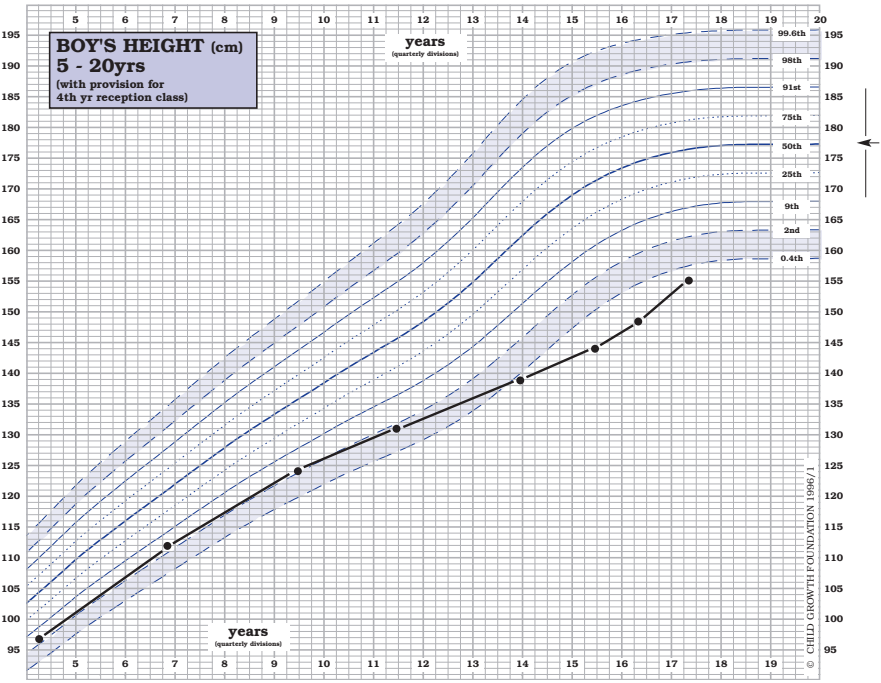


Figure 2: Delayed growth

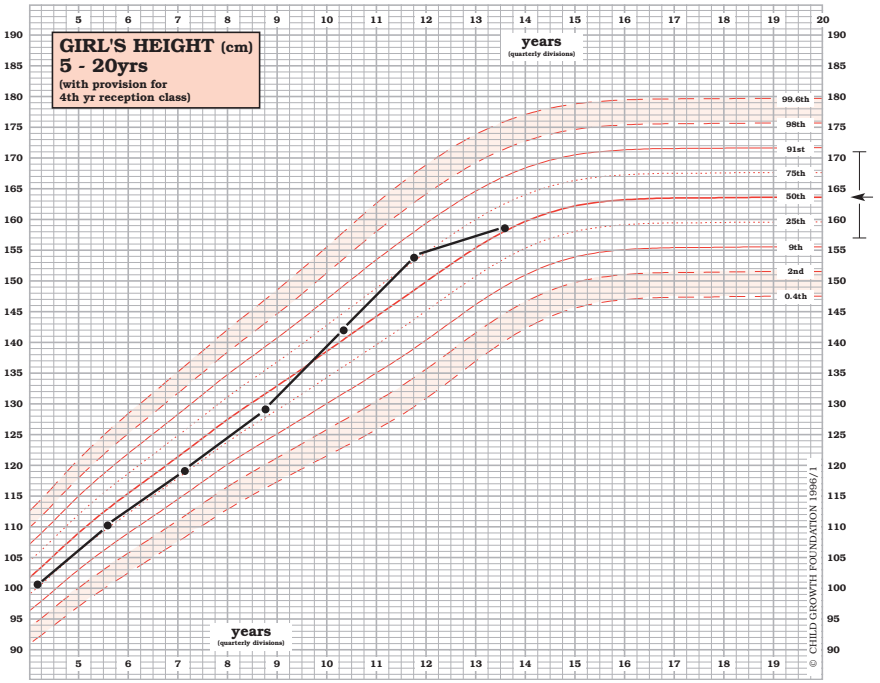


Figure 2b: Advanced growth

ENDOCRINE GLAND DISORDERS

The two main endocrine disorders that cause short stature are growth hormone deficiency and thyroid deficiency.

Growth Hormone Deficiency

Diagnosis: If MPHD (see below) at birth. If solely GHD possible by 18 months. 80% of cases of GHD should be diagnosed by school entry.
Treatment: Growth hormone (GH) replacement therapy

Growth Hormone Deficiency (GHD) is generally due to the pituitary gland being unable to produce sufficient GH to generate the growth process. GHD does not affect intrauterine growth, at least to an extent measurable by birth weight or length, but from the second year of life growth is slower than normal and occasionally growth failure commences from birth. Most cases of growth hormone deficiency are idiopathic, meaning of unknown origin. Idiopathic growth hormone deficiency occurs, it seems, in about 1 in 3800 births.

GHD may also be hereditary, at least in some cases. About 3% of children with GHD have brothers or sisters who also have the disorder. In a very few families one of the parents is affected. The deficiency is two to three times more common in boys than in girls, for reasons quite unknown.

Children with GHD are small with normal skeletal proportions, facial appearance and intelligence. They tend to be overweight (this reduces during GH treatment) and they often have a delayed bone age. The diagnosis is confirmed by measuring the level of growth hormone production in response to a stimulation test, which normally requires a morning in hospital. The deficiency may be of growth hormone only, although other pituitary hormones may also be affected (MPHD). The associated hormone deficiencies are:

- thyroid-stimulating hormone (TSH)
- the gonadotrophins - follicle stimulating hormone (FSH) and lutenising hormone (LH)
- adrenal-stimulating hormone (ACTH) is much less frequently involved, but the deficiency of this hormone is extremely important to detect.

If there is a deficiency of TSH, thyroxine is given, and if gonadotrophin deficiency becomes apparent at the time of puberty (which is usually late in growth hormone deficient children), the sex hormones have also to be given and treatment can initiate sexual maturation. Very occasionally antibodies develop to the injected growth hormone treatment and cancel out the effects of treatment but this is extremely rare with more modern biosynthetic human growth hormones; otherwise side-effects are unusual.

The treatment of growth hormone deficiency has been recognised since the first patient was given human growth hormone by Raben in 1958 in Boston, USA, although since October 1985, biosynthetic growth hormone has replaced the pituitary derived hormone in the UK. Provided treatment is started at a reasonably early age (at least before age 6 years) the results are nearly always excellent (even at later stages results are sometimes spectacular, but not invariably). Catch-up-growth occurs following initial treatment and thereafter a normal growth rate is usually maintained.

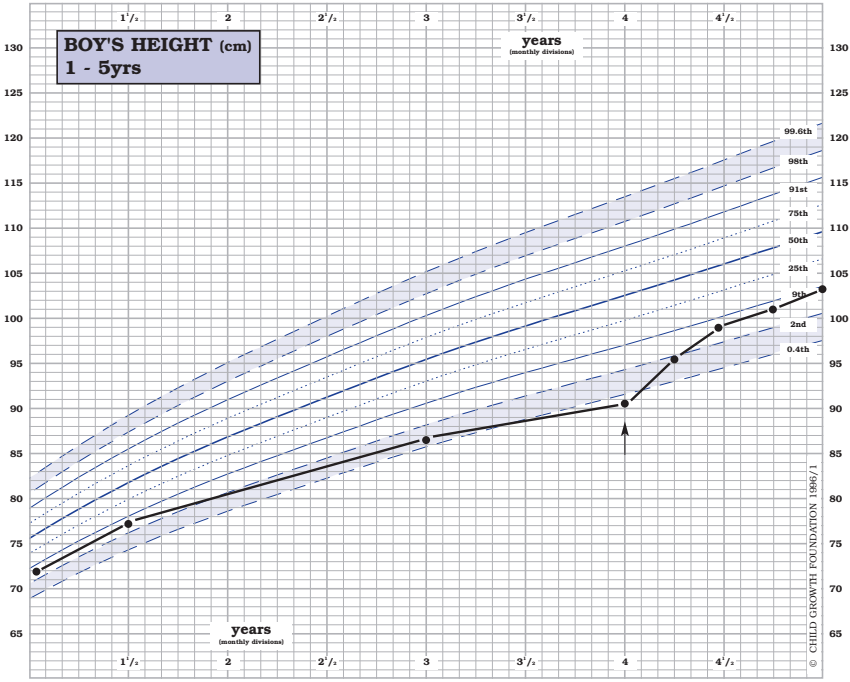


Figure 3: Idiopathic GHD: Height.
Vertical arrow indicates start of GH therapy.

Adults with growth hormone deficiency may require growth hormone treatment for metabolic reasons after they have stopped growing. The daily doses are usually much lower than those given to children. The lack of growth hormone may contribute to symptoms of general tiredness, weakness and weak bones (osteoporosis). Growth hormone is an approved treatment for adult GHD.

Oncology Survivors

Every child surviving oncological treatment is a candidate for growth hormone.

Growth hormone deficiency can also result from damage to the part of the brain controlling the pituitary gland, the pituitary itself, or both. Some tumours are benign, i.e. not cancerous, and the one that is the most common in the pituitary region is called a craniopharyngioma. This is not technically a brain tumour at all, but part of a piece of mouth epithelium (the lining of the mouth) pinched off and left behind during the development of a baby while still in the womb. A craniopharyngioma can be identified by taking a skull x-ray, MRI or by computer-assisted tomography of the brain. They are usually surgically removable. Occasionally, they recur, but are removable again.

The child with a pituitary tumour occasionally comes to the physician with the sole complaint of short stature, but more usually the symptoms are neurological e.g. headaches, nausea, affected vision. Treatment may involve radiotherapy and/or surgical removal of the tumour, after which the child may develop a combination of pituitary hormone deficiencies.

Most, though not all, have growth hormone deficiency. They are treated with growth hormone, often in conjunction with thyroxine, cortisol (hydrocortisone) and, at the time of puberty, gonadotrophins or sex hormones. In addition such children may need replacement of the posterior pituitary hormone, vasopressin, in order to restore a normal fluid balance in the body.

Further reading: **CGF booklets – see page 1**
Further contact: **Child Growth Foundation**

Hypothyroidism

Diagnosis: **Congenital - at birth. Late onset at any age during childhood**
Treatment: **Thyroxine tablets**

Lack of thyroid gland secretion (thyroxine) may also stop normal growth occurring, as all cells need a certain level of thyroid hormone in them in order to function properly. Hypothyroidism may start *in utero*, in which case the development of the brain is affected and diagnosis and treatment directly after birth is a matter of urgency. The condition can be diagnosed by measuring the levels of thyroid hormone in the blood and this is now a routine screening test for all new-borns.

Short stature is more usually caused by late onset of hypothyroidism, the type of hypothyroidism that starts during childhood, often subtly. The catch-up growth during thyroid hormone replacement treatment is marked but, unfortunately, rarely complete.

Further reading: **CGF booklets – see page 1**
Further contact: **Child Growth Foundation**

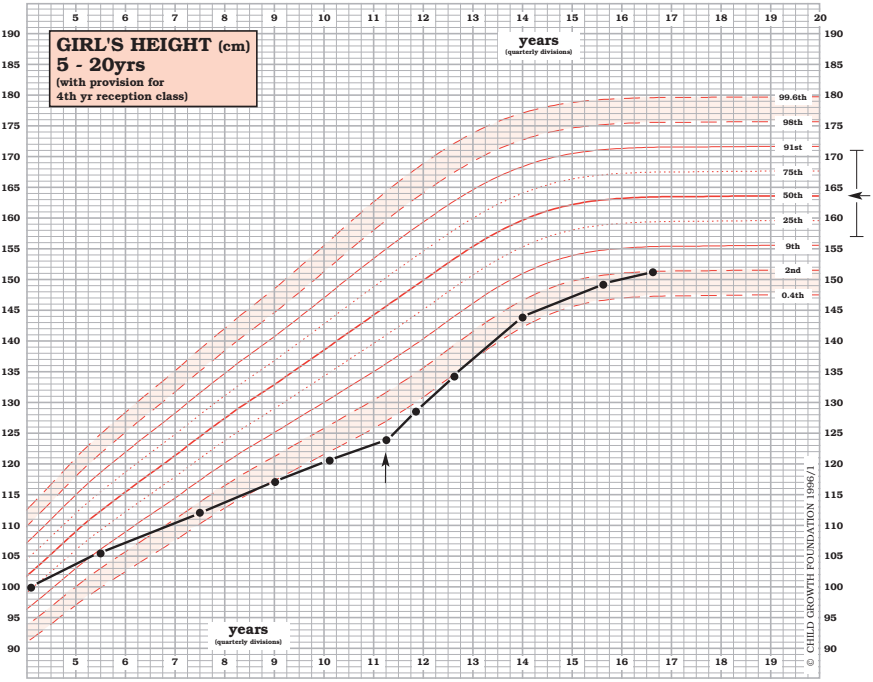


Figure 4: Acquired hypothyroidism: Height.
Vertical arrow marked T_4 indicates start of thyroxine treatment; clinical hypothyroidism started 18 months before

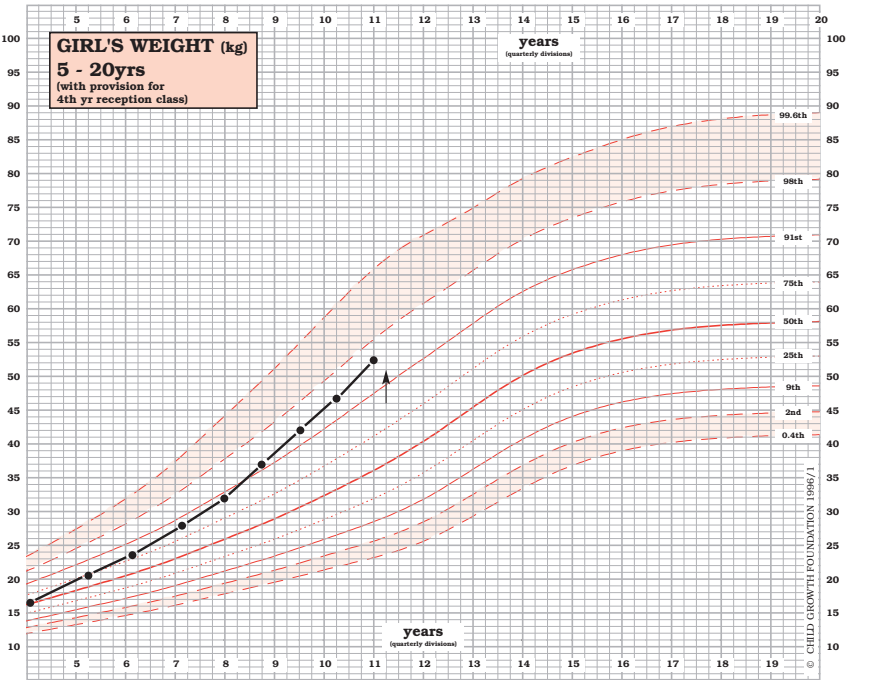


Figure 5: Acquired hypothyroidism: Weight

Premature Sexual Maturation (PSM) - including Precocious Puberty

Diagnosis: Under 8 years in girls and under 9 years in boys
Treatment: Drugs to suppress the onset of puberty

This is a rare condition in which the gonads, adrenal or other glands are affected leading to premature sexual maturation. In such cases the child grows at a faster rate than normal and develops secondary sexual characteristics (such as pubic hair, penile enlargement or breast development) at an inappropriately early age. It is important to distinguish this from precocious puberty, whereby normal puberty occurs but at an age earlier than 8 years in a girl and 9 years in a boy. There is a 20% possibility that it will occur before school entry.

Children with PSM, including precocious puberty, may be very large for their age but as growth stops early, the final adult height can be relatively short. Premature sexual maturation always requires investigation and assessment by a growth specialist. Treatment will depend on the underlying cause.

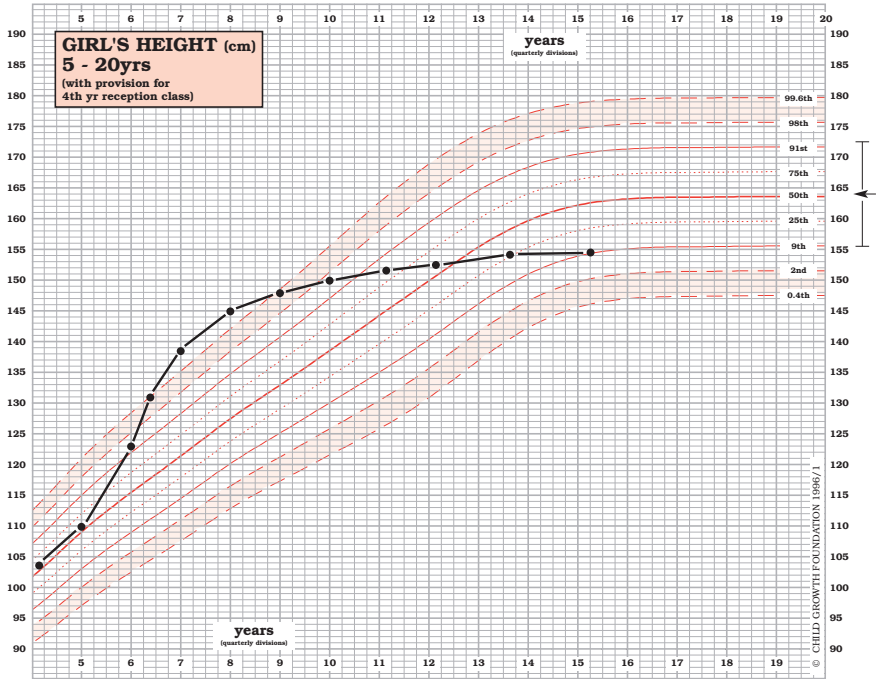


Figure 6: Central precocious puberty

Further reading: **CGF booklets – see page 1**
Further contact: **Child Growth Foundation/PSM group**

Cushing's Syndrome

Diagnosis: Any age
Treatment: Surgery – pituitary gland or adrenal glands

This is a rare condition where the adrenal glands (situated just above the kidneys) over-secrete the hormones cortisol and androgen (male hormone). The effects of excess cortisol are obesity and growth arrest, whereas those of androgen excess are early pubic hair growth, excess male hair growth, greasy hair and acne. The diagnosis is confirmed by measurements of steroid hormones in the blood and urine.

The syndrome is caused either by over activity of the pituitary gland (which controls the adrenal gland through the release of the hormone ACTH) or over activity of the adrenal gland itself. It is often difficult to separate the two causes and it can therefore take a considerable amount of time before investigations are complete and a full diagnosis made.

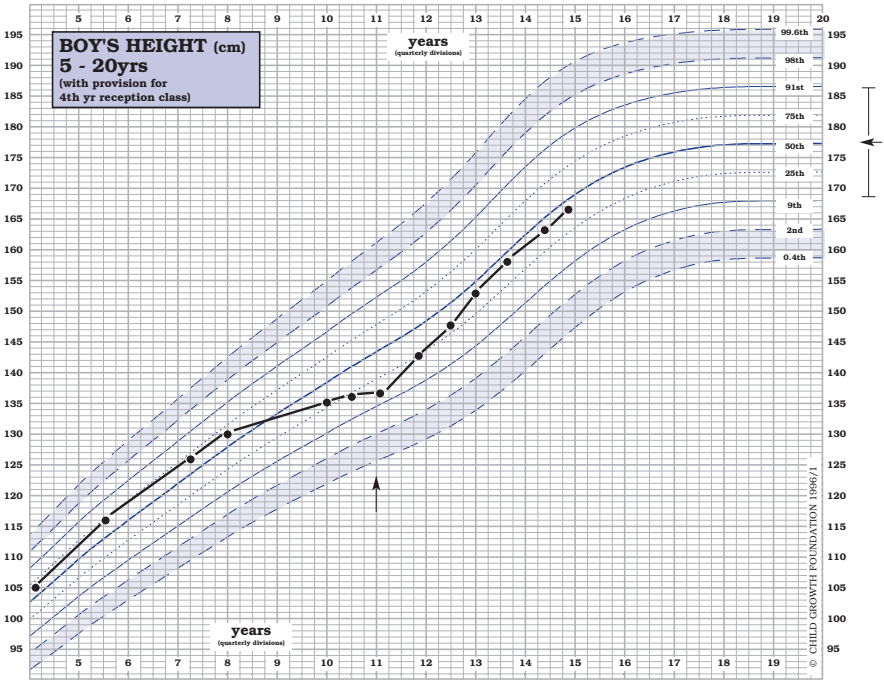


Figure 7: Cushing's disease: Height.
The vertical arrow indicates the time of the removal of the pituitary tumour which was over secreting ACTH.

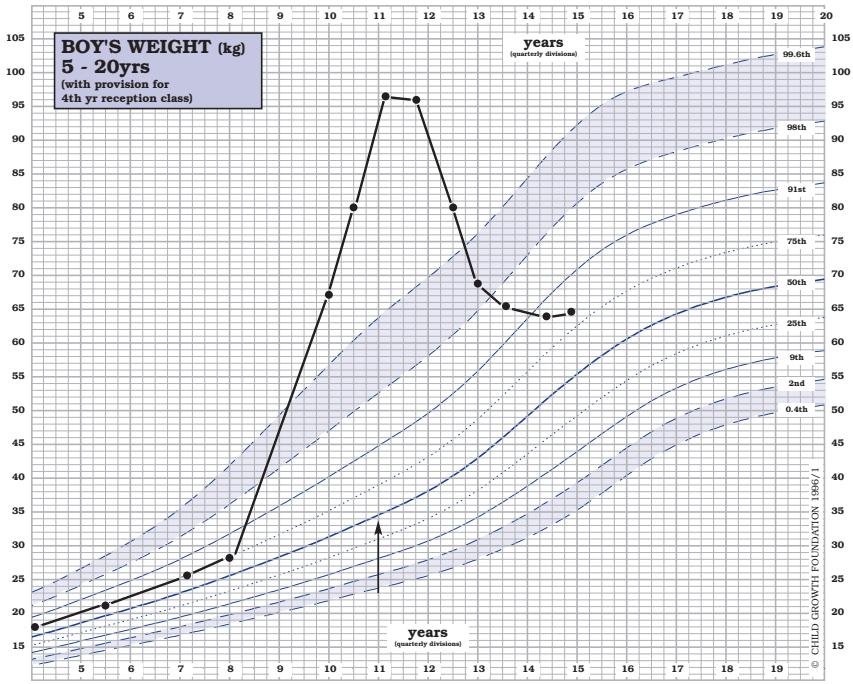


Figure 8: Cushing's disease: Weight.

Psychological and Psychosocial Stress

Diagnosis: Any age
Treatment: Change of environment away from the adverse circumstances

It is now well established that psychological stress in certain children may cause growth failure. They react to the stress by switching off their growth hormone secretion. These are not starved children, and are often overweight, so appearing clinically similar to children with growth hormone deficiency. There is usually a history of psychosocial stress within the family; the child seems often to present as an older version of the "battered baby" situation. One child may be the scapegoat for the whole family, just as in the battered baby syndrome, with the other siblings growing quite normally.

In classical cases, children with psychological/psychosocial stress have a disorder of eating in that they eat voraciously at some times and not at all at others. They sleep badly, get up in the night and "steal" food. These children may eat the food set aside for the dog or cat, placing themselves on the mat to do so; they rummage in the dustbin and drink water from the toilet. A stimulation test of growth hormone secretion done immediately on arrival at the clinic shows inability to respond. If the child is then admitted to hospital, and is therefore removed from their home environment, after a few days or weeks the levels of growth hormone return to normal and catch-up growth occurs.

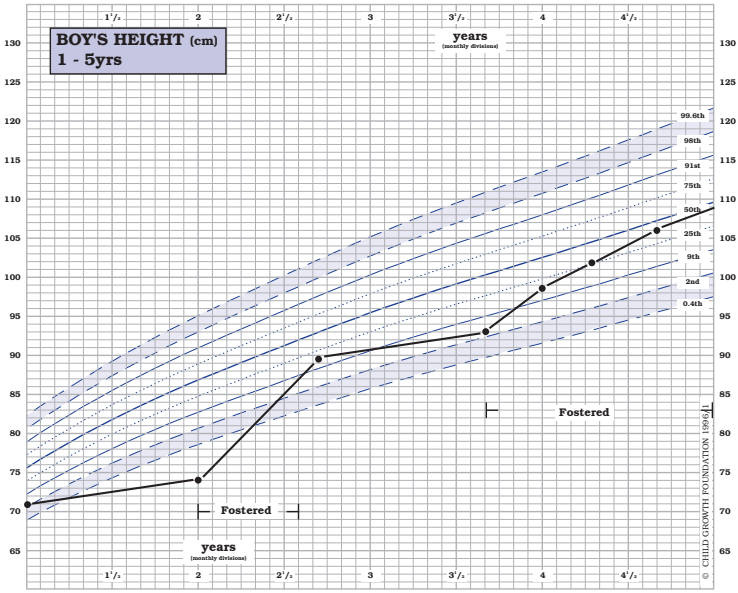


Figure 9: Psychological short stature.

Once the diagnosis is established, there is little to do but separate such children from the adverse environment. Away from home, even in hospital where the reversibility of hypopituitarism can be demonstrated, the catch-up growth is usually spectacular being as good as that of a growth hormone deficient child who is given growth hormone replacement therapy.

There are lesser degrees of this problem in which children grow at a sub-optimal rate when in a disturbed environment. It is not unusual to see "spontaneous" catch up growth in a short child after a period of time (i.e. if parents separate or if there has been a move of home or school.

INTRAUTERINE GROWTH RETARDATION

Diagnosis: Majority of cases should be diagnosed by age 2
Treatment: GH approved for treatment from the age of four years

Under-development of a baby *in utero* may be due to a problem with the fertilised ovum, the placenta that limits the supply of foods and oxygen to the fetus, or to disease or malnutrition in the mother. Certain of the first, and all of the second and third types of problem lead to poor growth of the baby and hence lead to a small size at birth. This smallness of size may be known only through weight. Though length would often be more informative, it is unfortunately not routinely measured in hospitals in the UK, although accurate apparatus for measuring length now exists.

Standards for birth weight and length are available for each week of gestational age; the centiles are different for girls and boys and for first-born and later-born. We are concerned here only with small-for-dates babies i.e. those who are below the centile limits for weight at their particular gestational age.

Babies who are simply born early, i.e. more than 32 weeks, and who are at the normal weight for that length of gestation, usually catch up to a perfectly normal height. Studies are currently ongoing to assess growth and "catch-up" in very premature babies (i.e. <32 weeks gestational age). Indeed 'catch-up' growth may occur up to the age of six years, although more usually this commences during the first year of life. Small-for-dates babies may be born at term, or may be born after a shorter gestational period.

Russell Silver Syndrome

The majority of small-for-dates children, particularly those born at term, grow within the normal centiles. However, they do not fulfil their genetic potential and so are often small for their parents' heights. Their average height centile seems to be about the 2nd. Others, however, fail to catch up in this way. They remain very short, lack subcutaneous fat and have a characteristic facial appearance. The face as a whole is triangular, with large eyes and small lower jaw; the forehead is large and prominent in relation to the face, and the ears are set low in the head and tend to stick out. The bridge of the nose is usually depressed and the mouth turned down at the corners. A proportion of these children have marked asymmetry of the limbs or body, one arm or leg being longer than the other, or one side of the face or chest more developed. The condition constitutes a specific syndrome known by the name Russell Silver after the two paediatricians who independently described it in the 1950s. Educational development often requires extra help.

It is very important to provide calorie supplements and usually a more aggressive approach is now taken with the insertion of a gastrostomy tube. Children with Russell Silver syndrome commonly have reduced calorie intake for several reasons, including a high-arched palate, decreased appetite and gut dysmotility. It is very important to involve the opinion of a paediatric gastroenterologist at an early stage. Growth hormone treatment is now licensed for short children with intrauterine growth retardation/Russell Silver syndrome, but only from the age of four years. Growth hormone treatment not only improves the short-term growth rate, but also improves final height attainment. There may also be important benefits by improving blood sugar control (see below). These children are healthy and active, though usually very thin but should not be regarded as delicate. In middle childhood they put on some subcutaneous fat and their puberty occurs at a slightly earlier time but in the normal sequence. The syndrome hardly ever occurs twice in the same family, so the mother of such a child can be reassured about the subsequent pregnancies.

The cause of the disorder is unknown, although in a small proportion of mildly affected children there is a chromosomal abnormality. The prognosis may be improved by the treatment given to low birthweight babies nowadays, which consists of feeding them more intensively than before. This may also be important in the prevention of hypoglycaemia (low level of sugar in blood) which is more common in these babies.

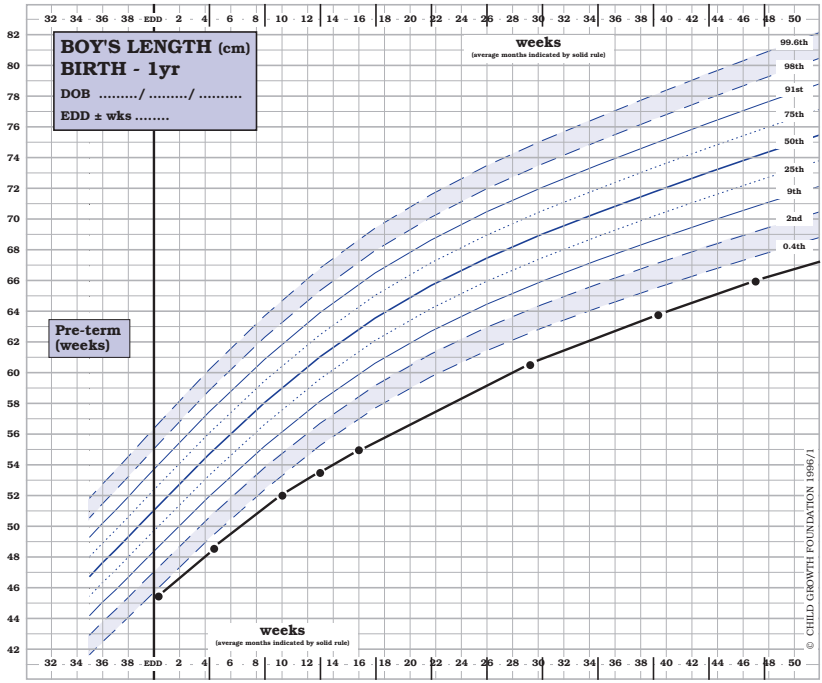


Figure 10: Russell Silver Syndrome

Further reading: **CGF booklets – see page 1**
Further contact: **Child Growth Foundation / Russell Silver Group**

Other low birth weight syndromes

During pregnancy, a large intake of alcohol may affect the fetus directly, causing a recognisable disorder called **Fetal Alcohol syndrome.** The baby's face has a characteristic appearance that is due to insufficient development of the areas around the eyes, nose and upper lip. Pregnant women should be strongly advised to limit their drinking and smoking as this too has an effect. Smoking during pregnancy results in an average reduction of 180g in full term birthweight and a 30% increase in perinatal mortality.

Some babies with low birth weight and subsequent short stature have rarer, more specific syndromes of maldevelopment. Although there are many such conditions, each is relatively rare. Most are due to genetic conditions and the area is a highly specialised one. Two specific conditions are **Cornelia de Lange syndrome and Prader Willi syndrome.**

CHROMOSOME ABNORMALITIES

Turner Syndrome

Diagnosis:	**Possibly *in-utero*[ultrasound/amniocentesis], at birth by physical characteristics, pre-school entry by growth failure and subsequently by delay of puberty**
Treatment:	**GH, anabolic and sex steroids (& combinations of these)**

Females normally have two X-chromosomes. The lack, partial lack, or abnormal formation of the second X chromosome produces the condition called Turner Syndrome. It is one of the most common chromosome disorders and occurs in 1 in 2500 live female births.

Girls with Turner Syndrome have normal intelligence, though in some cases it is associated with specific learning difficulties. They also have short stature with or without some physical characteristics such as puffy hands and feet soon after birth, webbing of the neck, broad chest, small nipples and characteristic face. Bone age is delayed only slightly or not at all.

The diagnosis is confirmed through examination of the chromosomes from blood cells (karyotype) and occasionally other body tissues such as skin. In early childhood, feeding difficulties may occur as well as frequent ear infections.

Short stature is the most common feature of Turner Syndrome and girls with this syndrome are often slightly small at birth. The average adult height is about 147cm, although a few may reach 152cm (5ft. 2ins.). Parental height plays the most important role in determining the adult height of girls with Turner Syndrome and a girl with tall parents is likely to be taller than a girl with short parents.

Although growth hormone secretion is nearly always normal, many studies have demonstrated that by giving additional growth hormone, there is a dramatic increase in growth rate and GH treatment is licensed for the treatment of short stature in girls with Turner Syndrome. The increase in final stature is variable and is dependent on the age of starting treatment. The mild anabolic steroid, oxandrolone, in combination with growth hormone, is under investigation, as is the optimum age to start low doses of oestrogen treatment.

Lack of sexual maturation during adolescence is another feature of Turner Syndrome. This occurs in the majority of girls because the ovaries do not develop normally to produce oestrogen. The missing, or abnormal, X chromosome affects ovarian function and this has to be explained to the parents and child.

At the appropriate age, girls with Turner Syndrome are given oestrogen replacement therapy, in gradually increasing doses, to stimulate breast and pubic hair development. In due course regular uterine withdrawal bleeds that are important for keeping the uterus healthy are introduced and girls with Turner Syndrome commonly wish to start their periods at the same time as their friends. These withdrawal bleeds can be produced by giving oestrogen and progestogen for 3 weeks, followed by a week without treatment. It is important that these girls, and their parents, understand that the uterus and vagina are normal and so with the new techniques of in-vitro fertilisation ("test-tube"), and with an egg donated from another woman, there is the potential for fertility.

The previous page describes the situation in the full Turner Syndrome karyotype, written XO. Sometimes, only a proportion of cells has this chromosome compliment, the remaining cells have the normal female XX chromosomes. This condition is referred to as Mosaic Turner Syndrome. Girls with mosaic forms of Turner Syndrome often have fewer of the physical features and may be more likely to show signs of sexual development without treatment, although they are unlikely to develop fully and to menstruate. The extent of the short stature, however, is not related to the specific karyotype. ***It follows*** that any girl with short stature of unknown cause should have a chromosome analysis done.

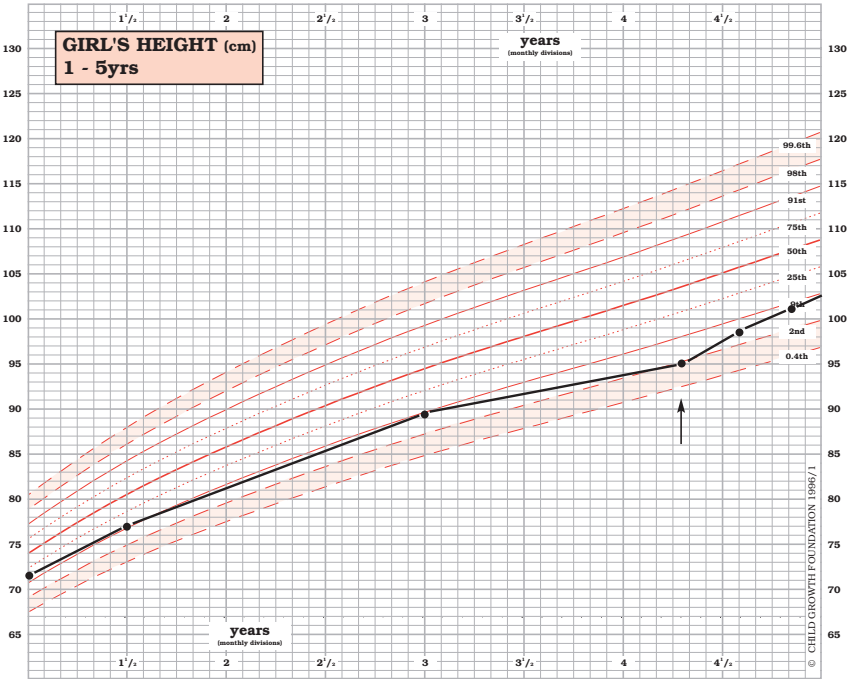


Figure 11: Turner Syndrome : Height.
Vertical arrow indicates start of GH treatment.

There are Turner Syndrome charts to monitor the girl once diagnosed as TS.

Further reading: **CGF booklets – see page 1**
Further contact: **Child Growth Foundation/Turner Syndrome Society**

Noonan Syndrome

Diagnosis: **70% by primary school age**
Treatment: **GH in trials**

Noonan Syndrome is a common condition, estimated to occur in approximately 1/2000 of the population. The physical appearance has characteristic facial and body features, dysmorphic signs and short stature. In addition these individuals often have abnormalities of blood clotting and congenital heart defects. The latter usually involves abnormalities of the right side of the heart or of the heart muscle. All children with Noonan Syndrome should see a cardiologist and have an ultrasound examination of the heart chambers and valves. They may also have abnormalities of blood clotting.

In many ways Noonan Syndrome resembles Turner Syndrome, although it occurs in both boys and girls. It is thought that there is a chromosomal abnormality although this has not yet been identified. This specific gene for Noonan Syndrome has not been identified yet but it would be relevant to seek specialist genetic advice to both confirm the diagnosis and to determine the risk of recurrence in further offspring.

Children with Noonan Syndrome are short, although the range of heights does overlap into the normal range. They commonly have delayed puberty, which may require therapeutic help. Special growth charts are available of growth in Noonan Syndrome and these may be helpful in giving an estimated final height for a child with Noonan Syndrome. Growth hormone treatment is under clinical study at the present time. Although it certainly improves short-term growth rate, it is not yet possible to say whether GH treatment will affect final height. However, initial evidence has suggested that this treatment is not associated with any deterioration in heart function, despite the commonly occurring heart defects.

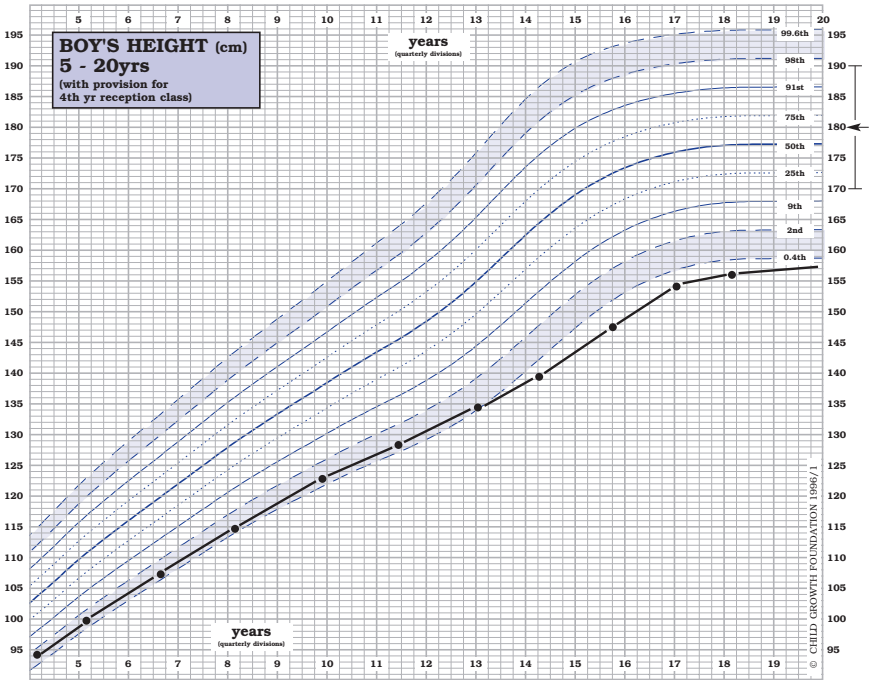


Figure 12: Noonan Syndrome

Down's Syndrome

Diagnosis: Usually at birth, confirmed by chromosome assessment
Treatment: Treatment of associated complications, e.g. hypothyroidism, as necessary

Down's Syndrome is a chromosome abnormality, that results from having three instead of two chromosomes number 21. Children with Down's Syndrome have a range of mental handicap and often have short stature. The physical appearance and behaviour makes diagnosis at an early age relatively easy: it is confirmed by examination of the chromosomes (karyotype). Hypothyroidism, which can also cause developmental delay and impaired growth, is common in children with Down's Syndrome and it is important that this is identified and treated.

There are Down's Syndrome charts to monitor the growth of any child so diagnosed.

CARTILAGE AND BONE DISORDERS

Diagnosis:	**Majority at birth by radiological examination**
Treatment:	**Usually surgical limb lengthening, GH in trials**

There are a large number of bone disorders that affect growth: they are mostly rare and many are inherited. They are known as skeletal dysplasias and the best known is achondroplasia.

Achondroplasia

Children and adults with achondroplasia have short upper arms and thighs, a normal length back, a large head, and a characteristic face with depressed nasal bridge, small nose and large forehead. They appear to have large muscles for their leg length. They are of normal intelligence and health. Achondroplasia is caused by a mutation of a single gene and has a dominant pattern of inheritance. This means that, on average, half the children of a parent with achondroplasia will also be affected. In most cases, however, there is a new mutation, without any family history and it seems that this particular gene is one of the most unstable in the human complex.

At present, treatment depends primarily on new surgical techniques of limb lengthening. Growth hormone treatment may improve short-term growth rate, especially if started at an early age. However, it is not yet known whether this improves final height and growth hormone use in this condition is therefore still being evaluated through clinical trials.

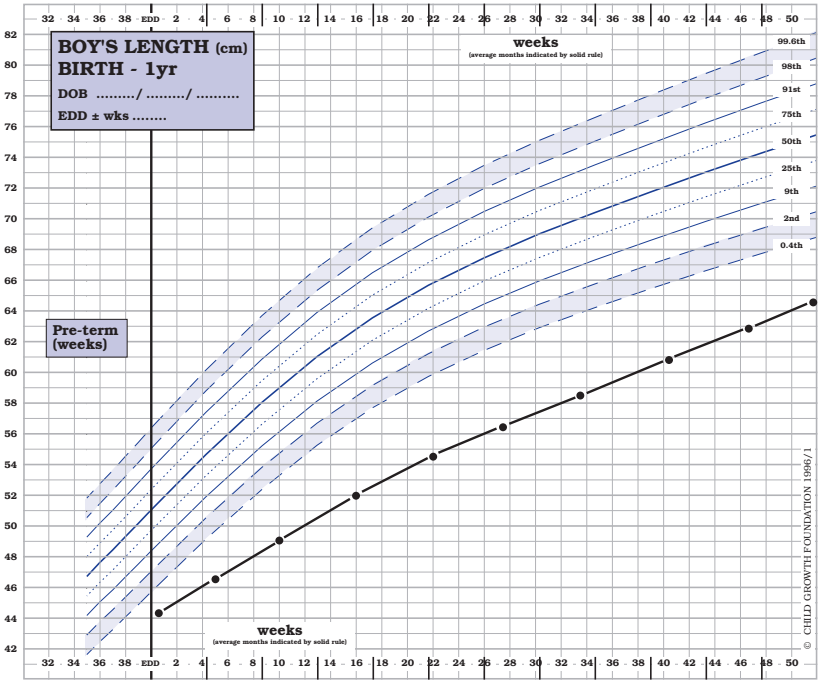


Figure 13: Achondroplasia

Hypochondroplasia

This is a similar syndrome to achondroplasia but the physical characteristics and short stature are less marked. Like achondroplasia, the short legs are responsible for the short stature. The face is normal (though it has some tell tale features to the experienced eye) and children with hypochondroplasia often may be diagnosed as being very short normals. Hypochondroplasia is also inherited as a dominant gene, but seems to be separate from the achondroplasia gene; the two conditions very seldom appear in the same family. In hypochondroplasia, one of the parents frequently has the disorder.

There is no certain way of confirming what is sometimes a difficult diagnosis. The most helpful feature is comparison of sitting-height and leg-length centiles. While in achondroplasia the x-ray signs are marked and characteristic, in hypochondroplasia they are minimal. The effect of growth hormone treatment is being evaluated through clinical trials.

Other Skeletal Dysplasias

There are over one hundred such conditions of which achondroplasia and hypochondroplasia are two of the most common. Other bone disorders are more rare; some affect limbs only, some the trunk and some both. To date, none have any specific treatment although surgical limb lengthening is potentially the most promising, while the use of growth hormone is being evaluated through clinical trials.

Further reading:	**Parents' Guide to Achondroplasia**
Further contact:	**Child Growth Foundation/Bone Dysplasia Group.**

DISORDERS OF ABSORPTION OF FOOD

If there is a prolonged malabsorption of food, growth is affected, just as it is in starvation. All malabsorptive diseases may cause growth failure if not treated successfully, but the most common to appear in the growth disorder clinic are Coeliac disease and Crohn's disease.

Coeliac Disease

Diagnosis:	**At any time following weening and the introduction of foods containing gluten**
Treatment:	**Gluten-free diet**

Usually, Coeliac disease causes gastro-intestinal symptoms, but in a few children these are lacking and the disease is manifested solely in short stature often, but not always, allied with an unusually protuberant abdomen. The diagnosis can only be confirmed by taking a biopsy of the small intestine (a small sample to look at under the microscope) through a tube that is swallowed. This sounds traumatic for a child but nowadays, in the skilled hands of the paediatric gastroenterologist, it is not so.

Coeliac disease is due to an abnormal reaction of the cells of the gut to a substance called gluten that occurs in flour and other foodstuffs. The results of treatment by a gluten-free diet are excellent and any child with short stature not otherwise diagnosed, who is relatively thin, should have a blood test which screens for this disease.

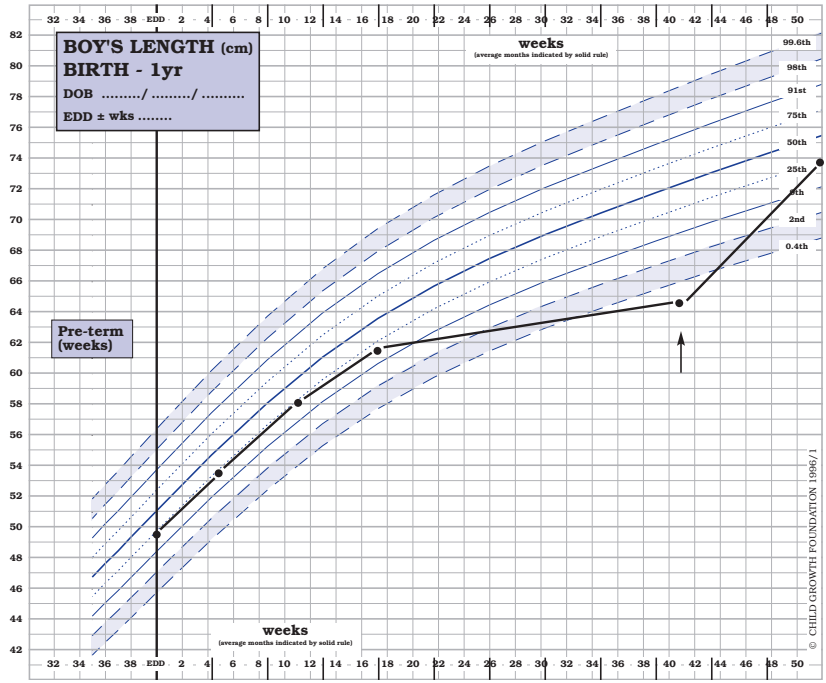


Figure 14: Coeliac disease: Height.
The vertical arrow indicates the start of a gluten free diet.

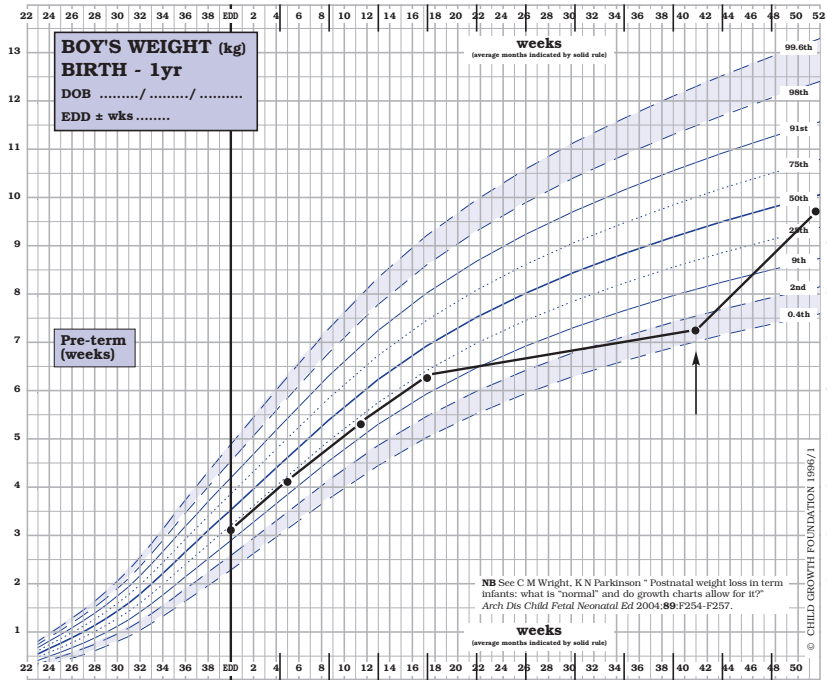


Figure 15: Coeliac disease: Weight.

Crohn's Disease

Diagnosis:	**From mid-childhood onwards.**
Treatment:	**Anti-inflammatory treatments including corticosteroids and surgery**

Like Coeliac disease, Crohn's disease is usually associated with gastro-intestinal symptoms, diarrhoea and abdominal pain, but may also present with short stature and severely delayed puberty. It is due to chronic inflammation of the bowel which leads to poor absorption of foodstuffs and hence the poor growth. The treatment of this condition is more complicated than Coeliac disease and often requires all the skills of a gastroenterologist.

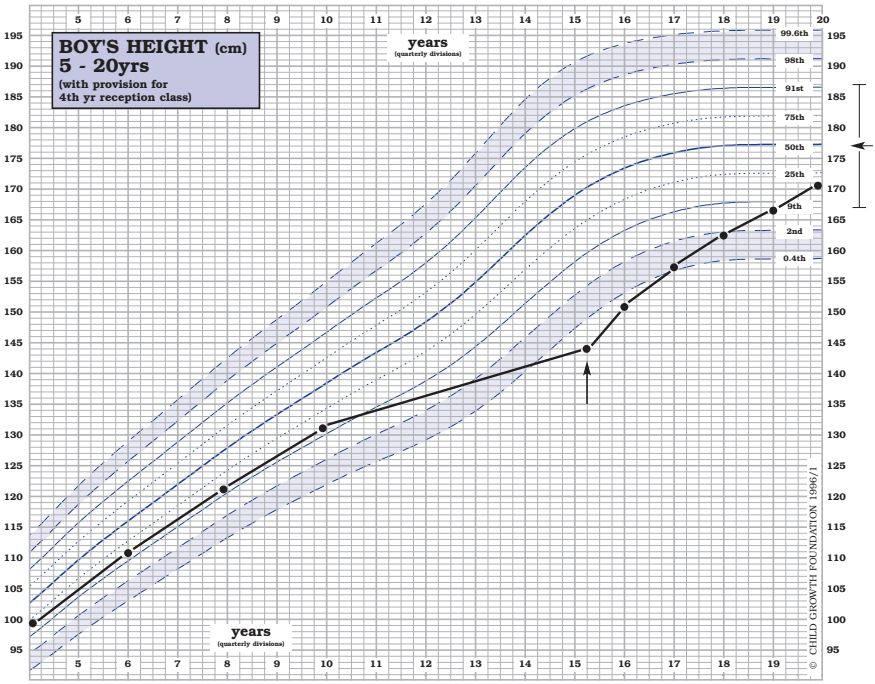


Figure 16: Crohn's disease: Height.
The vertical arrow indicates the time of the surgical resection of a diseased part of the large bowel.

GENERAL CHRONIC DISEASES

Almost all chronic diseases may cause short stature, mostly for reasons that are far from clear. However, major problems often arise in children who require long-term treatment with high doses of corticosteroids to control their disease. Also those heart and lung diseases which cause some degree of lack of oxygen to the tissues often result in poor growth. Many of the heart diseases, however, do not impair the child's growth at all.

The short stature associated with chronic renal failure does respond to GH therapy and this can be very beneficial. Additionally, growth may show dramatic catch up following a successful renal transplant.

Other conditions for which poor growth may result are; cyanotic heart disease, asthma, eczema, cystic fibrosis and very poorly controlled diabetes. Children with severe congenital neurological disease almost invariably grow badly.

TALL STATURE

Children with tall stature, i.e. above the 99.6th centile, are usually so because of genetic reasons – they simply have tall parents! This is referred to as constitutional tall stature. However, tall stature may also be associated with various paediatric syndromes that require specialist assessment. Two of these conditions are Marfan syndrome and Sotos syndrome.

Constitutional tall stature

Tall stature in childhood usually presents less initial concern than short stature because, at least in early childhood, being tall can be advantageous. However, excessive tall stature can cause problems, particularly at school. It may be difficult to remember that a five-year old child who has the stature of an eight-year-old only has the educational and emotional development of a five-year old. Their size can seem inappropriate for their classroom peers and so very tall children may be labelled as clumsy or aggressive.

If extreme tall stature is associated with psychological or behavioural difficulties then treatment can be offered. The older treatment option of sex steroids (oestrogen in girls and testosterone in boys) is not as effective as previously believed in slowing growth and there may be side effects. Theoretically, sex steroids rapidly fuse the growing ends of the bones and so stop growth prematurely. However, they also induce a growth spurt so on balance the outcome may be disappointing.

Other treatments that reduce growth hormone secretion are being evaluated through clinical trials. As a final option, a surgical reduction of leg length is a possibility.

Marfan syndrome

Diagnosis:	**From 18 months onwards**
Treatment:	**Treatment of associated complications as necessary**

Marfan syndrome is one of the most common tall stature syndromes. The characteristics are excessively long limbs, arachnodactyly (long thin fingers), eye abnormalities (in particular, a tendency to partial dislocation of the lens, myopia and retinal detachment) and cardiovascular problems (usually seen in childhood as a valve lesion). Dilation of the major blood vessels (aneurysms) which is associated with Marfan syndrome is rarely seen in childhood. Although the condition is inherited as an autosomal dominant trait, conditions can arise where there has been no family history.

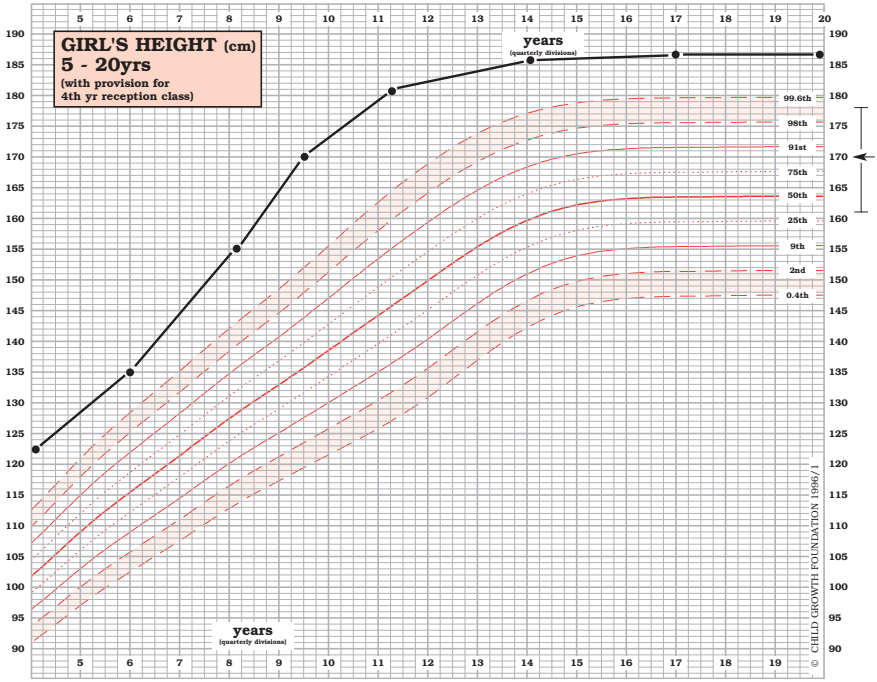


Figure 17: Marfan syndrome

Sotos syndrome or Cerebral Gigantism

Diagnosis:	**From around 2-4 years of age. Tall stature and dysmorphic features**

Sotos syndrome, or gigantism, usually presents in early childhood. The physical characteristics are tall stature, large hands and feet and poor circulation. There may also be special educational needs. Bone age is often advanced and puberty usually occurs early so excessive tall stature may not be a feature of adulthood.

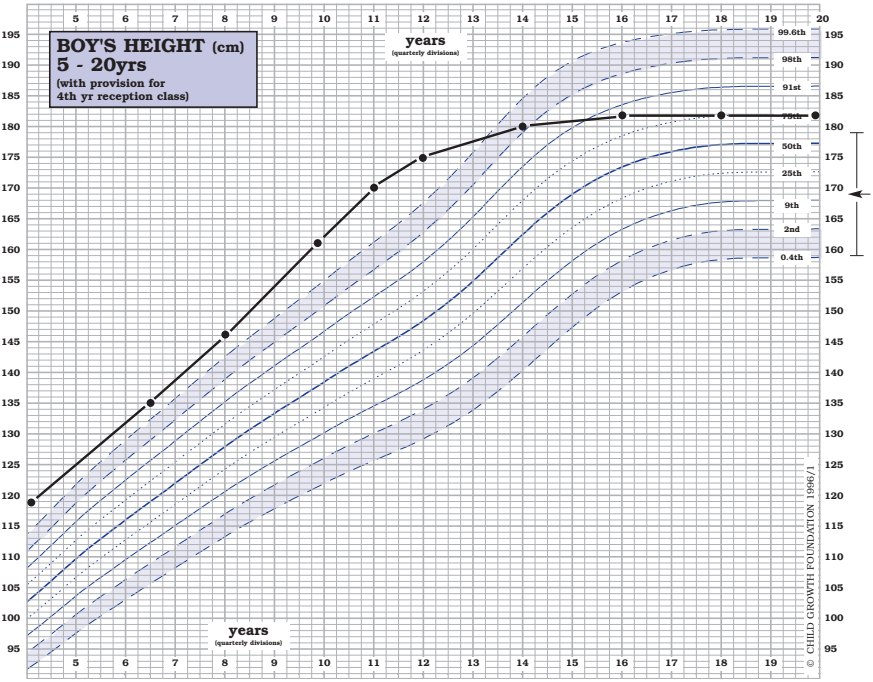
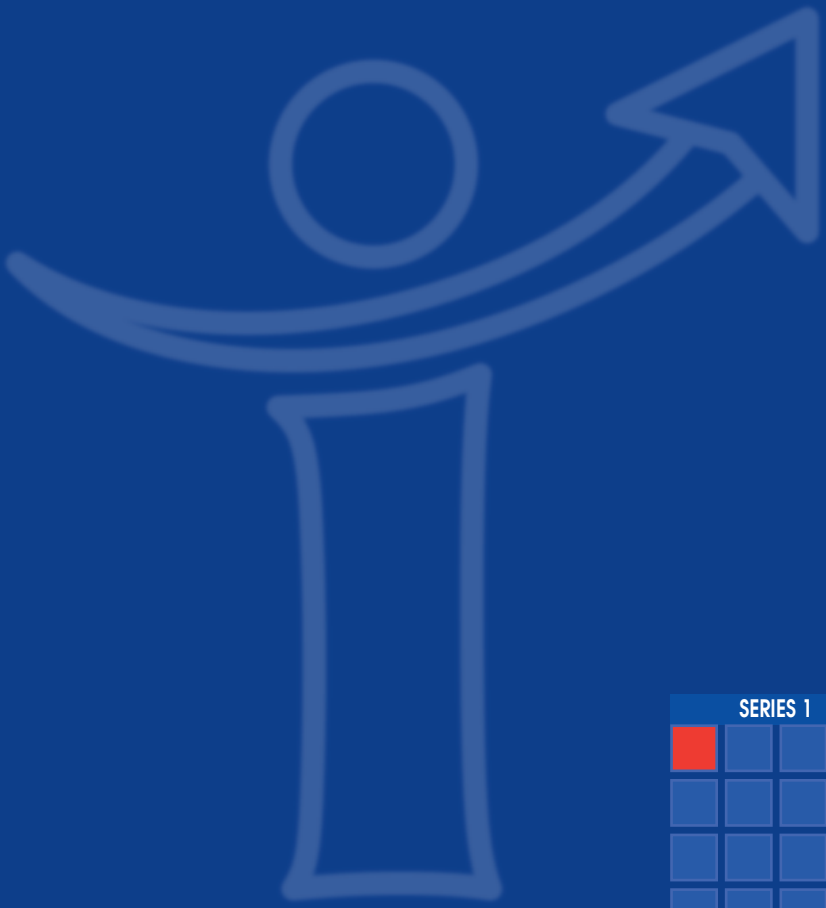


Figure 18: Sotos syndrome

Further reading:	**Sotos Info Pack**
Further contact:	**Child Growth Foundation/Sotos Syndrome Society**



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