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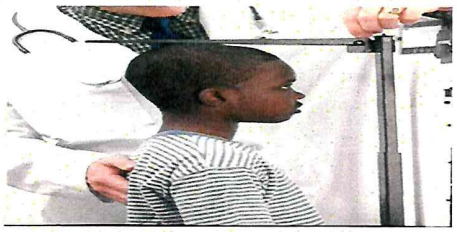
**FACULTE DE MEDECINE**

**DEPARTEMENT DE MEDECINE**

# MEMOIRE DE FIN D'ETUDES POUR L'OBTENTION DU DIPLOME DE DOCTORAT EN MEDECINE

## *THEME:* SHORT STATURE



***ETUDE FAITES AU NIVEAU DE SERVICE DE PEDIATRIE - KATUTURA***

***INTERMEDIATE HOSPITAL DE WINDHOEK, NAMIBIE***

***Présenté par:*** **Abisai Marta Kafute**

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# *Dedication*

***This piece of work is dedicated to my late father for having contributed a lot in my studies, may his soul continue resting in peace.***

***Special dedication to my mother and siblings for the support and all the sacrifices they have endured in life to make this possible.***

***May the Almighty grant them for everything they need.***

# *Acknowledgement*

***I would like to thank my professors and colleagues who helped me a lot during my studies in this faculty. It was not easy studying in French since I'm from an Anglophone country, but by the grace of God I managed to complete with my studies.***

# *Abstract*

Short stature is defined as height below 3rd centile or less than two standard deviations below the median height for that age and sex according to the population standard. Approximately 3% children in any population will be short, amongst which half will be physiological (familial or constitutional) and half will be pathological. Normal growth requires adequate nutrition along with various hormonal stimuli such as growth hormone (GH), insulin-like growth factor (IGF-1) and other growth factors.

Paediatricians need to develop a strategy for assessing and managing the short child because it is a common reason for referral to paediatric services. Understanding what is normal is a key prerequisite to the appropriate assessment of the short child. Most pathological causes of short stature will be associated with clues in the history or on examination. Factors that should trigger a more detailed assessment of the short child include malaise, dysmorphic features, slow growth and small size with a normal weight centile. Establishing that the healthy short child is growing appropriately for their family size can be reassuring for the family and clinician and will facilitate discharge**.**

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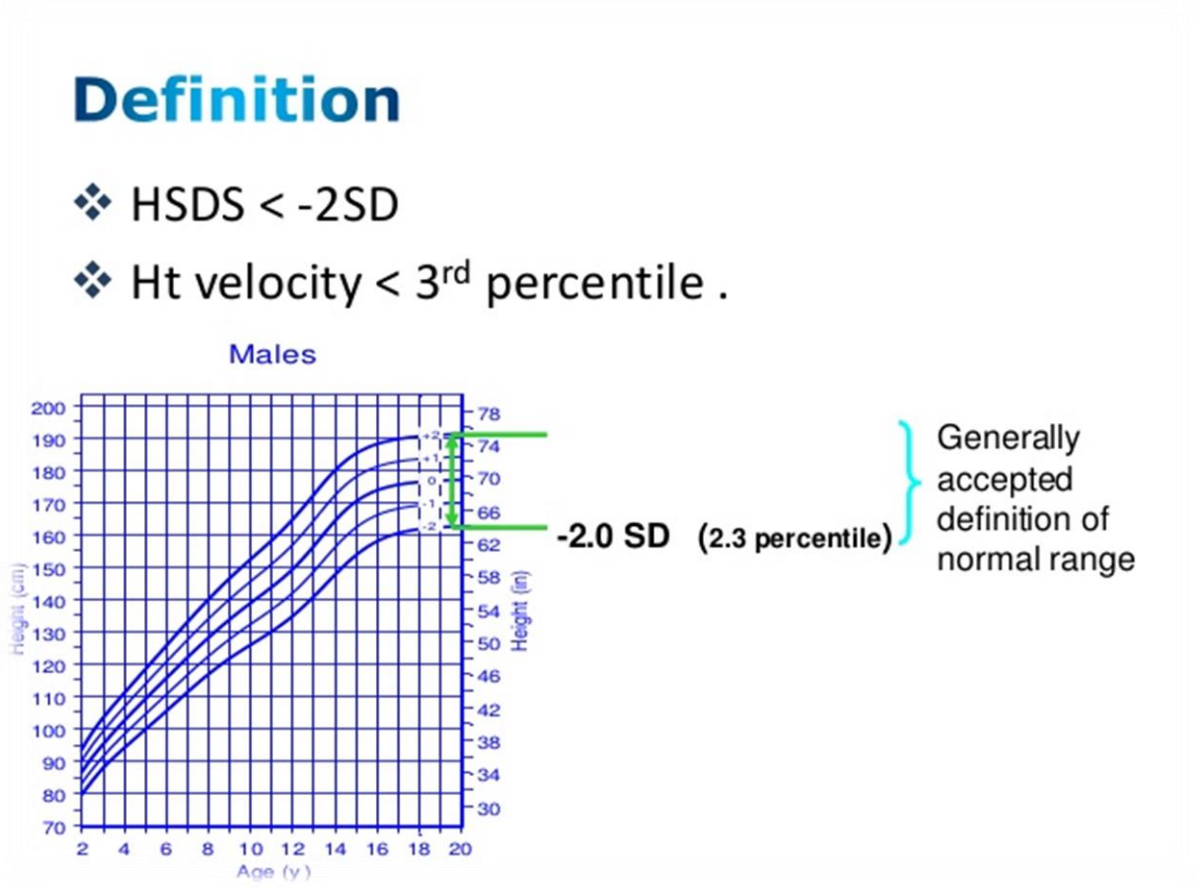
## I-Introduction

**Definition:**Shortstature is defined as height that is two standard deviations below the mean height for children of that sex and chronological age in a given population(height that is less than the 3rd percentile).

A growth velocity disorder is defined as an abnormally slow growth rate, which may manifest as height deceleration across two major percentile lines on the growth chart. One may more accurately identify children with growth disorders by the evaluation of the growth velocity.

In a population of children two standard deviations below the mean for height (-2SD) about 20 per cent may be expected to have pathological short stature, with the remaining 80 per cent equally divided between familial short stature and constitutional delay. In contrast, most children at -3SD below the population mean for height have pathological short stature.

The child with short stature should be examined carefully for dysmorphic feature, as many syndromes affect length/height. The upper to lower body segment ratio should also be measured since most skeletal dysplasias have predominantly long bone shortening and a consequent increase in this ratio.



## II-Pathophysiology

Growth implies an increase in the size, composition and distribution of tissues. It is associated with changes in their proportions, shapes and functions.

**4 phases of growth:**

1) ***Fetal:*** This is the fastest period of growth, accounting for about 30% of eventual height. Size at birth is largely independent of the father's height and of growth hormone. It is determined by the size of the mother and placental nutrient supply (depend on an adequate maternal diet), which in turn modulates fetal growth factors (IGF-2, human placental lactogen and insulin).
   Severe intra-uterine growth restriction and extreme prematurity when accompanied by poor postnatal growth can result in permanent short stature.

2) ***The infantile phase***: Growth during infancy to around 18 months of age is also largely dependent on adequate nutrition. Good health and normal thyroid function are also necessary.
   This phase is characterized by a rapid but decelerating growth rate, and accounts for about 15% of eventual height.

3) ***Childhood phase:*** This is a slow, steady but prolonged period of growth that contributes 40% of final height. Pituitary growth hormone (GH) secretion acting to produce insulin-like growth factor 1 (IGF-1) at the epiphyses is the main determinant of a child's rate of growth, provided there is adequate nutrition and good health. Thyroid hormone, vitamin D and steroids also affect cartilage cell division and bone formation.
   Profound chronic unhappiness can decrease GH secretion and accounts for psychosocial short stature.

4) ***Pubertal growth spurt:*** Sex hormones, mainly testosterones and oestradiol, cause the back to lengthen and boost GH secretion. This adds 15% to final height. The same sex steroids cause fusion of the epiphyseal growth plates and a cessation of growth.
   If puberty is early, which is not uncommon in girls, the final height is reduced because of early fusion of the epiphyses.

# III-Etiology of short stature

- ❖ Normal variants
- ❖ Pathological causes

## 1) NORMAL VARIANTS OF SHORT STATURE

a) ***Familial short stature*:** This isdefined by the height more than two standard deviations below the mid-parental height.

- ❖ Mid-parental height:
  Boys = [father's height in cm + mother's height in cm + 13 cm]/2
  Target height = mid-parental height ±7.5 cm

  Girls= [(father's height in cm – 13 cm) + mother's height in cm]/2
  Target height= mid-parental height ±6 cm

Most short children have short parents and fall within the centile target range allowing for mid-parental height. Care needs to be taken, though, that both the child and a parent do not have a dominantly inherited growth disorder.

In familial short stature, the height age (the chronological age corresponding to the $50^{th}$ percentile for the child's height) may be delayed several years, but the skeletal age is similar to the chronological age. Many family members may be short, and the child will grow at his or her genetic potential.

Familial short stature is the most common cause of short stature referred to clinical services. Calculating the target height range is required to demonstrate familial short stature, though if one parent is particularly short, one needs to consider whether they too may have a potentially inheritable underlying growth disorder. Children with familial short stature will have a height centile consistent with their short target height range and will demonstrate growth parallel to the centiles and consistent with a normal height velocity. Extensive investigations are not indicated but a careful explanation and reassurance for the child and parents is required to alleviate anxiety.

b) ***Constitutional delay of growth and puberty:***These children have delayed puberty, which is often familial, usually having occurred in the parent of the same sex. It is commoner in males. It is a variation of the normal timing of puberty rather than an abnormal condition. It may also be induced by dieting or excessive physical training. An affected child will have delayed sexual changes compared with his peers, and bone age would show moderate delay. The legs will be long in comparison to the back. Eventually the target height will be reached. The condition may cause psychological upset. The onset of puberty can be induced with androgens or oestrogens.

The height age and skeletal age are equally retarded with the respect to the chronological age. The members of the family are generally normal in height, but often have a history of delayed growth and delayed sexual maturation.

It's important to emphasize early detection of development delay to:

- Start early intervention and treatment
- Supply the parents an explanation for their inquiries about difficulties with their children as feeding, handling and sleeping
- To look for associated findings for management

***C) Small for gestational age infant:*** Short stature due to being small for gestational age is suggested when the birth weight is below the $10^{th}$ centile. Symmetrical growth failure implies adverse influences on fetal growth that have operated throughout much of development, whereas asymmetric growth failure in which head circumference is preserved implies growth failure restricted to the last part of pregnancy, often due to placental failure. There are many other underlying causes including:

- Major fetal defects (such as chromosomal and genetic defects, major structural malformations and intrauterine infection)
- Maternal influences including ill-health and excess cigarette and alcohol consumption.

❖ **Other causes:**

**1) Maternal causes**

- Utero starvation and placenta insufficiency

  -essential hypertension

  -pregnancy associated hypertension (PET)

  -chronic renal disease, long-standing diabetes

  -heart disease in pregnancy

  -multiple pregnancy

  -poor socio-economic circumstances

  -excess smoking, excess alcohol

**2) Fetal causes**

- Congenital abnormality ( chromosomal, syndromes e.g. potter's syndrome)
- Congenital infections ( STARCH or TORCH)
  STARCH- syphilis, toxoplasmosis, AIDS, rubella, CMV, HSV
  TORCH- toxoplasmosis, others, rubella, CMV, HSV
- Fetal toxins – alcohol, phenytoin and warfarin
- Infants usually display symmetrical growth retardation

❖ **Problems of small gestational age (SGA) baby**

**1) Hypoglycemia**

- Many SGA babies develop hypoglycemia probably due to the following:
  -reduced glycogen deposits (in liver, muscles and heart)
  -brain and heart are large and have high energy substrate demands
  -reduced glycogenolysis due to reduced catecholamine response to a falling B/glucose
  -infants show a reduced insulin response to a glucose load

-defective lipolysis
-hepatic gluconeogenesis is reduced

- Hypoglycemia may lead to neuroglycopenia
  -signs of apnea and convulsions can occur when B/sugars are < 1mmol/L
  -breast-feeding mothers encouraged to breast-feed 3hrly
  -hypoglycemia unlikely to be problematic after 48h of age

**2) Hypothermia**

-low surface area to birth weight ratio, low-subcutaneous fat

3) **Polycythemia**

-High altitude effect is associated with poor placental oxygen transfer leading to high red blood cells and erythropoietin levels leading to viscosity problems (thrombosis, disseminated intra-venues coagulation)

**4) Neutropenia and thrombocytopenia**

- Common with severe SGA, especially if birth weight<1000g

-platelets may be reduced because the bone marrow is committed to manufacturing red blood cells (due to hypoxia)

**5) Hypocalcemia**

-less commonly seen now, pathophysiology is not clear

**6) Infection**

-rare these days unless associated with very preterm

**7) Congenital abnormality**

-3-6% SGA babies have congenital abnormalities (chromosomal abnormalities, syndromes, disseminated congenital infections)

**8) Meconium aspiration**

**9) Pulmonary hemorrhage**

-probably related to intrapartum asphyxia and polycythemia

### ❖ Clinical features of SGA babies:

- Some infants have obvious congenital abnormalities, chromosome defects or intrauterine infection.
- Some appear scraggy with wasting (especially thighs)
- Fingernails are mature, long and cracking
- Desquamation of the skin (rapidly after birth)
- Infant usually active and vigorous
- Sucking is usually strong
- Weight loss after birth is less than for an appropriately sized baby

### ❖ Management for SGA:

- Early obstetric diagnosis and planned delivery
- Need for staff skilled in resuscitation

**Investigation:**

- Some will depend on clinical presentation
  -Check for blood glucose, Full blood count
  -Sepsis screen (blood culture, CRP, etc)
  -Viral culture (to rule out STARCH)
  -Ultrasound or CT head (in symmetric SGA)
  -Serum bilirubin
  -Karyotype DNA analysis (if necessary)

**Treatment:**

- Depending on the cause
- Treat infections if present
- Manage polycythemia if present
- Treat hypoglycemia
  -Advised to feed the baby as soon as is born
- Treat or prevent hypothermia e.g. Kangaroo mother care

**Outcome**

- Babies with asymmetric growth retardation have good prognosis
- Most of symmetrically growth retarded infants have bad prognosis
  -High mortality rate seen in babies with syndromes, chromosomal abnormalities and intrauterine infections.

D) ***Idiopathic short stature:*** This is a rare condition that causes extreme shortstature in children. These include absolute resistance to growth hormone (Laron syndrome), and primordial dwarfism.

Idiopathic short stature refers to short stature that does not have growth hormone resistance Primordial dwarfism Idiopathic short stature (ISS) a diagnostic explanation. In addition, abnormalities in a gene called SHOX (short stature homeobox) located on the X chromosome lead to severe short stature with skeletal abnormalities when present on both copies of the genes. Absence of one SHOX gene in Turner syndrome is thought to be the cause of short stature in this condition (and additional copies in Klinefelter syndrome produce taller than normal stature). Polymorphisms in this gene probably account for a proportion of idiopathic short stature.

Idiopathic short stature is the diagnostic group that remains after excluding known conditions in short children.

## 2) PATHOLOGICAL CAUSES OF SHORT STATURE

- ***Endocrine causes:*** Hypothyroidism, growth hormone (GH) deficiency, IGF-1 (insulin-like growth factor 1) deficiency and steroids excess are uncommon causes of short stature.
  They are associated with children being relatively over-weight i.e. their weight on a higher centile than their height.

1. ***Hypopituitarism and growth hormone deficiency:*** This disorderischaracterized by a deficiency of one, some, or all, of the peptide hormones secreted by the pituitary gland. The following circumstances may be associated with malfunction of the pituitary gland:
   - Cranial malformations, such as holoprosencephaly, septo-optic dysplasia, midline craniocerebral or midfacial abnormalities.
   - Embryonic defects, such as pituitary hypoplasia, pituitary aplasia, and congenital absence of the pituitary gland.
     Many of these defects have a genetic basis.
   - Long term survivors of childhood cancers may be at risk for hypopituitarism if the pituitary has not been shielded during cranial irradiation.
   - Infectious damage from meningitis or encephalitis
   - Infiltrative disorders such as histiocytosis
   - Trauma can lead to hypopituitarism

It is important to distinguish the patient with multiple anterior pituitary hormone deficiencies (i.e.deficiencies of TSH, ACTH and GH) from a patient with an isolated deficiency (e.g. GH deficiency only). Patients with suspected hypopituitarism should be investigated using stimulation tests at a referral center. Appropriate laboratory investigations would include thyroid function tests, serum cortisol, and insulin-like growth factor (IGF).

The evaluation of the growth hormone secretory status is complex, but it is possible to accurately assess GH secretion in the majority of children. As GH is relatively expensive, the decision to treat with GH must be made after careful evaluation of the possible benefits.

In other words, hypothyroidism is usually caused by autoimmune thyroiditis during childhood. This produces growth failure, usually with excess weight gain. It may go undiagnosed for many years and lead to short stature. When treated, catch-up growth rapidly occurs but often with a rapid entry into puberty that can limit final height.

Both congenital and acquired hypothyroidisms cause growth failure. Congenital hypothyroidism is diagnosed soon after birth by screening and so does not result in any abnormality of growth.Hypothyroidism suppresses GH secretion. Furthermore, in the absence of thyroid hormone action through its receptor sites, the growth and anabolic effects of GH and IGF-1 are down-regulated. The growth failure of hypothyroidism can be reversed by thyroxine treatment. Untreated congenital hypothyroidism and acquired hypothyroidism result in poor growth.

Growth hormone deficiency may be an isolated defect or secondary to hypopituitarism. Pituitary function may be abnormal in congenital mid-facial defects or as a result of a cranio-pharyngioma (a tumor affecting the pituitary region), a hypothalamic tumor or trauma such as head injury, meningitis and cranial irradiation. Craniopharyngioma usually presents in late childhood and may result in abnormal visual fields (characteristically a bitemporal hemianopia as it impinges on the optic chiasma), optic atrophy or papilloedema on fundoscopy (signs of intracranial pressure).

In growth hormone deficiency, the bone age is markedly delayed. Laron syndrome is a condition due to defective growth hormone receptors resulting in growth hormone insensitivity. Patients with this condition have high growth hormone levels but low levels of down-stream active product of growth hormone known as insulin-like growth factor 1 (IGF-1) produced at the growth plate and in the liver. Rare abnormalities in the gene producing IGF-1 have also recently been discovered in children.

A family history of other similarly affected individuals would suggest a mutation in the GHRH or GH-1 gene, or in genes that encode the transcription factors involved in pituitary development.

Investigations for possible GH deficiency are only indicated once baseline investigations for no-GH-related causes of short stature have been performed and found to be normal. GH is secreted in a pulsatile fashion and as levels are low throughout most of a 24 hour period, random blood samples to measure GH concentrations are generally unhelpful. Monitoring blood samples every 20 minutes to produce a 24 hour GH secretory profile is challenging both to organize and to interpret and so stimulatory tests of GH secretion are the most clinically useful way to diagnose GH deficiency.

The gold standard GH stimulation test involves insulin-induced hypoglycemia, which promotes a counter-regulatory GH secretory response and also allows measurement of the ACTH-induced cortisol response. However, this test is potentially dangerous and should only be performed in children over five years old in units experienced in its use. Alternative GH secretagogues include glucagon, which also stimulates cortisol release, clonidine and arginine, which stimulate GH alone, and GHRH, which stimulates the pituitary directly.

A GHRH stimulation test is poor at distinguishing hypothalamic forms of GH deficiency from a normal short child and is therefore rarely used in childhood testing. A high peak of GH response (in excess of 8.3 ng/dL) excludes a diagnosis of GH deficiency whereas intermediate values (5-8.3 ng/dL) suggest GH insufficiency if the growth pattern is consistent with this diagnosis. Low values (<5ng/dL) indicate moresevere forms of GH deficiency. In the UK, because of the limited sensitivity and specificity of these tests to diagnose GH deficiency, two abnormal responses to GH testing are required to make a diagnosis unless there is radiological evidence of intracranial abnormalities consistent with the diagnosis. If a diagnosis of GH deficiency is made, an MRI scan is mandatory to exclude an underlying tumor. Consideration of tests for wider pituitary dysfunction is then also necessary.

Prior to treating GH deficiency, it is important to obtain accurate growth data, preferably over a minimum one year period, against which the benefits of GH treatment can be assessed. GH produced by recombinant DNA technology is administered by daily subcutaneous injection. The growth response should be evaluated by measurements every four to six months. Large post-marketing surveillance studies of responses to GH therapy have shown that these are related to severity of GH deficiency, pre-treatment height velocity, age, difference in child's height from parents' heights, birth weight, current weight and dose of GH. Taking these factors together, it is now possible to predict response to GH and to 'personalize' the dose of GH for the child to ensure a maximal and cost-effective response.

A maximum growth response to GH therapy occurs in the first year, with tachyphylaxisaccurring thereafter, presumably due to down-regulation of the GH receptor. An increase in height velocity of at least 2cm/year is indicative of a successful response. Values less than this would call into doubt adherence to therapy or a diagnosis of GH deficiency.If a poor response persists, consideration should be given to discontinuation of therapy in the longer term. Once growth is complete after puberty, GH testing should be repeated, as mild forms of GH deficiency do not require ongoing therapy into adult life, during which lower levels of GH are required for maintenance of normal body composition, bone health and avoidance of cardiovascular risk factors. Ongoing monitoring for wider defects in pituitary function is important in supervising GH therapy.

In the very circumstances of GH resistance, GH therapy is ineffective and recombinant IGF-1 treatment is indicated.

2. ***Corticosteroid excess, Cushing syndrome:*** This is usually iatrogenic, as corticosteroid therapy is a potent growth suppressor. This effect is greatly reduced by alternate day therapy, but some growth suppression may be seen even with relatively low doses of inhaled or topical steroids in susceptible individuals.

   Non-iatrogenic Cushing syndrome is very unusual in childhood and may be caused by pituitary or adrenal pathology. Growth failure may be very severe, usually with excess weight gain, although normalization of body shape and height occurs on withdrawal of treatment or treatment of the underlying steroid excess. Cushing syndrome during puberty can result in permanent loss of height.

   Cushing syndrome is characterized by marked growth failure. Excess cortisol levels directly suppress both GH secretion and action as well as delaying the onset of puberty.

   Glucocorticoid excess in Cushing syndrome can retard bone maturation and most affected children will be short.

- ***Clinical features of Cushing syndrome***

-Growth failure/ short stature
-Face and trunk obesity
-Red cheeks
-Hirsutism
-Striae
-Hypertension
-Bruising
-Carbohydrate intolerance
-Muscle wasting and weakness
-Osteopenia
-psychological problems

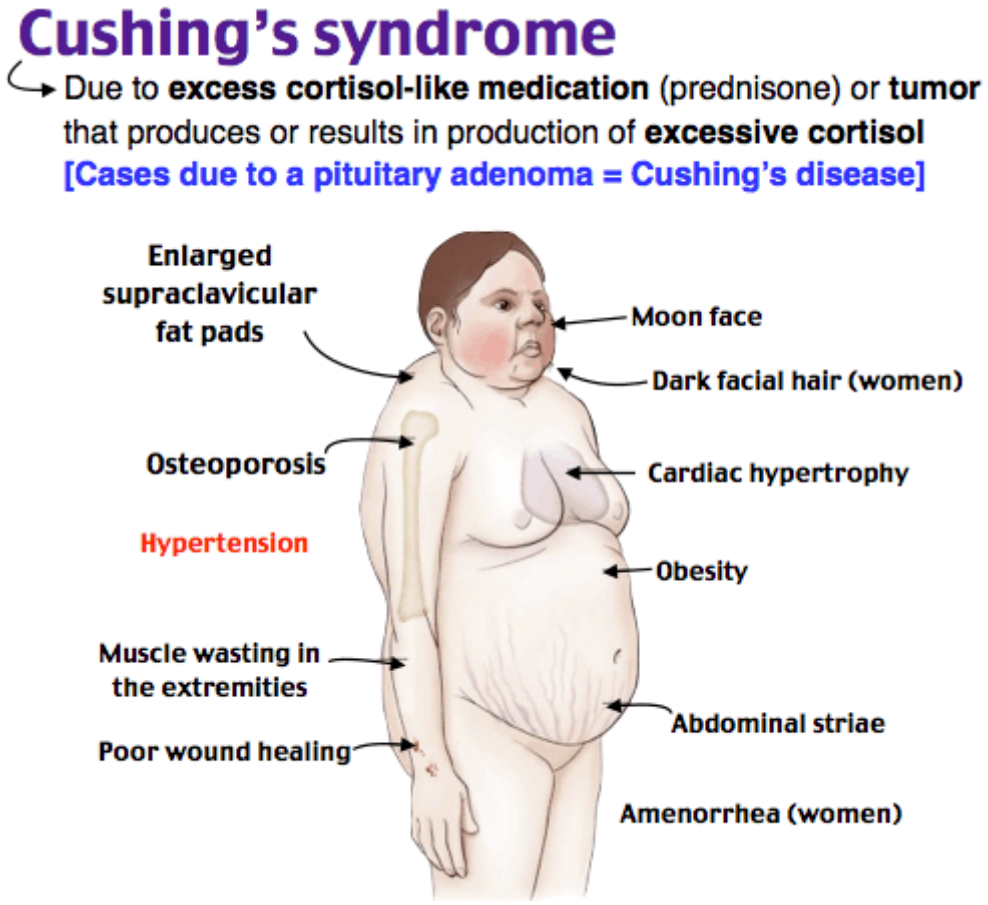



**Figure:** Cushing syndrome

A diagnosis of Cushing syndrome is often questioned in obese children. Most obese children from dietary excess are of above-average height, in contrast to children with Cushing syndrome, who are short and have growth failure.

If Cushing syndrome is a possibility, then the normal diurnal variation of cortisol (high in the morning, low at midnight) may be shown to be lost – in Cushing syndrome the midnight concentration is also high. The 24 hour urine free cortisol is also high. After the administration of dexamethasone, there is failure to suppress the plasma 09.00 h cortisol levels. Adrenal tumors are identified on CT or MRI scan of the abdomen and a pituitary adenoma on MRI brain scan.

Adrenal tumors are usually unilateral and are treated by adrenalectomy and radiotherapy if indicated. Pituitary adenomas are best treated by trans-sphenoidal resection, but radiotherapy can be used.

3. ***Congenital adrenal hypoplasia (CAH):***Excess doses of steroids or inadequate treatment with consequent androgen-induced advancement of bone age can result in short stature.
4. ***Pseudohypoparathyroidism:*** End-organ resistance to parathyroid hormone may present with a distinct phenotype that is *shortstature,*truncal obesity, short metacarpals, round face and mental retardation.
5. ***Poorly controlled diabetes mellitus:*** Children with poorly controlled diabetes exhibit poor growth. The combination of poor growth failure and hepatosplenomegaly due to excess hepatic deposition of glycogen in poorly controlled diabetics is known as Mauriac syndrome.

- ***Systemic disorders:*** Normal growth is an indicator of good health. Malnutrition and illness are associated with a decreased growth rate. When evaluating growth failure, nutritional deficiencies and systemic illness must be excluded.
  This is a relatively common cause of abnormal growth. These children are usually short and underweight: i.e. their weight is on the same or a lower centile than their height. Inadequate nutrition may be due to insufficient food, restricted diets or poor appetite associated with a chronic illness, or from the increased nutritional requirement from a raised metabolic rate.

  A careful clinical examination is necessary to rule out systemic chronic illnesses which may present with short stature:
  - Coeliac disease, which usually presents in the first two years of life, but can present late with growth failure. Coeliac disease may result in short stature without gastrointestinal symptoms
  - Crohn disease
  - Chronic renal failure – may be present in the absence of a history of renal disease
  - Rickets, metabolic disease (e.g. renal tubular acidosis), cardiac, pulmonary, hepatic, hematological and collagen vascular disease can all compromise growth.
  - Abnormal growth may also be a reflection of suboptimal therapy of a chronic condition (e.g. asthma). Growth failure is a common feature of infectious disease, including HIV infection.

    All diseases impair growth, so a child who is not growing needs a diagnosis and treatment. A short child growing at a rate appropriate for his age may need a diagnosis to explain why he is short, but an active disease process is unlikely in such a child.
    A systematic approach is needed to a child presenting with short stature in order to arrive at a diagnosis. After excluding systemic disease, genetic conditions (e.g. Turner's syndrome), malnutrition and having considered the possibility of 'normal' variants (specifically constitutional delay of puberty and familial short stature), an endocrine cause for the short stature may be considered. Clinical clues to the presence of an endocrine cause include a 'cherubic' appearance of the face (in growth hormone deficiency) and an increased weight to height ratio, with the child appearing to be obese. Neonatal clues to growth hormone deficiency include hypoglycaemia and micropenis.

- ***Genetic diseases with primary effects to growth (syndromic short stature):*** Many chromosomal disorders and syndromes are associated with

short stature**.** Down syndrome is usually diagnosed at birth, but Turner, Noonan and Russell-Silver syndromes may present with short stature. Turner syndrome may be particularly difficult to diagnose clinically and should be considered in all short females.
Fetal alcohol spectrum disorder can also cause syndromic short stature**.**

1. ***Russell-Silver syndrome:*** This syndrome is an example of an imprinted disorder, usually caused by maternal uniparentaldisomy of chromosome 7. Imprinted disorders are associated with assisted reproductive techniques and often cause abnormalities of growth.
   Russell-Silver syndrome is characterized by intrauterine growth restriction, increased risks of hypoglycemia and sweating, asymmetry (one side of the body being shorter than the other) and short stature with failure to catch up growth, thinness, a triangular-shaped face with a small pointed chin and clinodactyly. Treatment involves optimal dietary support and, for some, GH therapy.

***2.*** ***Fetal alcohol spectrum disorder:*** Alcohol is a teratogen and exposure in utero causes a number of problems, including impaired growth at anytime point postnatally, brain damage leading to poor concentration, behavior and learning difficulties and a characteristic facial appearance of microcephaly, a flat mid-face, low-set ears and micrognathia.

3. ***Turner's syndrome:*** This is caused by a loss or abnormality of one X chromosome, affecting 1 in 2500 girls.Although the phenotype is relatively mild for such a major chromosomal anomaly, reflecting the partial inactivation of the second X chromosome from early fetal life, 99% of conceptions result in miscarriage or stillbirth.

   About one third of genes on the short arm (Xp) are unsilenced, including the short stature homeobox (SHOX) gene, and these account for the characteristic features, which include: a skeletal dysplasia causing short stature, short fourth and fifth metacarpals, cubitus valgus, micrognathia, ovarian failure leading to pubertal failure and infertility, lymphoedema, neck webbing, a low hairline and increased naevi, congenital heart disease, particularly coarctation of the aorta, wide-spaced nipples, Madelung deformity (a focal dysplasia of the distal radial physis), middle-ear problems, renal anomalies, specific learning difficulties related to numeracy and visuospartial tasks, social vulnerability, and an increased risk of autoimmune and inflammatory disease.

   Many children with Turner's syndrome have few abnormal findings and so karyotyping is essential in any girl with impaired growth of unknown aetiology.

   Treatment requires GH therapy to improve growth, oestrogen induction of puberty and specific monitoring for cardiac, renal, autoimmune and hearing abnormalities.

4. ***Noonan's syndrome***: May affect as many as 1 in 1000 individuals. It is caused by mutations of genes involved in the *RAS/MAPK* signaling pathway (including the *PTPN11, SOS1, KRAS* and *RAF-1* genes) and is inherited in an autosomal dominant manner.
   Clinical features include short stature, scoliosis, low-set ears, ptosis, pectusexcavatum, cubitus valgus, pulmonary stenosis, cryptorchidism and delayed puberty, lymphoedema, mild educational difficulties and a coagulation defect.

5. ***Skeletal dysplasias:*** A range of bony dysplasias may cause short stature. Depending on which part of the skeleton is involved, impacts on growth may lead to skeletal disproportion, which justifies the measurement and comparison of both sitting and standing heights. Many skeletal dysplasias are inherited in an autosomal dominant pattern and so the possibility of an affected parent of a short child should be considered.
   Achondroplasia and hypochondroplasia cause rhizomeric (shortening of the proximal limb segment) short stature and are often found to be caused by mutations of the fibroblast growth factor receptor 3 (*FGFR3*) gene. The mutated receptor is constitutionally active and inhibits cartilage formation and thus bones growth. Spondyloepiphysealdysplasis leads to markedly impaired trunk growth and less severely affected short limbs, causing a disproportionately short sitting height. In children with short-limbed forms of short stature, height may be improved by leg-lengthening surgery.

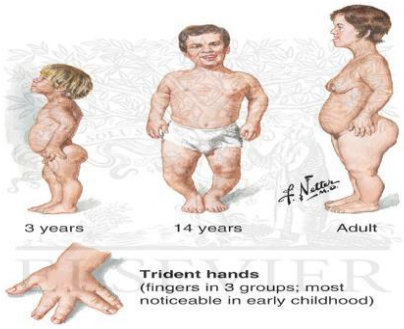



**Figure:** Achondroplasia

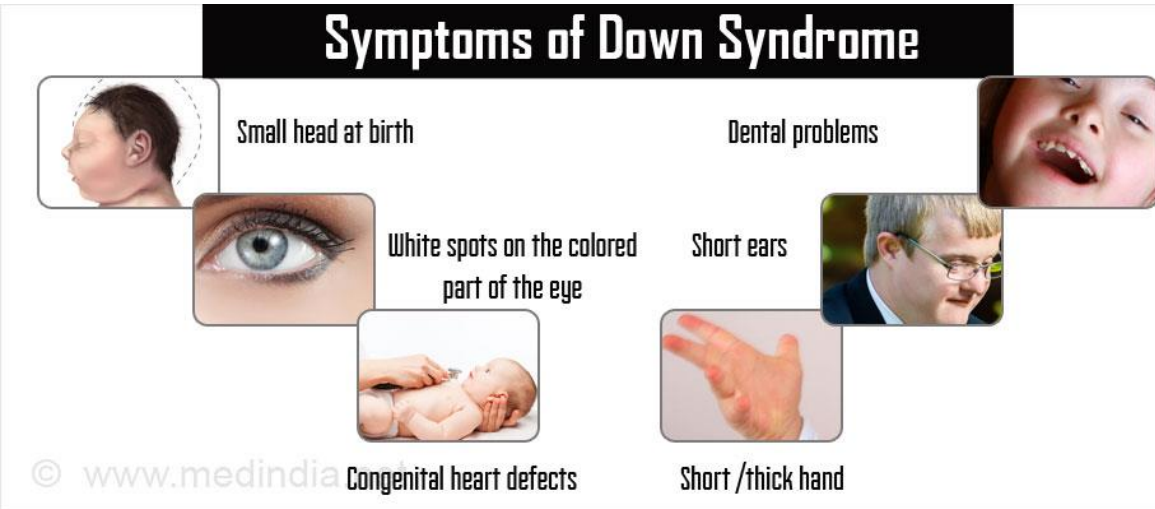
6. ***Down syndrome (trisomy 21):*** This is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. It is typically associated with physical growth delays (short stature), characteristic facial features, and mild to moderate intellectual disability.
   Down syndrome is the most common autosomal trisomy and the most common genetic cause of severe learning difficulties. The incidence (without antenatal screening) in live-born infants is about 1 in 650.

❖ ***Clinical features:***

Down syndrome is usually suspected at birth because of the baby's facial appearance. Most affected infants are hypotonic and other useful clinical signs include a flat occiput, single palmar creases, incurved fifth finger and wide 'sandal' gap between the big and second toe.

The diagnosis can be difficult to make when relying on clinical signs alone and a suspected diagnosis should be confirmed by a senior paediatrician.

Before blood is sent for analysis, parents should be informed that a test for Down syndrome is being performed. The results may take 1-2 days, using rapid FISH (fluorescent in situ hybridisation) techniques. Parents need information about the short and long-term implications of the diagnosis. They are also likely, at some stage in the future, to appreciate the opportunity to discuss how and why the condition has arisen, the risk of recurrence and the possibility of antenatal diagnosis in future pregnancies.

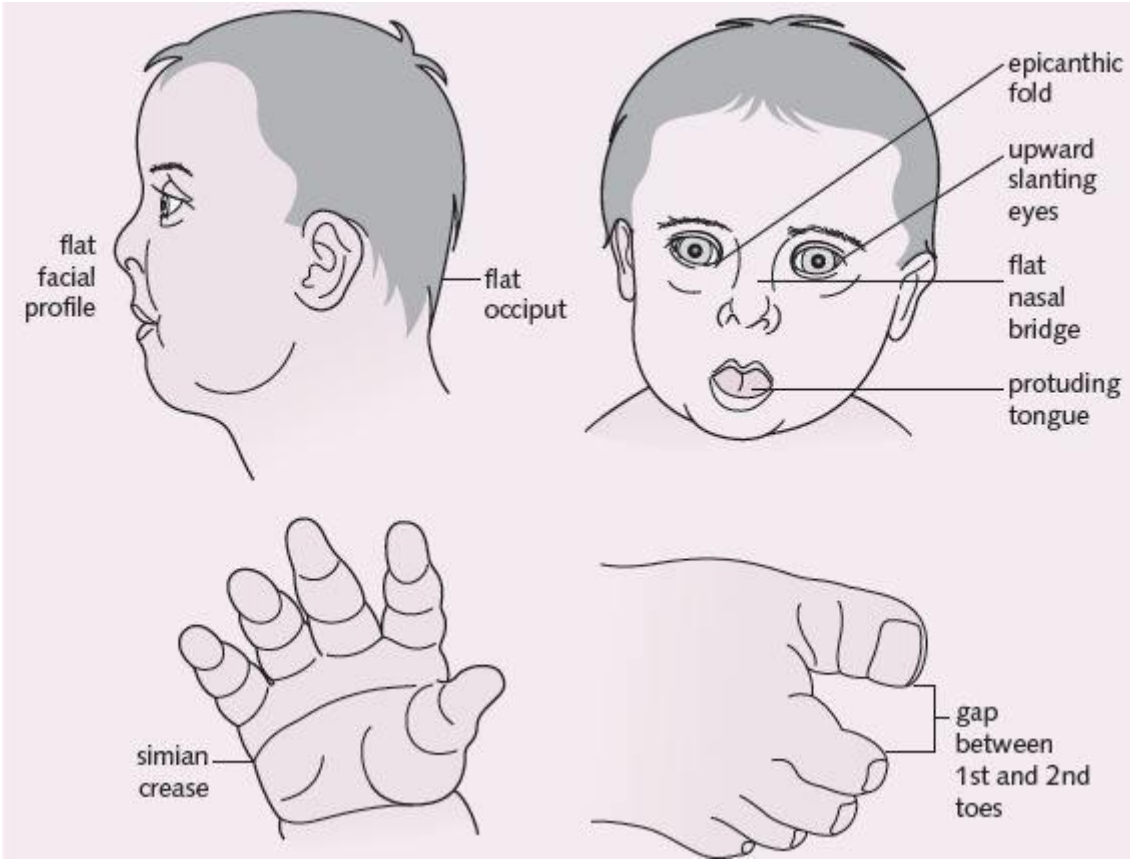


It is difficult to give a precise long-term prognosis in the neonatal period, as there is individual variation in the degree of learning difficulty and development of complications.

Over 85% of infants with trisomy 21 survive to 1 year of age. Congenital heart disease is present in 30% and, particularly atrioventricular canal defect, is a major cause of early mortality. At least 50% of affected individuals live longer than 50 years. Parents also need to know what assistance is available from both professionals and family support groups. Counseling may be helpful to assist the family to deal with feelings of grief, anger or guilt.

The Child Development Service will provide or coordinate care for the parents. This will include regular review of the child's development and health.

Children with Down syndrome are at increased risk of hypothyroidism, impairment of vision and hearing and of antlanto-axial instability.



**Characteristics clinical manifestations of Down syndrome**

***Typical craniofacial appearance:***

- Round face and flat nasal bridge
- Upslanted palpebral fissures
- Epicanthic folds (a fold of a skin running across the inner edge of the palpebral fissure)
- Brushfield spots in iris (pigmented spots)
- Small mouth and protruding tongue
- Small ears
- Flat occiput and third fontanelle

***Other anomalies:***

- Short neck
- Single palmar creases, incurved fifth finger and wide 'sandal' gap between toes
- Hypotonia
- Congenital heart defects (40%)
- Duodenal atresia
- Hirschsprung disease

***Later medical problems:***

- Delayed motor milestones
- Moderate to severe learning difficulties
- Small stature (short stature)
- Increased susceptibility to infections
- Hearing impairment from secretory otitis media
- Visual impairment from cataracts, squints, myopia
- Increased risk of leukaemia and solid tumours
- Risk of atlanto-axial instability
- Increased risk of hypothyroidism and coeliac disease
- Epilepsy
- Alzheimer's disease

# IV-Assessment of a child with short stature

1. ***History-taking*****:** Growth failure can arise from genetic abnormalities**,** nutritional and endocrine problems and defects in almost any organ system. Therefore, when assessing a child referred with a possible growth disorder, a detailed and wide-ranging history is required. Details should be sought of:
    - Family history, including parental heights and their timing of puberty, given the important influence of genetics on such factors
    - Pregnancy, mode of delivery and birth weight, which may impact on the infant phase of growth
    - Feeding history
    - Development of signs of puberty
    - Headache, visual disturbance or symptoms to suggest pituitary dysfunction or intracranial disease
    - Details of systemic symptoms that might suggest any coexistent medical disorder
    - Social history, including details of how the short stature is affecting the child

***2. Measurement:*** Growth must be measured accurately, with attention to correct technique and accurate plotting of the data:
    - Weight – readily and accurately determined with electronic scales but must be performed on a naked infant or a child dressed only in underclothing as an entire month's or year's weight gain can be represented by a wet nappy or heavy jeans, respectively.
    - Height – the equipment must be regularly calibrated and maintained. In children over 2 years of age, the height is measured vertically using a stadiometer (preferably wall-mounted) and the child is measured without shoes or socks, with heels, buttocks and shoulders against the backplate and the head in the Frankfurt plane (an imaginary line connecting the lower border of the eye socket with the external auditory meatus). There is no evidence that undertaking stretched measurements with upward pressure on the mastoid processes achieves greater consistency, but the same technique should be used when comparing sequential measures.

**Figure:** Height measurement for children under 2 years of age

**Figure:** Height measurement for children over 2 years of age

Height measurements should be compared with weight (assessed in a child wearing minimal clothing) by plotting measurements on a growth chart. In the UK, the UK-WHO growth charts are used. These are a composite of the UK90 charts derived from cross-sectional growth data and the WHO growth standards, which describe the growth of healthy breastfed children from six countries. Because of the association of weight with height (tall children tend to be heavier), interpretation of weight data requires adjustment for height. This should be done by calculating the body mass index (weight in kilograms/ (height in metres) $^2$) and plotting this on a centile chart.

To help interpret the growth pattern, height measurements should be compared with other measurements taken in the past by plotting all available measurements on a growth chart to evaluate whether crossing of centiles has occurred, which implies an abnormal height velocity.

The appropriateness of the child's height for their genetic background is assessed by calculating the target height range (requires parental height measurements), which is the mid-parental centile (the mid-point between the parents' centiles) +/- 8.5 cm.

In children under 2 years, length is measured lying horizontally using the mother to assist. Supine table measurements or a neonatometer and two observers are required to assess length, ensuring that the Flankfurt plane is vertical and that the child's head is in firm contact with the headboard and the foot dorsiflexed against the movable baseplate.

Accurate length measurement in infants can be difficult to obtain, as the legs need to be held straight and infants often dislike being held still. For this reason, routine measurement of length in infant is often omitted from child surveillance, but it should always be performed whenever there is doubt about an infant's growth.

- Head circumference – the occipitofrontal circumference is a measure of head and hence brain growth. The maximum of three measurements is used. It is of particular importance in developmental delay or suspected hydrocephalus.

These measurements should be plotted as a simple dot on an appropriate growth centile chart. Standards for a population should be constructed and updated every generation to allow for the trend towards earlier puberty and taller adult stature from improved childhood nutrition.

In 2009, the UK adopted the World Health Organization (WHO) new global Child Growth Standards for infants and children 0-4 years old. The new charts are based on the optimal growth of healthy children totally breast-fed up to the age of 6months. These charts allow for the lower weight of totally breast-fed infants and are therefore less likely to identify some breast-fed babies as underweight and may also allow early identification of bottle-fed babies gaining weight too rapidly.

Height in a population is normally distributed and the deviation from the mean can be measured as a centile or standard deviation. The bands on the growth reference charts have been chosen to be two-thirds of a standard deviation apart and correspond approximately to the 25$^{th}$, 9$^{th}$, 2$^{nd}$ and 0.4$^{th}$ centiles below the mean, and the 75$^{th}$, 91$^{st}$, 98$^{th}$ and 99.6$^{th}$ centiles above the mean. The further these centiles lie from the mean, the more likely it is that a child has a pathological cause for his short or tall stature. For instance, values below the 0.4$^{th}$or above the 99.6$^{th}$ centile will occur by chance in only 4 per 1000 children and can be used as a criterion for referral from primary to specialist care. A single growth parameter should not be assessed in isolation from the other growth parameters: e.g. a child's low weight may be in proportion to the height if short, but abnormal if tall.

Serial measurements are used to show the pattern and determine the rate of growth. This is helpful in diagnosing or monitoring many paediatric conditions. The WHO charts include an adult height predictor and a BMI centile ready-reckoner.

**SUMMARY : MEASUREMENT OF CHILDREN**

- Measurement must be accurate for meaningful monitoring of growth
- Growth parameters should be plotted on charts
- Significant abnormalities of height are:
  -Measurements outside the 0.4$^{th}$ or 99.6$^{th}$ centiles if the mid-parental height is not short or tall
  -If markedly discrepant from weight
  -Serial measurements which cross growth centile lines after the first year of life.

3. ***Examination:*** A fundamental requirement when examining children with growth disorders is an accurate measurement of their growth.
   Because of the effect of time of day (human height shortens as the day progresses) and inter-observers variation on measurement, serial growth measurements should be undertaken at approximately the same time of the day and preferably by the same measurer. Over the age of two years, a stadiometer (preferably wall-mounted) should be used and the child measured without shoes or socks, with heels, buttocks and shoulders against the backplate and the heard in the Flankfurt plane (an imaginary line connecting the lower border of the eye socket with the external auditory meatus). There is no evidence that undertaking stretched measurements with upward pressure on the mastoid processes achieves greater consistency, but the same technique should be used when comparing sequential measures.
   Under the age of two years, supine table measurements or a neonatometer and two observers are required to assess length, ensuring that the Flankfurt plane is vertical and that the child's head is in firm contact with the headboard and the foot dorsiflexed against the movable baseplate.
   A skeletal dysplasias may impair growth of different parts of the skeleton differentially, the sitting height, which is a proxy for vertebral body growth, should be measured using a table-mounted stadiometer. Subtracting sitting height from standing height produces the sub-ischial leg length, which is a measure of long bone growth in the leg. Head circumference should be measured in children under the age of two years.

Height measurements should be compared with weight (assessed in a child wearing minimal clothing) by plotting measurements on a growth chart. In the UK, the UK-WHO growth charts are used. These are the composite of the UK90 charts derived from cross-sectional growth data and the WHO growth standards, which describe the growth of healthy breastfed children from six countries. Because of the association of weight with height (taller children tend to be heavier), interpretation of weight data requires adjustment for height.

This should be done by calculating the body index mass (weight in kilograms / height in meters)$^{2}$) and plotting this on a centile chart. To help interpret the growth pattern, height measurements should be compared with other measurements taken in the past by plotting all available measurements on a growth chart to evaluate whether crossing of centiles has occurred, which implies an abnormal height velocity. The appropriateness of the child height for their genetic background is assessed by calculating the target height range (requires parental height measurements), which is the mid-parental centile (the mid-point between the parents centiles) ± 8.5cm.

Additional features that should be assessed on thorough physical examination of a child with abnormal growth include:

- General appearance and nutritional state
- Dysmorphic features, particularly of the craniofacial skeleton or suggestive of skeletal disproportion or an underlying syndrome
- Pubertal staging, which is important in evaluating the chronology of physical development which has major influences on growth
- A detailed systems review including blood pressure, visual fields and fundoscopy, as disease of almost any system may present with growth abnormalities.

Plotting present and previous heights and weights on appropriate growth charts, together with the clinical features, usually allows the cause to be identified without any investigations. Previous height and weight measurements should be available from the parent-held personal child health record. The bone age may be helpful, as it is markedly delayed in some endocrine disorders e.g. hypothyroidism and growth hormone deficiency, and is used to estimate adult height potential.

❖ **Growth charts**

These are constructed for boys and girls separately, using the data from large populations of normal children living under near-optimal conditions and therefore representing the range of normal growth achieved by children at different ages. The most important feature of growth charts is that they provide the health professional with a measure with which to compare and monitor the physical status of childhood populations or of an individual child on an ongoing basis.

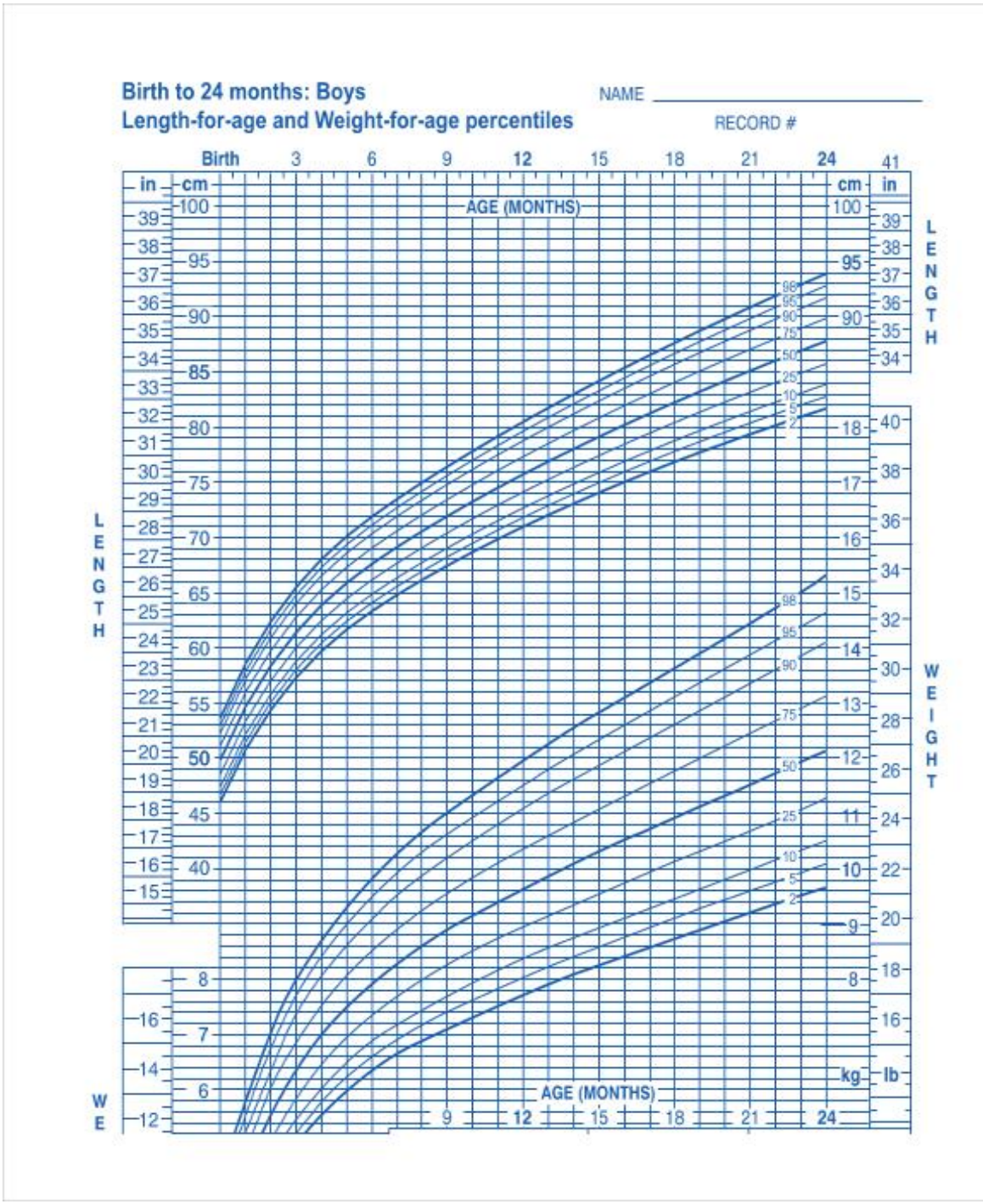



**Figure:** Growth chart for boys


**Figure:** Growth chart for girls

❖ **Z-scores and centiles**

Normal children vary widely in length or height, weight and head circumference at any age, and in the velocity of growth from one age to the next. This variation within the normal range at a given age is expressed conventionally by comparing the individual child's measurements to

standard deviations (z-scores) or centiles around the mean (z-score = 0 or $50^{th}$ centile). The World Health Organization (WHO) growth standards from birth to five years of age are based on the growth of normal, health breastfed infants in various regions of the world.

The z-scores indicate the number of standard deviations away from the mean with zero representing the mean. WHO growth reference charts are based on original data from North American children from the National Center for Health statistics supplemented by more recent data.

Length for height for boys and girls from birth to 5 years of age and head circumference charts from 0-5 years of age are normally used. The weight for age charts only go up to the age of 5years since this parameter is difficult to interpret beyond that age due to marked variations in height and stage of puberty. Body mass index (BMI) is calculated by dividing the weight in kilograms by the height$^2$ in metres (kg/m$^2$).

It is important to understand the meaning of z-scores and centiles. If the height or weight percentiles were constructed from a population of 1000 healthy children at a given age, the smallest 2.5 per cent would have height or weight measurements less than two standard deviations from the mean, corresponding to a z-score of <-2, approximately 15 per cent would be less than one standard deviation (z-score <-1) and 50 percent would be less than the mean.

Similar principles apply to measurements above the mean. Height and weight have a normal (Gaussian) distribution and a z-score = 0 corresponds to the mean and median height and weight of the population measured. Thus a weight or a length/height below a z-score of -2 is not necessarily abnormal because 2.5 per cent of the normal population will be below a z-score of -2. However, it should serve as a warning that there may be an underlying problem. When percentiles are used, two standard deviations above and below the mean are more conveniently represented by the $2^{nd}$ or $3^{rd}$ and $97^{th}$ or $98^{th}$ centile.

With respect to the Integrated Management of Childhood Illness (IMCI), if the weight for age is below a z-score of -2, the child is regarded as low weight-for-age and requires careful follow up and referral after one month if there has been no weight gain. When the weight-for-age is below a z-score of -3 the child is regarded as very low weight for age, which is classified as a danger sign and warrants immediate referral.

Individuals tend to 'track' along the same z-score or centile over time and repeat measurements are far more useful than single measurements. Visual inspection of a child's tracking will tell whether the child is progressing normally. Progressive deviation from the z-score line indicates a problem of growth and is a strong indication for early intervention. For example, a single measurement on the z-score line of -2 may represent normal genetic potential on the one hand, or gross deviation on the other, if earlier measurements had been on the z-score line of zero or higher.

**SUMMARY: ASSESSMENT OF A CHILD WITH SHORT STATURE**

**Examination of the growth chart:**

- Following growth centile lines for length/height, weight and and head circumference?
  Consider familial, low birth weight, constitutional delay of growth and puberty, syndromes and skeletal dysplasias
- Growth failure with crossing of centile lines?
  Consider endocrine (including therapeutic corticosteroids), nutrition/chronic illness, psychosocial deprivation

**Determine the mid-parental height:**

- For genetic target range

**History:**

- Birth length, weight, head circumference and gestational age
- Pregnancy history: infection, intra-uterine growth restriction, drug use, alcohol/smoking
- Feeding history
- Developmental milestones
- Family history of constitutional delay of growth and puberty or other diseases?
- Consanguinity pertaining to inherited conditions
- Features of chronic illness, endocrine causes, e.g. hypothyroidism, pituitary tumour, Cushing syndrome or psychosocial deprivation?
- Medications, e.g. corticosteroids?

**Examination:**

- Dysmorphic features – chromosome/syndrome present?
  (But in Turner syndrome other stigmata may be absent)
- Chronic illness, e.g. Crohn, cystic fibrosis, coeliac disease?
- Evidence of endocrine causes?
- Disproportionate short stature from skeletal dysplasia?
- Pubertal stage?

**Diagnosis:** *Cause can usually be determined from the above and no tests are required*

# V – Investigations

Before considering any investigations, the findings from the history and examination should be integrated into a differential diagnosis. The following investigations should be considered:

- If features suggestive of a defect in a clinical system have been identified, then appropriate further tests of the relevant system to confirm the diagnosis should be organized
- In a short or slowly-growing child with no obvious pathology, an X-ray of the left wrist to calculate a bone age should be performed to assess the degree of delay in physical development, along with a blood sample for:
    - Full blood count, blood film and ESR or C-reactive protein
    - Urea, electrolytes and creatinine
    - Calcium and phosphate
    - Thyroid function tests
    - IgA and anti-tTG (anti-tissue transglutamonase) antibodies or other screening test for celiac disease
    - Karyotype in girls to exclude Turner's syndrome
    - IGF-1, though this is of limited sensitivity for screening for GH deficiency and may also be affected by nutritional state
    - Formal stimulation tests of GH secretion – only indicated once the above tests have been performed and (with the exception of IGF-1) found to be normal

❖ **Bone age:**

Perform anteroposterior radiography of left hand and wrist to assess bone age. It should be undertaken as part of the routine evaluation of children with growth failure over one year of age.

Although the most common usage of bone age assessment is to differentiate familial from constitutional short stature, there are other benefits. Bone age evaluation is important in investigating patients with short stature and diagnosis of GHD in which it is usually delayed.

**The two most widely used systems are:**

I. ***Greulich-Pyle Atlas method (GP method):*** In which a left hand wrist radiograph is compared by means of a sequence of radiographs grouped in the atlas according to age and gender.

II. ***Tanner-Whitehouse 2 bones method (TW2 method):*** In which a maturity score is awarded to individual epiphyses, the sum of which is then converted to a bone age which is plotted on the growth chart as height for bone age.

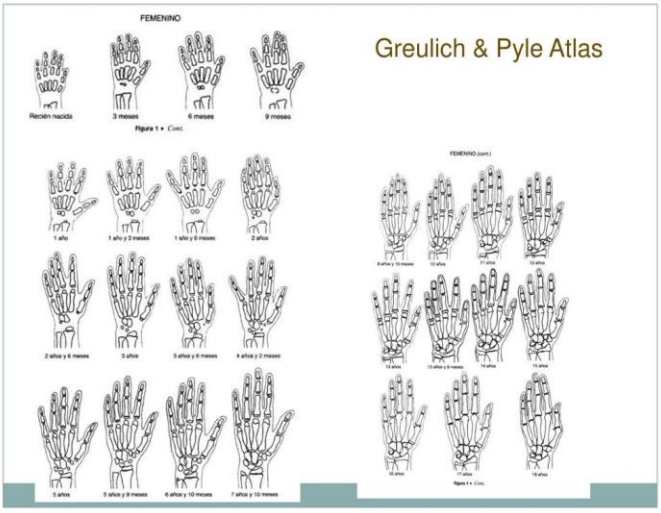



**Figure:** Greulich-Pyle Atlas method

BA=bone age
CA=chronological age

| | CA>BA | CA=BA | CA<BA |
|---|---|---|---|
| Normal growth velocity | Constitutional delay of growth | Familial short stature | |
| Abnormal growth velocity | Malnutrition, chronic systemic disorders or endocrine disorders | Malnutrition or chromosomal disorder | Precocious puberty |

- ✓ **Benefits:** Bone age assessment provides precious information for predicting aduld height in normal children but if not properly used, can be misleading and it should always be considered ancillary to the clinical and auxological examination.
- ✓ **Bone age is useful:**
  - In evaluating any child with growth/puberty disorders
  - In deciding the time to start replacement therapy in hypogonadism
  - In monitoring children on growth hormone therapy

**Table:** Investigations considered for short stature

| Investigation | Significance |
|---|---|
| X-ray of wrist and hand for bone age | Some delay in constitutional delay of growth and puberty<br>Marked delay for hypothyroidism or growth hormone deficiency or other endocrine causes |
| Full blood count | Anaemia in coeliac or Crohn diseases |
| Creatinine and electrolytes | Creatinine raised in chronic renal failure |
| Calcium, phosphate, alkaline phosphatise | Renal and bone disorders |
| Thyroid-stimulating hormone (TSH) | Raised in primary hypothyroidism |
| Karyotype | Turner syndrome shows 45XO, other chromosomal disorders |
| Endomysial and anti-tissue transglutaminase IgA antibodies | Usually present in coeliac disease |
| CRP (acute-phase reactant) and erythrocyte sedimentation rate (ESR) | Raised in Crohn disease |
| Growth hormone provocation tests (using insulin, glucagon, clonidine, or arginine in specialist centres) | Growth hormone deficiency |
| IGF-1 | Disorders of the growth hormone axis, including IGF-1 deficiency |
| 0900 cortisol and dexamethasone suppression test | Cushing syndrome |
| MRI scan if neurological symptoms/signs | Craniopharyngioma or intracranial tumour |
| Limited skeletal survey | Skeletal dysplasia, scoliosis |

**VI- Management:** when possible, treatment should be directed towards the *underlying cause* (e.g. providing thyroid hormone for a hypothyroid child), but due to the common availability of recombinant growth hormone, it is now being widely used.

- Counseling of parents (for psychological causes)
- Dietary advice (undernutrition, Celiac disease)
- Growth hormone subcutaneous injections
- Limb lengthening procedures (skeletal dysplasias)
- Levothyroxine (in hypothyroidism)

❖ **Growth hormone treatment of short stature:** Growth hormone deficiency is treated with biosynthetic growth hormone, which is given by subcutaneous injection, usually daily. It is expensive and management of growth hormone deficiency is undertaken at specialist centres. The best response is seen in children with the most severe hormone deficiency. Other indications include Turner syndrome, Prader-Willi syndrome, chronic renal failure, SHOX (short stature homeobox) deficiency and intrauterine growth restriction (IUGR). In Prader-Willi syndrome (an imprinting disorder resulting in early hypotonia and feeding difficulties followed by short stature, obesity and learning difficulties), growth hormone improves muscular strength and body composition as well as modestly improving final height. Recently, recombinant IGF-1 has been used to treat children with growth hormone resistance (e.g. Laron syndrome) and IGF-1 deficiency who would have previously not responded to growth hormone treatment. Recombinant IGF-1 therapy is still very expensive and is confined to a few specialized centres.

- **Dosage and administration:** The dosage of somatropin should be tailored to the needs of each individual child and varies according to the condition being treated:
  - 23-39 microgram/kg daily for growth hormone deficiency
  - 45-50 microgram/kg daily for Turner syndrome
  - 35microgram/kg daily for growth disturbance in children born small for gestational age
  - *Somatropin is self-administered or given to the child by an adult, at home, usually as a subcutaneous injection, 6-7 times a week. The maximum recommended daily dose should not be exceeded.*

- **Predicted treatment outcome:**
  - Gains in final height for children treated with somatropin compared with untreated children ranged from approximately 3 to 11 cm
  - For growth hormone deficiency 8-11 cm
  - Turner syndrome 5 cm
  - Chronic renal insufficiency 3-9 cm

- Long-term continuous GH treatment in short children born short for gestational age without signs of persistent catch-up growth leads to a normalization of adult height.

- **Discontinuation of treatment:** Treatment with somatropin should be discontinued if any of the following apply:
  - Final height is attained
  - Decision by patient that he/she is tall enough
  - Growth velocity increases less than 50% from baseline in the first year of treatment
  - Final height is approached and growth velocity is less than 2cm total growth in 1 year
  - Bone age> 14years in girls and 16years in boys
  - There are insurmountable problems with adherence

- **Follow-up:**
  - Required as there is risk of primary hypothyroidism / adrenal insufficiency, so periodic follow up is needed. Patients must be monitored at least every 3 months (sooner at the initiation of therapy) to ensured continued efficacy of the treatment and lack of unwanted and sometimes serious side effects.

- **Side effects**: pseudotumourcerebri, increased intracranial pressure, slipped capital femoral epiphyses,leukemia,hyperglycemia, acute pancreatitis, liver abnormalities, gynaecomastia

***PRACTICAL PART***

## Introduction:

By definition, short stature is defined as a height which is 2 standard deviations less than the mean height of a specific population for children of that sex and chronological age (and ideally of the same racial-ethnic group). Short stature is a problem in children globally and especially in developing countries.

The general health of children can be monitored by growth which is an important parameter. It is a continuous biologic process that depends on many factors including nutrition and hormone status. Short stature may be caused by many reasons related to the endocrine system, nutritional status and genetic causes.

Monitoring of growth in children is part of preventive child health programs. The monitoring of normal growth can be performed by growth charts. Abnormal growth may refer to the presence of underlying disease in the apparently normal child. Early detection and diagnosis of short stature decrease the effect of any underlying health condition and optimizes final adult height.

Short stature is considered as a sign of poor health in childhood. It is unrecognized in early infancy that's why it is diagnosed at a late age which affects the improvement on health outcomes and stature.

## Discussion:

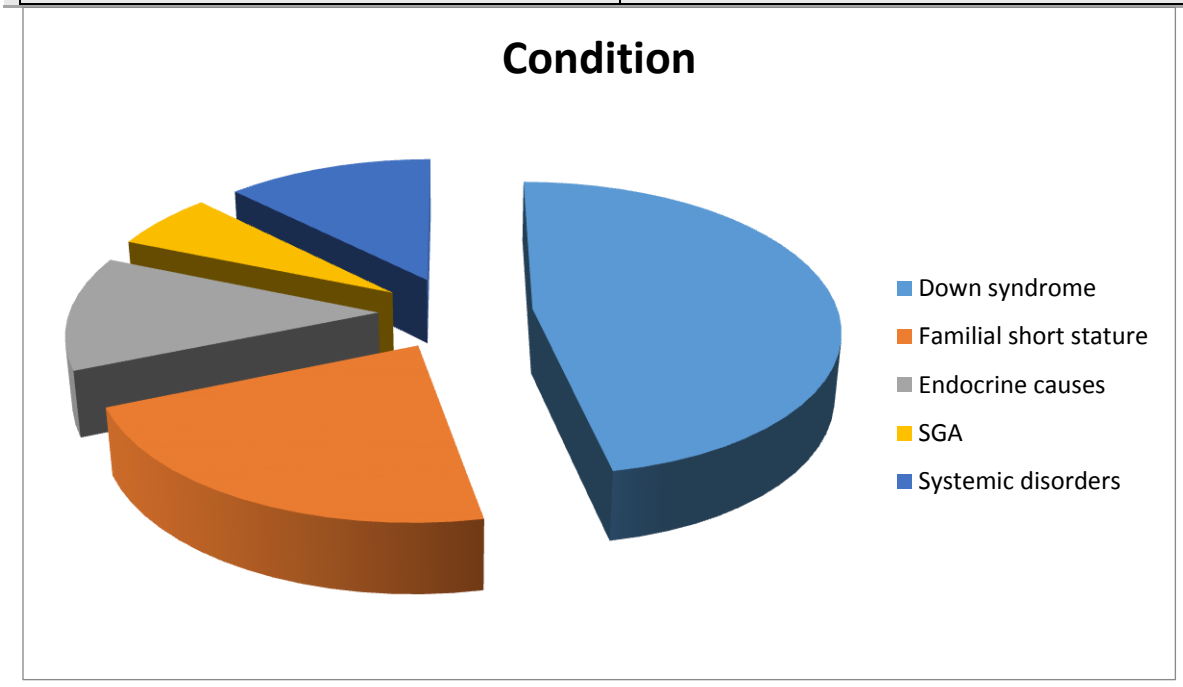
Namibia is one of the developing countries in the world, located in the southern west of Africa, with the estimated population of 2.5 million.


**Figure:**Location of Namibia

A case study was done on a population of children aged 0-15 years, from October 2017 to October 2018 in the pediatric department at Katutura Intermediate hospital in Windhoek, the capital city of Namibia.

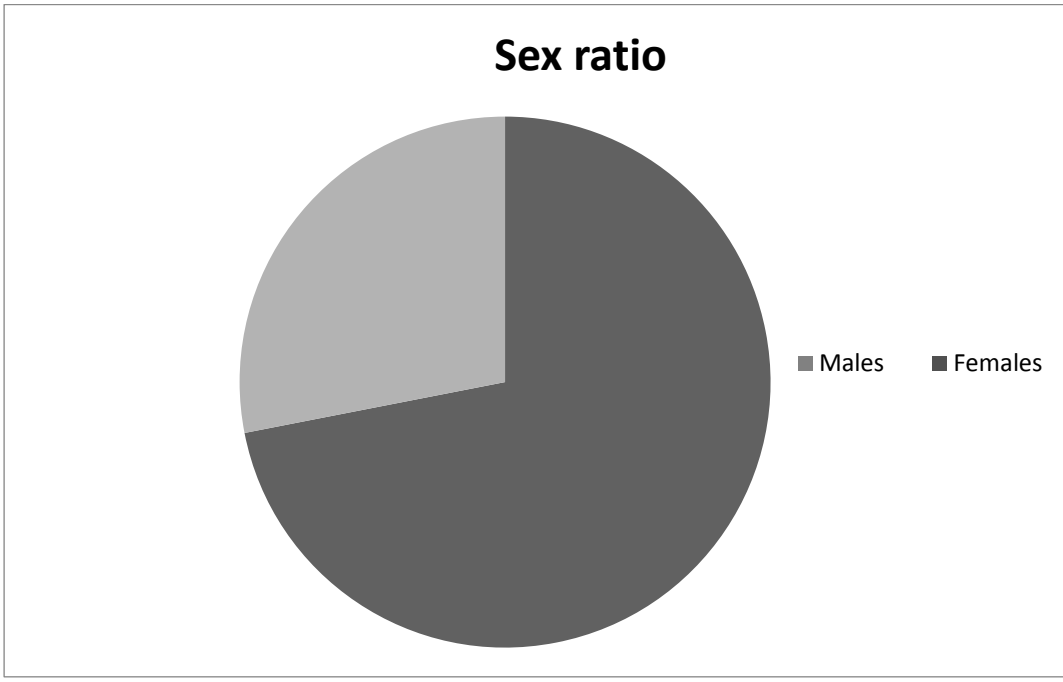
**Findings:** This condition is less common in Namibia. However, from the population on which the study was done, majority were Down syndrome (trisomy 21) patients and familial short stature. Few cases of children with endocrine causes (hypothyroidism and growth hormone deficiency), small for gestational age infant and systemic disorders were noted.

| **Condition** | **Number of patients** |
|---|---|
| Down syndrome (Trisomy 21) | 15 |
| Familial short stature | 7 |
| Endocrine causes | 4 |
| Small for gestational age infant | 2 |
| Systemic disorders | 4 |
| **Total** | **32** |



- In this group of 32 patients, 20 were females and 12 were males.
  - Sex ratio→ Male : Female →3 : 5
  - Percentages:

    Males = 3/8 × 100 = 37.5 %
    Females = 5/8 × 100 = 62.5 %




- **Problems encountered during this case study:**
  - Lack of specialist centres and resources such as karyotypage
  - No other sources of information of the same study to compare with
  - Time of study was inadequate to provide the best information needed

# Conclusion:

- Short stature is a common problem in pediatric practice and it is a less common condition in Namibia
- According to the case study that was done, Down syndrome is the most common cause whereby the genetic disorder is present with all or part of a third copy of chromosome 21; typically associated with physical growth delays, characteristic facial features and mild to moderate intellectual disability.
  The likelihood of giving birth to a child with Down syndrome increases with maternal age (over 35 years of age), however, 80 percent of babies with Down syndrome are born to women

under 35 years of age because this age group gives birth most frequently.

- Short stature is found to be more common in females than in males. This is probably because males are naturally taller than females in general and historically in most societies hold power.

**What I think should be done:**

- Pathological short stature should be diagnosed at the early stage of the child's development for early management, benefits for growth prognosis and well-being of the child
- More specialist centres should be initiated
- Down syndrome is the most common cause of short stature in Namibia. However, this is a genetic condition that affects all women below or above 35 years of age. In this case, it is very important to create awareness that will help support people born with Down syndrome. For example, in Namibia, there is an Organization called Down's Syndrome Association of Namibia (DSAN) which was established on the 25th October 2012, to raise awareness about this condition in the Namibian society at large and to reach out to parents of people with Down syndrome and provide practical support to them in terms of health care, education and work opportunities for these people to be able to live a healthy, active and happy life.

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