

Short Stature in Children: A Review of Literature

Zainab Ahmad Mohammad Jafari

Address: Jazan -Saudi Arabia ,Affiliation: Jazan University, Email: Zainabahmad992@hotmail.com,

Phone number: 0544799357

ABSTRACT

Longitudinal growth assessment is essential in child care. Short stature can be promptly recognized only with accurate measurements of growth and critical analysis of growth data. Short stature may be normal. Obtaining the family history of growth patterns and direct measurement of the parents is crucial to determine the genetic potential for growth in the child. Short stature can also be the sign of a wide variety of pathologic conditions or inherited disorders when it results from GF or premature closure of the epiphyseal growth plates. The causes of short stature can be divided into 3 broad categories: chronic disease (including undernutrition genetic disorders), familial short stature, and constitutional delay of growth and development. Treatment may be medical or surgical; both of them depend on the cause of short stature.

Keywords: short stature, children, genetic disorder.

INTRODUCTION

Short stature refers to a height of a human being which is below typical. Whether a person is considered short depends on the context. Because of the lack of preciseness, there is often disagreement about the degree of shortness that should be called short . In a medical context, short stature is typically defined as an adult height that is more than two standard deviations below the mean for age and gender, which corresponds to the shortest 2.3% of individuals ¹.

Growth monitoring in infancy and childhood has been part of preventive child health programs for more than a century, and short stature or growth retardation are regarded as relatively early signs of poor health. Growth failure occurs all over the world, and there are no indications that pathological causes of primary or secondary growth failure have a different prevalence in different countries, except for growth failure caused by malnutrition which is obviously strongly dependent on socioeconomic circumstances ².

Despite the similarity of the clinical presentation of growth failure in different parts of the world, there is a substantial variation in the national guidelines for the diagnostic approach to short stature ¹. Although at a consensus meeting on idiopathic short stature (ISS), a list was proposed, there was little scientific basis for it ².

Causes of short stature

Shortness in children and young adults nearly always results from below-average growth in childhood ³. The causes of short stature can be divided into 3 broad categories: chronic disease (including undernutrition, genetic disorders), familial short stature, and constitutional delay of growth and development ⁴.

A- Pathological causes of growth failure

1- Malnutrition

It is a condition that results from eating a diet in which nutrients are either not enough or are too much such that the diet causes health problems. It may involve calories, protein, carbohydrates, vitamins or minerals ³. The symptoms of micronutrient deficiencies depend on the micronutrient that is lacking. Nutrition plays a fundamental role in determining the growth of individuals. An appropriate growth progression is considered a harbinger of adequate nutrient intake and good health ⁴.

On the other hand; growth deceleration with or without short stature may indicate inadequate nutrition, even when there is no body weight deficit for height. Nutritional growth retardation (NGR) is most prevalent in populations at risk of poverty. However, in affluent communities patients with NGR are often referred to the specialist because of short stature and delayed sexual development. The diagnosis may be overlooked and/or be established after exhaustive evaluations, if the pattern of weight progression over time is not considered ⁵.

Patients with so-called idiopathic short stature may present diminished nutrient intake and decreased IGF-I levels, however their nutritional status and body weight progression patterns are usually not addressed by pediatric endocrinologists. NGR patients may cease to gain appropriate weight and fail to grow in height, even without exhibiting body weight deficits for height. They adapt to decreased nutrient intake by decreasing growth progression and thereby achieve equilibrium by decreasing the nutrient demands ⁶.

This occurs by diminishing their metabolic rates and erythrocyte Na⁺, K⁺- ATPase activity; however they may not present alterations in other clinical biochemical markers of malnutrition.

Therefore, accurate weights and heights plotted on the growth chart over time are necessary to detect NGR. Nutritional rehabilitation is accompanied with catch up growth, though it may be difficult to change the dietary habits of adolescents who exhibit NGR⁵.

2- Wiedemann-Steiner syndrome

It is a rare genetic disorder that causes developmental delay, unusual facial features, short stature, and reduction in muscle tone (hypotonia). It is inherited in an autosomal dominant fashion, but all cases reported so far were sporadic⁷.

Features described in Wiedemann-Steiner syndrome include:⁸

- Short stature.
- Developmental delay.
- Low muscle tone (hypotonia) especially in infancy.
- Characteristic facial features.
- Hairy elbows (hypertrichosis cubiti).

Wiedemann-Steiner syndrome results from mutations in the MLL (also known as KMT2A) gene on the long arm of chromosome 11. The gene encodes a histone-modification enzyme that is; it helps modify the expression of other genes⁹.

3- Prader-Willi syndrome (PWS):

It is a genetic disorder due to loss of function of specific genes. In newborns symptoms include weak muscles, poor feeding, and slow development, short stature. Beginning in childhood the person becomes constantly hungry which often leads to obesity and type 2 diabetes. There is also typically mild to moderate intellectual impairment and behavioral problems. Often the forehead is narrow, hands and feet small, height short, skin light in color,

and those affected are unable to have children¹⁰.

4- Chronic kidney disease (CKD):

It is a type of kidney disease in which there is gradual loss of kidney function over a period of months or years. Early on there are typically no symptoms. Later, leg swelling, feeling tired, vomiting, short stature, loss of appetite, or confusion may develop. Complications may include heart disease, high blood pressure, bone disease, or anemia¹¹.

Causes of chronic kidney disease include diabetes, high blood pressure, glomerulonephritis, and polycystic kidney disease. Risk factors include a family history of the condition. Diagnosis is generally by blood tests to measure the glomerular filtration rate and urine tests to measure albumin. Further tests such as an ultrasound or kidney biopsy

may be done to determine the underlying cause. A number of different classification systems exist¹².

5- Glucocorticoid therapy

Since glucocorticoids are used for treatment of a variety of diseases, they are a common cause of growth failure in children. The growth failure can develop with or without other symptoms of glucocorticoid excess, known as Cushing syndrome. They suppress growth through several different mechanisms, including interference with endogenous growth hormone secretion and action, bone formation, nitrogen retention, and collagen formation. The growth effects of glucocorticoids are related to the type, dose, and duration of the exposure. If glucocorticoids are discontinued, children usually experience some catch-up growth¹¹.

The relative effects of different glucocorticoids on growth are similar, but not identical, to the relative potencies for hypothalamic-pituitary-adrenal axis suppression. Growth impairment is more pronounced with agents with a longer duration of action. It is most pronounced when glucocorticoids are administered daily as compared with an alternate-day regimen¹³.

Some inhibition of linear growth occurs even at the doses that are used for physiological replacement (i.e., prednisone doses of 3 to 5 mg/m² per day; approximately 0.075 to 0.125 mg/kg per day), and progressive growth impairment is seen with increasing doses. As an example, in a large series of children with growth failure due to chronic treatment with glucocorticoids for a systemic disease, the mean prednisone-equivalent dose was 0.5 ± 0.6 mg/kg per day. Growth impairment can even occur with prolonged administration of inhaled glucocorticoids during childhood, although the overall effect of these agents on adult height appears to be small¹⁴.

Prolonged treatment with systemic glucocorticoids may have persistent effects on growth after therapy is discontinued. In a study of 224 children with cystic fibrosis who previously had been treated for up to four years with either alternate-day prednisone or placebo, mean height after age 18 years (on average six to seven years after cessation of therapy) was significantly lower in boys who had received either high- or low-dose prednisone (170.5 and 170.7 versus 174.6 cm with placebo; $p = 0.03$). This effect was most pronounced in boys who had started taking prednisone at six to eight years of age. In contrast, there was no persistent growth impairment in girls treated similarly¹⁵.

6- Gastrointestinal disease

Children with growth failure resulting from gastrointestinal disease tend to have a greater deficit in weight than height (i.e., they are underweight-for-height) in contrast to those with endocrine disorders, who are often overweight-for-height¹⁶.

Up to 50 percent of children with Crohn disease have a decrease in height velocity before the onset of gastrointestinal symptoms, and about 10 percent of children with Crohn disease have short stature when the Crohn disease is diagnosed. The growth failure is closely related to the inflammatory disease process (mediated by proinflammatory cytokines), as well as decreased food intake, malabsorption, and/or high-dose glucocorticoids if used for treatment¹⁵.

Similarly, celiac disease can present with growth failure, especially in younger children. Both of these disorders are important considerations in the evaluation of a child whose linear growth has slowed, particularly if there are gastrointestinal symptoms and/or slow weight gain¹⁶.

7- Rheumatologic disease:

Childhood rheumatologic diseases, especially systemic juvenile idiopathic arthritis (JIA), are frequently associated with growth retardation. This may be a consequence of the proinflammatory cytokines associated with disease activity and is also caused by the high-dose glucocorticoids that are often used for treatment. Common presenting symptoms in JIA are fever, arthralgias, rash, and lymphadenopathy, in addition to growth failure¹⁷.

8- Turner syndrome (TS):

It also known as **45,X** or **45,X0**, is a condition in which a female is partly or completely missing an X chromosome. Signs and symptoms vary among those affected. Often, a short and webbed neck, low-set ears, low hairline at the back of the neck, short stature, and swollen hands and feet are seen at birth. Typically, they develop menstrual periods and breasts only with hormone treatment, and are unable to have children without reproductive technology. Heart defects, diabetes, and low thyroid hormone occur more frequently. Most people with TS have normal intelligence. Many, however, have troubles with spatial visualization that may be needed for mathematics. Vision and hearing problems occur more often¹⁷.

Turner syndrome is not usually inherited from a person's parents. No environmental risks are known, and the mother's age does not play a role. Turner syndrome is due to a chromosomal abnormality in which all or part of one of the X

chromosomes is missing or altered. While most people have 46 chromosomes, people with TS usually have 45. The chromosomal abnormality may be present in just some cells in which case it is known as TS with mosaicism. In these cases, the symptoms are usually fewer and possibly none occur at all. Diagnosis is based on physical signs and genetic testing¹⁸.

No cure for Turner syndrome is known. Treatment, however, may help with symptoms. Human growth hormone injections during childhood may increase adult height. Estrogen replacement therapy can promote development of the breasts and hips. Medical care is often required to manage other health problems with which TS is associated¹⁹.

9- Noonan syndrome:

Noonan syndrome is a relatively common autosomal dominant disorder with an estimated incidence of one in 1000 to 2500 live births. Approximately 50 percent of children with Noonan syndrome have a mutation in the *PTPN11* gene, mapped to chromosome 12q24.1, which encodes the non-receptor protein tyrosine phosphatase SHP2. Children with mutations in *PTPN11* have mild growth hormone resistance. Less common mutations have been described in *KRAS*, *SOS1*, and *NRAS* (which, like *PTPN11* mutations, result in upregulation of the RAS-MAP kinase pathway, as well as mutations in *RAF1*, *RIT1*, *MAP2K1*, and *BRAF*. Mutations in one these genes are found in approximately 70 percent of individuals with Noonan syndrome. Noonan syndrome and neurofibromatosis type 1 may occur together in patients with certain *NF1* mutations. Some patients with *PTPN11* mutations also have a syndrome that includes giant cell lesions of bone or soft tissues²⁰.

Noonan syndrome is characterized by minor facial dysmorphism (hypertelorism, downward eye slant, and low-set ears), proportionate short stature, and heart disease, most often pulmonic stenosis and hypertrophic cardiomyopathy. Other common findings include a short webbed neck, chest deformity (pectus excavatum), cryptorchidism, intellectual disability (mental retardation), coagulation abnormalities with or without bleeding diathesis, lymphedema, and problems with motor performance. There appears to be a modest association between Noonan syndrome and several types of cancer, including neuroblastoma, acute leukemia, low grade glioma, and embryonic rhabdomyosarcoma²¹.

The cardiac manifestations were assessed in an echocardiographic study of 118 patients with Noonan syndrome. A dysplastic pulmonary valve was present in eight patients (7 percent), six of

whom had significant stenosis. Among the 110 patients without valve dysplasia, significant pulmonic stenosis was present in 22 (20 percent). Other abnormalities included secundum atrial septal defects, localized anterior septal hypertrophy, and diffuse hypertrophy²².

Short stature associated with Noonan syndrome can be treated effectively with growth hormone and is an approved indication by the US Food and Drug Administration (FDA)²¹.

10- Silver-Russell syndrome:

Silver-Russell syndrome, also known as Russell-Silver syndrome and Russell-Silver dwarfism) is characterized by severe intrauterine growth restriction and postnatal growth retardation with a prominent forehead, triangular face, downturned corners of the mouth, and body asymmetry (hemihypertrophy). The facial features tend to become less obvious with age. The majority of infants have feeding difficulties, and mild developmental delay is seen in about one-third of subjects. In about 60 percent of subjects, the syndrome is associated with epigenetic alterations involving either hypomethylation of an imprinting control region that regulates expression of the insulin-like growth factor-2 (IGF-2) gene and others on chromosome 11p15.5. IGF-2 is known to have important effects on growth, especially during fetal development. About 10 percent of cases are caused by maternal uniparental disomy of chromosome 7. Accordingly, one study describes severe pre- and post-natal growth restriction in four members of the same family with clinical features of Silver-Russell syndrome, due to a paternally-inherited mutation in the IGF-2 gene²³.

A few reports suggest modest efficacy of growth hormone (GH) treatment of individuals with Silver-Russell syndrome; the growth hormone was given based on the indication for individuals born small for gestational age. When GH was started at a young age, the mean adult height in treated subjects was -1.3 standard deviations (SD), compared with an adult height of -4.2 to -2.9 SD in untreated subjects with this disorder. In a separate large study, mean adult height in GH-treated subjects was -2.17 SD, despite a mean total height gain of 1.3 SD. A comparison group of children born SGA, but without Silver-Russell syndrome, had somewhat better adult height outcomes (mean -1.65 SD). Of note, individuals with the hypomethylation defect tend to have inappropriately high levels of IGF-I and IGFBP-3, suggesting a reduced sensitivity to IGF-I²⁴.

11- Skeletal dysplasias:

Skeletal dysplasias associated with short stature are caused by inherited defects in

cartilage/bone development and are often associated with disproportionate short stature (with limbs disproportionately short for the trunk, or vice versa). Some present prenatally and are detected on prenatal ultrasound, whereas others present during childhood with short stature. These disorders should be suspected in a child presenting with short stature and bone deformities, recurrent fractures, or abnormal findings on radiographs (e.g., enchondromas, bowing or shortening of the long bones, vertebral defects, or rib abnormalities).

There are a variety of types, with very variable phenotypes, including achondroplasia, hypochondroplasia, spondyloepiphyseal dysplasia, and osteogenesis imperfect²⁵. In one study, subtle skeletal dysplasias were found in 18.5 percent of patients previously labeled as either idiopathic short stature (ISS) or having been born small for gestational age (SGA). The most common forms were dyschondrosteosis (due to *SHOX* mutations in 61.5 percent of those undergoing genetic testing) and hypochondroplasia (due to *FGFR* mutations in 25 percent of those subjects undergoing genetic testing). These disorders were especially prevalent among those with parents who are also very short²⁴.

12- Osteochondrodysplasia or skeletal dysplasia:

It is a general term for a disorder of the development (dysplasia) of bone ("osteo") and cartilage ("chondro"). It has different types, one of them is (Achondroplasia). Achondroplasia is a type of autosomal dominant genetic disorder that is the most common cause of dwarfism. Achondroplastic dwarfs have short stature²⁶.

13- Sexual precocity:

Several conditions are associated with increased secretion of gonadal steroids (estradiol in girls and testosterone in boys), which have two consequences. One is sexual precocity. The other is accelerated epiphyseal development, which causes rapid childhood growth but more rapid advancement of bone age. As a result, height age is advanced compared with chronologic age, but it lags behind the markedly accelerated bone age. If their growth is not halted, these tall children will be short adults because early epiphyseal closure stops linear growth prematurely²⁷.

There are two types of sexual precocity:

*Gonadotropin-dependent precocious puberty (GDPP), also known as central (or true) precocious puberty, refers to the early occurrence of normal puberty. Precocious puberty historically had been defined as sexual development in girls before the age of eight years and in boys before the age of nine years; however, data for girls, particularly black girls, indicate that the age of

onset of normal puberty is younger. The hallmarks of precocious puberty are accelerated growth and advanced bone age, plus breast development in girls and penile enlargement and sexual hair growth in boys. The pattern of secretion of pituitary gonadotropins and gonadal sex steroids is normal but early ²⁸.

*Gonadotropin-independent precocious puberty (GIPP), also known as peripheral precocious puberty, refers to sexual precocity due to adrenal or gonadal disorders (or rarely tumor production of human chorionic gonadotropin in boys). This pattern also may be seen in the setting of McCune-Albright syndrome or exposure to exogenous sex steroids. The clinical manifestations are similar to those of GDPP, except that the sexual development may be that of the opposite sex, e.g., androgen effects in girls with congenital adrenal hyperplasia ²⁷.

Children with untreated chronic hyperthyroidism may rarely have a similar pattern with rapid growth accompanied by early epiphyseal maturation. Pubertal timing is generally normal ²⁸.

14- Cancer:

Children with cancer may grow poorly before diagnosis because of poor food intake, nausea, vomiting, and increased caloric utilization. After diagnosis, anorexia, nausea, and vomiting induced by chemotherapy and radiotherapy also can contribute to impaired growth. These effects often subside within one to two years of initiating treatment, and some children then have catch-up growth.

Late growth failure is common in children who received cranial radiotherapy because it can damage the hypothalamus and cause insufficiency of one or more hormones from the pituitary, including growth hormone, gonadotropins, and thyroid stimulating hormone (TSH). In younger children, especially girls, cranial radiotherapy can cause precocious puberty and adult short stature. Primary hypothyroidism also can occur if the thyroid gland was in the radiation field. Spinal irradiation may result in slow growth of the spine with relative preservation of normal limb growth) ²⁸.

15- Pulmonary disease:

Cystic fibrosis is both a pulmonary and gastrointestinal disease. Growth failure in this disorder may be caused by multiple mechanisms, including poor food intake, maldigestion or malabsorption, chronic infection, and increased energy requirements (work of breathing).

Immune deficiencies also may present with pulmonary symptoms and/or growth failure ²⁹.

Asthma has been associated with a deceleration of height velocity, which is most pronounced with severe disease. Growth failure in children with asthma is more often due to treatment with glucocorticoids ³⁰.

16- Cardiac disease:

Growth failure is common in children with severe heart disease of any cause. The major pathogenetic factors are thought to be anorexia and increased basal energy requirements. Occasionally, growth failure is the presenting feature of the heart disease ³¹.

17- Immunologic disease:

Human immunodeficiency virus (HIV) infection is associated with growth failure. Mechanisms include anorexia, malabsorption, diarrhea, severe infections, and failure of one or more organ systems. Growth failure also can occur with other immunological deficiencies such as common variable immunodeficiency or severe combined immunodeficiency syndrome. As with HIV infection, multiple factors are probably involved ³¹.

18- Metabolic diseases:

Growth failure is common in children and adolescents with many of the inborn disorders of metabolism. Among acquired metabolic diseases, the most common is type 1 diabetes mellitus. In the past, type 1 diabetes mellitus was an important cause of short stature and attenuated growth because of caloric deficit resulting from severe glucosuria. However, it is now rare because of improvements in therapy. Children with type 1 diabetes have some decrease in IGF-I production or action, and there is a negative correlation between hemoglobin A1C (as an index of metabolic control) and adult height. Nonetheless, in children with fair to good metabolic control, growth and adult height are usually within normal ranges. Occasionally, children with diabetes and very poor glycemic control develop Mauriac syndrome, characterized by attenuated linear growth, delayed puberty, hepatomegaly, and Cushingoid features) ³⁰.

Any disorder associated with vitamin D deficiency or decreased vitamin D action can cause hypophosphatemia and rickets; rickets is characterized by abnormal epiphyseal development, bowing of the extremities, and diminished growth. Vitamin D deficiency in the absence of rickets does not seem to affect linear growth) ²⁹.

19- Endocrine causes of growth failure:

Primary endocrine disorders with effects on growth are uncommon but are important to identify because they can be treated. In general, these disorders are characterized by excessive weight for

height. They should be considered in any child with markedly reduced height velocity, and especially in those with other pituitary disorders, brain tumors, septo-optic dysplasia (also known as optic nerve hypoplasia), midline brain and facial defects, neonatal hypoglycemia, history of cranial irradiation, or a familial pattern of growth hormone deficiency. Any patient with an abnormality of one pituitary hormone (central hypothyroidism, Cushing disease, or growth hormone deficiency) should be evaluated for other pituitary hormone deficiencies²⁸.

20- Cushing syndrome:

Cushing syndrome is caused by excessive glucocorticoids and is characterized by the combination of weight gain and growth retardation, resulting in excessive weight-for-height³¹.

Endogenous Cushing syndrome (caused by excessive endogenous production of cortisol) is rare in children. The most common cause is a corticotropin (ACTH)-secreting pituitary adenoma (Cushing disease). The syndrome also may be caused by an adrenal adenoma, especially in younger children. In one series of children with endogenous Cushing syndrome, growth retardation was common (83 percent), but most patients had bone age within normal limits at diagnosis. Other key clinical features are central obesity, suprascapular fat pad ("buffalo hump"), abdominal striae, hirsutism, acne, and neuropsychological symptoms. The best tests to establish the diagnosis are a 24-hour urine collection for free cortisol (and creatinine), or a dexamethasone suppression test. Measurements of serum cortisol are not reliable screening tests, unless performed late at night. Exogenous sources of glucocorticoids (e.g., due to glucocorticoid therapy for asthma or inflammatory bowel disease) are a much more common cause of Cushing syndrome³².

21- Hypothyroidism:

Growth failure is a well-recognized consequence of hypothyroidism during childhood and may be the presenting feature. The bone age is usually delayed; as a result, many children with hypothyroidism have a reasonably normal growth potential once the disorder is identified and treated. The evaluation should include measurements of both TSH and free thyroxine to allow detection of both primary and central hypothyroidism. Measurement of serum TSH alone will not detect central hypothyroidism as it can be low, normal, or even slightly elevated. Growth hormone deficiency³³.

22- Growth hormone deficiency:

Usually results from deficiency of growth hormone-releasing hormone (GHRH). It can also be

caused by sellar and parasellar tumors (e.g., craniopharyngioma) that destroy the pituitary gland itself, in which case there may be deficiencies of multiple hormones produced by the anterior pituitary. Children with growth hormone deficiency can have striking catch-up growth during growth hormone replacement therapy. Children with a sellar or parasellar tumor that causes growth hormone deficiency occasionally experience rapid catch-up growth after surgical resection of the tumor without growth hormone treatment; this phenomenon is known as "growth without growth hormone" and is not fully understood. A rare cause of growth hormone deficiency is an inactivating mutation of the GHRH receptor that is inherited in an autosomal recessive manner²⁶.

If growth hormone deficiency is congenital and complete, the diagnosis is relatively easy to confirm. Affected children present with severe postnatal growth failure, delayed bone age, and very low serum concentrations of growth hormone, IGF-I, and IGF-binding protein-3 (IGFBP-3, the major circulating binding protein for IGF-I). Additional findings are hypoglycemia, prolonged jaundice, and micropenis, especially if gonadotropins are deficient as well. In children with less severe growth failure, whose height may still be within the normal range for age, the decision to undertake detailed testing should be based on strict auxological criteria. It is therefore mandatory to obtain accurate serial measurements of height. Any evidence of central nervous system disease or other anterior pituitary hormone deficiencies should lead to measurement of IGF-I and provocative testing of growth hormone (growth hormone stimulation tests). These provocative tests are not definitive but can be a valuable diagnostic tool when combined with auxological and bone age data and measurements of IGF-I and IGFBP-3²⁷.

Congenital growth hormone insensitivity is a very rare disorder characterized by high serum growth hormone concentrations with low serum IGF-I and IGFBP-3 concentrations. In its complete form, this condition is called Laron-type dwarfism (complete growth hormone insensitivity)²⁸.

B- Normal variants of growth

1- Familial short stature:

Familial or genetic short stature is most often a normal variant, termed familial or genetic short stature. These individuals usually have low-normal height velocity throughout life. The otherwise normal height velocity generally distinguishes these children from those with pathologic causes of short stature. Their bone age is consistent with their chronological age, which helps

distinguish them from children with constitutional delay of growth ²⁹.

2- Constitutional delay of growth and puberty:

Constitutional delay of growth and puberty (CDGP, sometimes called constitutional short stature for prepubertal children) results in childhood short stature but relatively normal adult height. Children with CDGP are usually of normal size at birth. However, a downward shift in growth rate begins at three to six months of age that is parallel to that seen in most normally growing children in this age group, but tends to be more severe and prolonged. By three or four years of age, children with CDGP usually are growing at a low-normal rate (e.g., about 4 to 5 cm/year in preadolescent girls, and 3.5 to 4.5 cm/year in preadolescent boys). The result is a growth curve that remains below, but parallel to, the third percentile for height. In addition to a low preadolescent growth rate, they tend to have delayed pubertal development. This leads to a marked height discrepancy during the early teenage years compared with their peers, but is followed by catch-up growth when they do enter puberty ²⁹.

The hallmark of CDGP is delayed skeletal age; it is more closely related to the height age (age at which one's height would be average) than the chronologic age. For these patients, height data should be interpreted according to bone age rather than chronological age to accurately reflect height potential. Because the bone age is delayed, growth typically continues longer than normal, often resulting in adult stature within the normal range. In many cases, there is a family history of delayed growth and puberty in one or both parents (sometimes described as being a "late bloomer") ³².

3- Idiopathic short stature:

A practical definition of idiopathic short stature (ISS) is a height below 2 standard deviations (SD) of the mean for age, in the absence of any endocrine, metabolic, or other diagnosis. These children have normal (often at the lower limit) height velocity and no biochemical or other evidence for a specific growth retarding condition, which implies normal results for endocrine screening tests, including those for growth hormone deficiency. Genome-wide studies indicate that the majority of the variation in adult height is explained by several hundred genetic variations, each with a small effect.

However, in a small proportion of the population, short stature is caused by specific genetic variations with large effect. As an example, emerging evidence suggests that mutations in the Short Stature **H**Omeobo**X** (SHOX) gene are responsible for 1 to 4 percent of individuals who

would otherwise have been classified as having "idiopathic" short stature ³⁰. In addition to these genetic contributors to ISS, it appears that epigenetic changes may play a role in some cases of ISS ³³. In one study, ISS was associated with increased methylation of two promoter regions for the insulin-like growth factor I (IGF-I) gene; these epigenetic changes are predicted to reduce the individual's sensitivity to growth hormone ³¹.

There is ongoing controversy about the nomenclature of ISS. Here, we use the term to refer to non-familial cases (ie, those without patterns of familial short stature). Others consider familial short stature and CDGP to be subcategories of ISS ³¹.

4- Small for gestational age infants with catch-up growth:

Most infants born small for gestational age (SGA) experience catch-up growth by two years of age, sufficient to be within the normal range (length above -2 SD, ie, >2.3rd percentile). Catch-up growth may be delayed in infants who are born preterm in addition to SGA, but often continues into childhood to approach the range predicted by the family's height. SGA can be caused by maternal, placental, or fetal factors. In many cases these factors (such as intrauterine constraint from a small uterus) are transient and are followed by vigorous catch-up growth during infancy ³³.

About 10 percent of SGA infants, particularly those born with more severe SGA, do not experience catch-up growth to reach the normal range by two years of age. This group of SGA infants can be considered to have a pathologic pattern of growth ³².

Treatment of short stature:

Medical care depends on the etiology of the short stature. Recombinant human growth hormone (rhGH) administration has not been proven to remarkably improve final adult height in children with normal variant short stature ³³.

A double-blinded, randomized study from the National Institutes of Health suggests GH has a small effect on adult height in children with normal short stature if they are treated with GH injections for many years. Other randomized studies have shown variable results, with some demonstrating benefit and others not. A study by Schena et al indicated that in children with short stature who are not GH deficient (ie, those with idiopathic short stature), long-term treatment with rhGH yields results similar to those in GH-deficient children who undergo this therapy, although this study did not have an untreated control group and pretreatment growth velocity data for the

patients was missing. Thus, the risk-benefit ratio for treatment of children with idiopathic short stature is not well defined ³².

There is also controversy regarding GH dosing. Fixed dosing based on weight has long been used. However, a 2-year, open-label, randomized trial that measured the response to somatotropin (rDNA origin) therapy based on serum insulinlike growth factor-I (IGF-I) levels in children with GH deficiency and in children with idiopathic short stature suggested that IGF-based dosing of GH may safely provide superior growth outcome in both groups.

Recombinant human GH has been used for over 4 decades, with a good track record of safety. A preliminary report from the French part of the European Union Safety and Appropriateness of GH treatments in Europe (EU SAGhE) study showed increased overall mortality in adults treated with rhGH during childhood, raising concerns about the long-term safety of this therapy. Data from Belgium, The Netherlands, and Sweden, however, did not show a similar distribution of causes of death. After reviewing information from the EU SAGhE study and other sources, the US Food and Drug Administration (FDA) recommended continued rhGH prescription and use according to the labeled recommendations ³³.

SUMMARY

Short stature is defined as height that is 2 standard deviations (SD) or more below the mean height for children of that sex and chronological age in a given population. This translates to a height that is below the 2.3rd percentile. The two most common causes of short stature are familial (genetic) short stature and constitutional delay of growth and puberty (CDGP), which are normal variants of growth. These growth patterns often can be distinguished from one another, but some children have features of both. Almost any serious systemic disease can cause growth failure. Systemic disorders or processes that may present with growth failure and/or delayed puberty include undernutrition, glucocorticoid therapy, gastrointestinal disease (especially Crohn disease and celiac disease), and renal disease. A variety of genetic syndromes and congenital malformations are associated with short stature. Turner syndrome is particularly important because shortness and/or absent pubertal development may be the presenting feature, with or without other characteristic clinical features. Most of these syndromes can be recognized by characteristic clinical features. These include Noonan, Silver-Russell, and Down syndromes. Treatment by medical care depends on

the etiology of the short stature. Recombinant human growth hormone (rhGH) administration has not been proven to remarkably improve final adult height in children with normal variant short stature.

REFERENCES

1. **Grote FK, Oostdijk W, de Muinck Keizer-Schrama SM, Dekker FW, Verkerk PH, Wit JM (2005):** Growth monitoring and diagnostic work-up of short stature: an international inventorization. *J Pediatr Endocrinol Metab.*, 18(11): 1031–1038.
2. **Wit JM, Clayton PE, Rogol AD, Savage MO, Saenger PH, Cohen P(2008):** Idiopathic short stature: definition, epidemiology, and diagnostic evaluation. *Growth Hormone & IGF Research*,18(2):89-110.
3. **Cohen P, Rogol AD, Deal CL, Saenger P, Reiter EO, Ross JL, Chernausek SD, Savage MO, Wit JM, 2007 ISS Consensus Workshop participants(2008):** Consensus statement on the diagnosis and treatment of children with idiopathic short stature: a summary of the Growth Hormone Research Society, the Lawson Wilkins Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology Workshop. *The Journal of Clinical Endocrinology & Metabolism*,93(11):4210-7.
4. **Zachor DA, Roberts AW, Hodgens JB, Isaacs JS, Merrick J(2006):** Effects of long-term psychostimulant medication on growth of children with ADHD. *Research in developmental disabilities*,27(2):162-74.
5. **Steiner CE, Marques AP(2000):** Growth deficiency, mental retardation and unusual facies. *Clinical dysmorphism*,9(2):155-6.
6. **Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg F(1993):** Prader-Willi syndrome: consensus diagnostic criteria. *Pediatrics*,91(2):398-402.
7. **Kaneko N, Kawagoe S, Hiroi M(1990):** Turner's syndrome—review of the literature with reference to a successful pregnancy outcome. *Gynecologic and obstetric investigation*,29(2):81-7.
8. **Wynn J, King TM, Gambello MJ, Waller DK, Hecht JT(2007):** Mortality in achondroplasia study: A 42-year follow-up. *American Journal of Medical Genetics Part A.*,143(21):2502-11.
9. **Wood AR, Esko T, Yang J, Vedantam S, Pers TH, Gustafsson S, Chu AY, Estrada K, Luan JA, Kutalik Z, Amin N(2014):** Defining the role of common variation in the genomic and biological architecture of adult human height. *Nature genetics*,46(11):1173.
10. **Cuttler L, Marinova D, Mercer MB, Connors A, Meehan R, Silvers JB(2009):** Patient, physician, and consumer drivers: referrals for short stature and access to specialty drugs. *Medical care*,47(8):858-65.
11. **Punthakee Z, Legault L, Polychronakos C(2003):** Prednisolone in the treatment of adrenal insufficiency: a re-evaluation of relative potency. *The Journal of pediatric*,143(3):402-5.
12. **Allen DB, Julius JR, Breen TJ, Attie KM, National Cooperative Growth Study(1998):** Treatment of glucocorticoid-induced growth suppression with growth

- hormone. *The Journal of Clinical Endocrinology & Metabolism*,83(8):2824-9.
13. **Wolthers OD, Pedersen S(1991):** Growth of asthmatic children during treatment with budesonide: a double blind trial. *BMJ*,303(6795):163-5.
 14. **Doull IJ, Freezer NJ, Holgate ST(1995):** Growth of prepubertal children with mild asthma treated with inhaled beclomethasone dipropionate. *American journal of respiratory and critical care medicine*,151(6):1715-9.
 15. **Lai HC, FitzSimmons SC, Allen DB, Kosorok MR, Rosenstein BJ, Campbell PW, Farrell PM(2000):** Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis. *New England Journal of Medicine*,342(12):851-9.
 16. **Kanof ME, Lake AM, Bayless TM(1988):** Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. *Gastroenterology*,95(6):1523-7.
 17. **Nakamura T, Gulick J, Pratt R, Robbins J(2009):** Noonan syndrome is associated with enhanced pERK activity, the repression of which can prevent craniofacial malformations. *Proceedings of the National Academy of Sciences*,106(36):15436-41.
 18. **Hüffmeier U, Zenker M, Hoyer J, Fahsold R, Rauch A(2006):** A variable combination of features of Noonan syndrome and neurofibromatosis type I are caused by mutations in the NF1 gene. *American Journal of Medical Genetics Part A* ,140(24):2749-56.
 19. **Kratz CP, Rapisuwon S, Reed H, Hasle H, Rosenberg PS(2011):** Cancer in Noonan, Costello, cardiofaciocutaneous and LEOPARD syndromes. In *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, Vol. 157, No. 2, pp. 83-89). Wiley Subscription Services, Inc., A Wiley Company.
 20. **Butler MG(2009):** Genomic imprinting disorders in humans: a mini-review. *Journal of assisted reproduction and genetics*,26(9-10):477-86.
 21. **Wollmann HA, Kirchner T, Enders H, Preece MA, Ranke MB(1995):** Growth and symptoms in Silver-Russell syndrome: review on the basis of 386 patients. *European journal of pediatrics*,154(12):958-68.
 22. **Flechtner I, Lambot-Juhan K, Teissier R, Colmenares A, Baujat G, Beltrand J, Ajaltouni Z, Pauwels C, Pinto G, Samara-Boustani D, Simon A(2014):** Unexpected high frequency of skeletal dysplasia in idiopathic short stature and small for gestational age patients. *European journal of endocrinology*,170(5):677-84.
 23. **Rogol AD(2001):** Early menarche and adult height: Reprise of the hare and the tortoise?. *The Journal of pediatrics*,138(5):617-8.
 24. **Nandagopal R, Laverdière C, Mulrooney D, Hudson MM, Meacham L(2008):** Endocrine late effects of childhood cancer therapy: a report from the Children's Oncology Group. *Hormone Research in Paediatrics*,69(2):65-74.
 25. **Ogilvy-Stuart AL, Shalet SM(1995):** Growth and puberty after growth hormone treatment after irradiation for brain tumours. *Archives of disease in childhood*,73(2):141-6.
 26. **Karlberg J, Kjellmer I, Kristiansson B(1991):** Linear growth in children with cystic fibrosis: I. Birth to 8 years of age. *Acta Paediatrica*,80(5):508-14.
 27. **Thommessen M, Heiberg A, Kase BF(1992):** Feeding problems in children with congenital heart disease: the impact on energy intake and growth outcome. *European journal of clinical nutrition*,46(7):457-64.
 28. **McKinney RE, Wesley J, Robertson R(1993):** Effect of human immunodeficiency virus infection on the growth of young children. *The Journal of pediatrics*,123(4):579-82.
 29. **Magiakou MA, Mastorakos G, Oldfield EH, Gomez MT, Doppman JL, Cutler Jr GB, Nieman LK, Chrousos GP(1994):** Cushing's Syndrome in Children and Adolescents--Presentation, Diagnosis, and Therapy. *New England Journal of Medicine*,331(10):629-36.
 30. **Zantleifer D, Awadalla S, Brauner R(1993):** Growth response to growth hormone during the first year as a diagnosis criterion of growth hormone deficiency. *Hormone Research in Paediatrics*,40(4):123-7.
 31. **Leschek EW, Rose SR, Yanovski JA, Troendle JF, Quigley CA, Chipman JJ, Crowe BJ, Ross JL, Cassorla FG, Blum WF, Cutler Jr GB(2004):** Effect of growth hormone treatment on adult height in peripubertal children with idiopathic short stature: a randomized, double-blind, placebo-controlled trial. *The Journal of Clinical Endocrinology & Metabolism*,89(7):3140-8.
 32. **Carel JC, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguelidou F, Rey G, Coste J(2012):** Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of the French SAGhE study. *The Journal of Clinical Endocrinology & Metabolism*,97(2):416-25.
 33. **Sävendahl L, Maes M, Albertsson-Wikland K, Borgström B, Carel JC, Henrard S, Speybroeck N, Thomas M, Zandwijken G, Hokken-Koelega A(2012):** Long-term mortality and causes of death in isolated GHD, ISS, and SGA patients treated with recombinant growth hormone during childhood in Belgium, The Netherlands, and Sweden: preliminary report of 3 countries participating in the EU SAGhE study. *The Journal of Clinical Endocrinology & Metabolism*,97(2):E213-7.