Paediatrica Indonesiana

VOLUME 42 September - October • 2002 NUMBER 9-10

Review Article

Management of growth disorders

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Growth is the most fundamental characteristic of childhood. As multi factorial and complex as growing process, children normally grow in a remarkably predictable manner. Deviation from this normal pattern of growth can be the first manifestation of diseases. Both endocrine and non-endocrine disorders may occur and involve any organ system of the body. Frequent and accurate assessment of growth therefore is of primary importance for physicians and nurses caring for children.[1]

Measurements of growth

Measurement of height

Measurement of supine length is used for children less than 2 year old,[1,2] while erect height is used in older children. Inaccuracies involved in measuring length in infants are often obscured by the rapid skeletal growth characteristic of this age. For measurement of supine length, it is best to use a firm box with an inflexible board against which the head lies and a movable footboard on which the feet are placed perpendicular to the plane determined by the supine length of the infant. It is optimal for the child to be relaxed, with the legs fully extended and the head positioned in the Frankfurt plane, in which the line connecting the outer canthus of the eyes and the external auditory meatus is perpendicular to the long axis of the trunk.

When children are old enough to stand, it is best to use a wall-mounted Harpenden stadiometer. Free-standing stadiometers are also available, but requires frequent calibration. The traditional measuring device consisting of a flexible arm mounted to a weight balance is notoriously unreliable.[1,2] The patient should be fully erect, with the head in the Frankfurt plane. The back of the head, thoracic spine, buttocks, and heels should be touching the axis of the stadiometer. Every effort should be made to correct discrepancies related to lordosis or scoliosis. Serial measurements should be made at the same time of the day because of diurnal variation. It is critical that height determination is performed by well-trained personnel. We recommend measuring height in three times. Variation among measurements should be no more than 0.3 cm. The mean of these three measurements should be recorded. For determination of height velocity, it is advisable that all measurements are performed by a single person. Even when efforts are made to maximize the precision of height determinations, a minimum interval of 3 months is necessary for accurate height-velocity calculation. However, data from 6 months are preferable.

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Standing height

Standing height is recommended for children over the age 2-3 years.[1,2] Before taking standing height, the child should remove shoes and stocks. Ask the child to stand straight and tall (like a soldier) with heel firmly on the floor, shoulders relaxed and looking straight ahead. The eyes and outer ears should be in the horizontal plane (Frankfurt plane), ask the child to breathe in whilst applying gentle pressure on the mastoid process, then breathing out and observe the height. Read to the nearest millimeter and plot on the appropriate chart

Height velocity measurements

To estimate the rate at which a child is growing, it is necessary to measure height on more than one occasion over a period of time, and divide the increment in height by the time elapsed. The amount of time depends upon the accuracy of the measurements. Using trained observers, the accuracy of height is within 0.2-0.3 cm,[3] this is perfectly acceptable for a single assessment of height. However, this error will have an impact on the calculation of growth velocity, particularly if successive heights are measured within a few months. Therefore, height velocity should be assessed over intervals of at least 6 months.[1,2]

Body proportions

Many abnormal growth states, including short stature and tall stature, are characterized by disproportionate growth. Evaluation of short stature should include head circumference, lower body segment, upper body segment, and arm span.[1,3] Age-related standards exist for these body proportions. The ratio of the upper segment to the lower segment, for example, ranges from 1.7 in the neonate to slight less than 1.0 in the adult.[3]

Sitting height

Linear height is the sum of different values, which are not linearly related in time. Therefore, the first step is to split height into its different components. The distance between the top of the head and the buttocks is called sitting height.[4] The relation between sitting height and height is often expressed as an age-dependent ratio. The use of ratio can be misleading. Therefore, a more clear approach is to simply plot height against sitting height; or to plot sitting height and subischial leg length. Sitting height is measured using a sitting height table. The table comprises a rigid vertical backboard and a horizontal headboard running free perpendicular to the backboard and without cross play. The surface of the headboard must be in contact with the top of the head. A 0.5 kg weight is placed on the headboard. This weight flattens the child's hair. The child must be sitting with his feet on a footrest so that his full weight is on the buttocks. Arching of the back is avoided by gently applying upward pressure to the mastoid processes. In older children, stretching of the back is achieved by asking them to breathe in deeply. The child's head is held in the Frankfurt plane, the lower borders of the orbits are in the same horizontal plane with the external auditory meatus.

Crown rump length is used for the supine position. The footboard is then pressed against the buttocks.

Leg length (lower segment)

Leg length is defined as the arithmetic different between height and sitting height or between supine length and crown rump length.[1,3] This measurement is useful for assessing proportions and/or non-ambulatory patients. Before measuring ask the patients to sit as tall and straight as possible, thighs should be at right angles to the lower limbs, then ask the patient to breath in and out, maintaining pressure on the mastoid process, and read the height to the nearest millimeter.

In children who can stand, the leg length measurement can be done by asking the patient to stand straight and tall, looking over the top of child's head, palpate the top of the pubic symphysis and measure from that point vertically to the ground. The accuracy is often compromised in obese patients. This measurement is important in assessing disproportionate growth. Normally, upper to lower segment ratio in babies 1.7/1; 8 years 1/1, adult male 0.92/1, and adult female 0.95/1.[2]

Arm span

The measurement of the upper limbs is another tool for the evaluation of body proportions, therefore this measurement is important when assessing

disproportionate growth. Arm span is the most common way to measure upper limb length. However by measuring the span of the out-stretched arms from the tips of the longest fingers, the width of the trunk is added.[4] To measure arm span, a measuring rod can be used. Standing against a flat surface (for example a wall) with the arms fully extended, the distance between the tips of the stretched middle fingers when the arms are held horizontally, is measured.[2,4] It is usually within 5 cm of the child's height.

Head circumference

Head circumference is routinely measured in newborn infants since it correlates well with skull volume. Skull volume is highly correlated with gestational age, body weight and body length. The head circumference provides important information, especially in the first year of life. In term newborns, the head circumference increases about 1 mm per day initially. Measurement of the growth velocity of the head may therefore be used to monitor the infant's general condition.[4] The measurement is applied using a non-stretchable tape placed around the head at the most protruding points of occiput and forehead.[4]

Weight

Weight is best related to height as well as to a reference population. Weight as an isolated measurement provides little information for clinical use. Weight in relation to height can be expressed in several ways. The simplest and the most informative way is to plot weight against height, using the original data.[1,3] Indices give no information on the original measurements of weight and height. Nevertheless the Ponderal Index for infants is commonly used.[4] The Ponderal index is expressed as

$$100 \quad \frac{W_t}{L^3_t}$$

where W is weight in grams, L is length in centimeters and t is age, ranging from 25 weeks gestational age to 1 year. This ratio has to be related to age dependent reference values. In certain situations the index may be normal even though the height and weight are atypical. For example, infants with late intrauterine growth impairment have an excessive loss of weight compared to height, resulting in a low Ponderal index. In infants with early intra uterine growth retardation both weight and height are affected, resulting in a normal Ponderal index. To measure weight, the child's outer clothing and socks should be removed. A suitable scale, accurate to the nearest 100 gram, is appropriate.

Body mass index (BMI)

The most widely used clinical tool for assessment of obesity is body mass index (BMI), defined as weight in kilograms divided by square of height in meters. (BMI; weight/height^2 = kg/m^2). BMI is a good indicator of size but does not differentiate between fat mass and muscle mass. Skin fold measurements make it possible to differentiate. Because BMI is dependent on age and pubertal stage, individual BMI values should be expressed as BMI standard deviation scores (SDS) for age. However, BMI-SDS can only be used as a parameter of overweight relative to the reference population and not in absolute terms, particularly if age references are regularly updated.[1,3]

Evaluation of growth

Nowadays height SDS values are preferred over centiles. Height SDS refers to the distance of a measured height from the mean height for that age. Unlike centiles, the distribution of the curve is normal or bell-shaped. In centiles, it is difficult to produce an exact number, whereas in with SDS one can calculate exact values. This is especially useful for extreme heights.[5] Height SDS is calculated using a formula;

$$\text{Height SDS of the patient} = \frac{\text{height} - \text{mean height for age}}{\text{SD for age}}$$

SDS values compared to percentile values are as follows; SDS 1.88 » P_3, SDS 1.28 » P_{10}, SDS 0.67 » P_{25}, SDS 0,00 » P_{50}.

Genetic factors are of great importance as for linear growth. The parental target height (TH) can be calculated as follows:

$$\text{Male TH} = \frac{\text{father's height} + \text{mother's height} + 13}{2}$$

$$\text{Female TH} = \frac{\text{father's height} + \text{mother's height} - 13}{2}$$

The 2 SD range for this calculated parental target height (approximately 8,5 cm) is called target height range. When a child grows outside its target height range, underlying pathology should be considered.[1,2,3,5] Target height SDS can be calculated as follows:

$$\text{Target height SDS} = \frac{\text{target height} - \text{mean height population}}{\text{SD}}$$

Skeletal maturation (bone age)

The growth potential inherent in the tubular bones of the body can be assessed by evaluation of the progression of ossification within the epiphyses. The ossification centers of the skeleton appear and progress in a predictable sequence in normal children. Skeletal maturation can therefore be compared with normal age-related standards. This forms the basis of bone age, or skeletal age. Beyond the neonatal period, a radiograph of the left hand and wrist is commonly used for determination of bone age, which can be related to the published standards of Greulich and Pyle. An alternative method for assessment of bone age from radiographs of the left hand, which involves a scoring system for 20 bones, has been developed by Tanner and colleagues. It is important to note, that the hand it self does not contribute to height and that accurate evaluation of growth potential might necessitate radiographs of the legs and spine.[1,3]

A number of important caveats concerning bone age must be considered. First, experience in determination of bone age is essential, and clinical studies involving bone age usually benefit from having one reader perform all interpretations. Second, the normal rate of skeletal maturation differs between males and females, and ethnic variability exists. The standards of Greulich and Pyle are divided by sex but were developed in white US children.

Finally, both the Greulich-Pyle and Tanner-Whitehouse standards were based on normal children and therefore they are not applicable to children with skeletal dysplasias.[3]

Prediction of adult height

The extent of skeletal maturation can be used to predict final height potential. The more delayed the bone age, the greater is the length of time before epihyseal fusion prevents further growth. The classic method of height prediction, based on Greulich and Pyle's was developed by Bayley and Pinneau and relies on the patient's bone age and height.

These methods of predicting adult height are based on normal children and can not be used for children with growth abnormalities.[1,3]

Short stature

Short stature is defined as height less than 2 standard deviation or less than the third centile for the reference range.[2] Most children are part of the continuum of a normal distribution curve. Only a minority will have a defined abnormality. Reference ranges of growth have been developed in many countries based on cross-sectional data. An international reference range has been recommended by the World Health Organization (WHO) based on the growth standards developed within the United States during the 1970s. These are not appropriate for populations with different ethnic groups, like in Indonesia. Population standards are subject to secular changes. For example, the mean final height for males in Japan has increased 8 cm since 1950. Indonesian reference standards should be based on measurement of different ethnic groups.[2,3] Standards may not be appropriate for migrants. It is advisable to use standards from the country of origin.

Growth failure

There are two criteria to describe growth failure,[2,5] i.e. height velocity below the 25th percentile and loss of height SDS more than 0.25 SDS within 1 year

Normal variant short stature

Familial short stature (FSS)

Children with FSS grow below but parallel to the normal linear growth curves. Final height is short but, by definition, appropriate for parental height.[6] This is the most common diagnosis encountered in clinical practice.[1,2,3] The diagnosis should still be considered if the short family member is more distant. It is important to remember that the affected family members may have underlying pathology that should be excluded; examples include skeletal dysplasias.

In FSS bone age is normal. As a general rule height or height velocity that is clearly inconsistent with that of siblings or parents warrants further evaluation.[7] Most children who have FSS are of normal weight and length at birth, most will cross linear growth percentiles downward during the first 2 years of life in search of their genetic-appropriate linear growth percentile. Onset of puberty and its rate of progression are normal.

Constitutional delay growth and puberty (CDGP)

Constitutional delay of growth and puberty is another frequent cause of short stature in childhood. This diagnosis is considered in individuals with late onset of puberty and absence of systemic symptoms or signs. Characteristically, individuals present between the age of 10 to 16 years with loss of height velocity and delayed pubertal development. There is a positive family history, with father or mother commonly being short as a child and experiencing a late pubertal growth spurt. Slowing linear growth occurs during the first 3 years of life, and normal or near-normal rate of linear growth below but parallel to the 3rd percentile during pre pubertal years. Bone age is delayed and usually corresponds to the height age,[2,6,7] but final adult height usually within normal range.

When constitutional delay is found in the context of familial short stature, children may experience both a delayed adolescent growth spurt and short final height. Such children should be considered to have elements of both constitutional delay and familial short stature.[3]

Idiopathic short stature (ISS)

Idiopathic short stature refers to a heterogeneous group of children with marked growth failure of unknown cause. The diagnosis made after exclusion of other causes of short stature.[2] By definition there will not be any evidence of short family members or family history of delayed puberty. Systemic, endocrine and prenatal factors should have been excluded.

These children usually have normal GH secretory dynamics, although provocative test results may be blunted under some circumstances. Such children are usually considered as variants of normal and achieve a final adult height within the range considered acceptable for the family.[2,3,6,7] The cause of the slowed childhood growth and frequently delayed pubertal spurt has not been established in these children. Continuing efforts are under way to develop a rational categorization and to develop the means of separating these children from those with an abnormality of the GH-IGF axis. Additional causes of idiopathic short stature will likely be identified at each level of the hypothalamic-pituitary-IGF axis.[3]

Primary Growth Abnormalities

Intrauterine growth retardation (IUGR)/ small for gestational age(SGA)

Intrauterine growth retardation is defined as birth length below –2SD for gestational age. It concerns around 2,5% of newborn babies. They may also be referred to as small-for-gestational age.[1,2,3]

Despite the critical importance of endocrine system in postnatal growth, normal intrauterine growth is largely independent of fetal pituitary hormones. Intrauterine growth retardation can arise from placental insufficiency, maternal disorders or intrinsic abnormalities in fetus such as congenital infections and chromosomal abnormalities. Most children reach normal height during the first or second year of life. However 15-20% remain small at the age of 4 years. Among the children who do not catch up during childhood, 50% have a short final height. One third of these children have inappropriate GH secretion. About 20% of the adult short population have had IUGR.[1,3]

Skeletal dysplasias

The skeletal dysplasias represent a heterogeneous group of disorders characterized by intrinsic abnormalities of cartilage or bone or both. These conditions share the following features: genetic transmission; abnormalities in the size or shape of bones of the limbs, spine, or skull; and radiological abnormalities of bones. More than 100 conditions have been identified based on physical features and radiological characteristics. The ongoing characterization of biochemical and molecular abnormalities in these conditions will undoubtedly lead to an increase in the number of these disorders.

The diagnosis skeletal dysplasia can be problematic and often relies on careful radiological evaluation. Clues that suggest a diagnosis of skeletal dysplasia include the following: extreme short stature, strong family history (many dysplasias are dominant disorders), abnormal body proportions and abnormalities of the limbs or trunk. The family history is critical, although many cases represent new mutations. Two of the more common forms are achondroplasia and hypochondroplasia.

Chromosomal abnormalities

Abnormalities of both the autosomes and sex chromosomes may be characterized by growth retardation. In general, these disorders are also associated with somatic abnormalities and mental retardation.[3] Such abnormalities, however, may be subtle. For example, the diagnosis of Turner syndrome (TS) must be considered in any girl with unexplained short stature.

Turner Syndrome

Short stature is the most common feature of TS, occurring more frequently than delayed puberty, cubitus valgus, or webbing of the neck. Reviews of large series of individuals with TS have indicated that short stature occurs in 100% of girls with a 45,X karyotype.[1,3] Some common phenotypic features are noted but in many girls, these characteristic are not obvious. (**Table 1**) Ranke and colleagues identified several distinct phases of growth in girls with TS; mild intrauterine growth retardation; normal height gain from birth until 3 years of age; progressive decline in height velocity from age 3 until approximately 14 years; and a prolonged adolescent growth phase, characterized by a partial return toward normal height, followed by delayed epiphyseal fusion. Recent studies of TS from the United States and Europe have reported mean adult height ranging from 142.0 to 146.8 cm. The cause of growth failure in TS remains unclear. GH levels are normal. Nevertheless, GH therapy is capable of both accelerating short- term growth and increasing adult height. The diagnosis of TS should be considered in any female with unexplained growth failure.[1,3,8]

Seckel syndrome

Although originally described by Mann and Russell in 1959, this condition is most commonly called Seckel syndrome or Seckel's birdheaded dwarfism. This autosomal recessive condition is characterized by intrauterine growth retardation and severe postnatal growth failure, as well as microcephaly, prominent nose and micrognathia. Final height is typically 90 to 110 cm, with moderate to severe mental retardation. The nature of the underlying defect is unknown.[1,3]

Noonan syndrome

Although this condition shares certain phenotypic features with TS, the two disorders are clearly distinct. In Noonan syndrome, no abnormality of the sex chromosomes has been documented, and transmission is apparently autosomal dominant. Both males and females may be affected. Like TS, patients typically have webbing of the neck, a low posterior hairline, ptosis, cubitus valgus and malformed ears. Cardiac abnormalities, however, primarily involve right-side lesions (pulmonary valve) rather than left-side lesions (aorta, aortic valve) characteristic of TS. Microphallus and cryptorchidism are common, and puberty is frequently delayed or incomplete. Mental retardation is observed in approximately 25% to 50% of patients.[1,3]

Russell-Silver syndrome

The Russell-Silver syndrome was independently described by Russell and Silver. Typical finding include IUGR, postnatal growth failure, hemihypertrophy, and small triangular facies. Nonspecific findings include clinodactyly, precocious puberty, delayed closure of the

TABLE 1. CLINICAL FINDINGS COMMONLY DESCRIBE IN PATIENTS WITH TURNER SYNDROME[8]

Primary defects	Secondary features	Incidence (%)
Skeletal growth disturbances	Short stature	100
	Abnormal upper to lower segment ratio	97
	Characteristic facies with micrognathia	60
	Cubitus valgus	47
	Short neck	40
	Short metacarpals	37
	High arched palate	36
	Genu valgum	35
	Scoliosis	12.5
	Madelung deformity	7.5
Lymphatic obstruction	Low posterior hairline	42
	Webbed neck	25
	Rotated ears	Common
	Edema of hands/feet	22
	Severe nail dysplasia	13
	Characteristic dermatoglyphics	35
Unknown factors	Cardiovascular anomalies	55
	Renal and renovascular anomalies	39
	Multiple pigmented nevi	26
	Strabismus	17,5
	Ptosis	11
Germ cell chromosomal defects	Gonadal failure	90
	Infertility	95

fontanels, and delayed bone age. Adult are short, with final heights about –4SDS. Endogenous GH secretion in prepubertal children with the Russell-Silver syndrome is similar to that in other short children with IUGR. Because no genetic or biochemical basis for this disorder has been identified, the Russell-Silver syndrome is often diagnosed as designation for IUGR of unknown cause.[1,2,3]

Progria

The senile appearance characteristic of progria typically appears by 2 years of age. There is a progressive loss of subcutaneous fat accompanied by alopecia, hypoplasia of the nails, joint limitation, and early onset of atherosclerosis. This is typically followed by angina, myocardial infarction, hypertension, and congestive heart failure. Skeletal hypoplasia results in severe growth retardation, which typically becomes evident by 6 to 18 months of age.[1,3]

Prader-Willi syndrome

In Prader-Willi syndrome, growth failure may be evident at birth but generally is more impressive postnatally. The neonatal period is characterized by hypotonia, feeding problems and, in the male, cryptochidism and microphallus. With advancing age, hyperphagia and obesity become prominent. Hypogonadism may persist into adult life. The etiology of growth failure is unclear. Many patient with Prader-Willi syndrome have been found to have deletions of the short arm of chromosome 15 plus parental imprinting.[1,3]

Down Syndrome

Trisomy 21, or Down syndrome (DS), probably is the most common chromosomal disorder associated with growth retardation, affecting approximately 1 in 600 live births. Birth weight and length are below normal. Growth failure continues postnatal and is typically associated with delayed skeletal maturation and a poor, delayed pubertal growth spurt. The etiology of growth failure in DS is unknown. It is likely in such conditions that growth failure reflects a generalized biochemical abnormality of the epipyseal growth plate.[1,3]

Secondary Growth Disorders

Malnutrition

Given the worldwide presence of under nutrition, it is not surprising that inadequate intake of calories, protein, or both represents by far the most

common cause of growth failure. Marasmus refers to patients with a global deficiency of calories, although it is often accompanied by protein insufficiency. Kwashiorkor, on the other hand, refers to inadequate protein intake, although it may also be characterized by caloric under nutrition. Frequently, the two conditions overlap. Linear growth is very sensitive to the effect of protein-calorie insufficiency, and individuals will present with dramatic growth failure. Weight is usually more affected than height. Head size is relatively preserved. Inadequate caloric or protein intake may also complicate chronic diseases that are characterized by growth failure. Anorexia is a common feature of renal failure and inflammatory bowel disease but may also be associated with cyanotic heart disease, congestive heart failure, central nervous system disease, and other illnesses. Furthermore, some of these conditions may be characterized by deficiencies of specific dietary components, such as zinc, iron and vitamins necessary for normal growth and development.[1,3]

Cardiovascular disease

Both cyanotic heart disease and congestive heart failure may be associated with growth failure. Many infants with cardiac problems have syndromes with dysmorphic features and intrauterine growth retardation. Postnatal growth failure is usually attributable to hypoxia and increased energy demands. Feeding difficulties are common in these children.

Corrective surgery often results in complete restoration of normal growth, frequently with a phase of catch-up growth.[3]

Renal disease

Conditions that affect renal function can result in significant growth retardation. Both uremia and renal tubular acidosis can lead to growth failure before other clinical manifestation become evident. Several factors are involved in growth retardation. For example decreased caloric intake, loss of electrolytes necessary for normal growth, metabolic acidosis, protein wasting, inadequate formation of 1,25-dihydroxycholecaliferol, insulin resistance, chronic anemia, and compromised cardiac function. Long-term glucocorticoid therapy in the treatment of nephritic and nephrotic conditions exacerbates the growth retardation characteristic of renal disease.

Although the growth failure of renal disease is not due to either GH or IGF deficiency, GH therapy has proved to be useful in accelerating skeletal growth.[1-3]

Hematological disorders

Chronic anemia's, such as sickle cell diseases, are characterized by growth failure. In general the decrease in height and weight is more pronounced in adolescent years. The onset of the adolescent growth spurt is delayed and menarche is late. In sickle cell disease, however growth spurt and final height may be normal. Causes of growth retardation include impaired oxygen delivery to tissues, increased work of the cardiovascular system, energy demands of increased hematopoiesis, and impaired nutrition.

In thalassemia, in addition to the consequences of chronic anemia, endocrine deficiencies can result from hemosiderosis of the pituitary. Despite vigorous effects to maintain hemoglobin levels near normal and to avoid iron overload, growth failure is a common feature of thalassemia, especially in adolescents. It is likely that anemia, impaired IGF-I synthesis, hypothyroidism, gonadal failure, and hypogonadotropic hypogonadism, all contribute to growth failure. GH resistance is suggested by generally adequate GH production with low IGF-I levels. In most patients GH treatment increases growth at least initially.[1,2,3]

Chronic infection

In many developing countries, chronic infestation with parasites contributes to nutritional debilitation and growth failure. A complex cascade of cytokines has deleterious effects on the endocrine system, mineral and nutrient metabolism, as well as bone metabolism.[3]

Endocrine Disorders

Hypothyroidism

Growth failure is common in chronic acquired hypothyroidism, although it may also be observed

in congenital hypothyroidism. Growth retardation may take several years to become clinically evident. Once present, growth failure is typically severe and progressive. The poor growth is more apparent in height than in weight gain. Therefore children tend to be overweight in relation to their height. Body proportion is immature, with an increased upper/lower body segment ratio. Skeletal age is usually markedly delayed. Although chronic hypothyroidism is usually associated with delayed puberty, precocious puberty and premature menarche can occur as well.[1,3]

The diagnosis of primary hypothyroidism is usually straightforward. Serum levels of T4 are reduced, and thyrotropin levels are elevated. Replacement therapy results in rapid catch-up growth. However this does not result in restoration of full growth potential, due to the rapid increase in skeletal age during the first 18 months of treatment.[1-3]

Diabetes Mellitus

Prepubertal children with IDDM have normal growth, even those with marginal control. During puberty growth velocity may decrease. Such growth failure occurs in children with long-standing poor glycemic control. Inadequate insulin therapy and resultant hyperglycemia leads to GH resistance. IGF-I levels are reduced, where as GH levels are elevated. If this situation occurs during the period of the pubertal growth spurt, patients will exhibit reduction in growth velocity.[3]

Growth hormone deficiency (GHD)

The diagnosis and treatment of GHD during childhood and adolescence have been subject to controversy. Establishing the diagnosis requires clinical and auxological assessment, biochemical tests of IGF-I, GH and radiological evaluation. GHD may present as an isolated problem or as part of multiple pituitary hormone deficiency (MPHD).[9]

Clinical and auxological criteria

Evaluation for GHD in a short child should not be initiated until other causes of growth failure, such as hypothyroidism, systemic disease, Turner syndrome, or skeletal disorders have been excluded. Key points in the history and physical examination that may indicate that GHD could be present include;[9] hypoglycemia, prolonged jaundice, microphallus, or traumatic delivery in neonates, history of cranial irradiation, head trauma or central nervous system infection, consanguinity and/or an affected family member, and craniofacial midline abnormalities. However, short stature is often the only feature. The criteria to initiate investigation include short stature (height SDS <2.5), height more than 1.3 SD below the mid-parental height, height more than 2 SD below the mean and a height velocity over 1 year more than 1 SD below the mean for chronological age, or a decrease in height SD of more than 0.5 over 1 year in children over 2 years of age, in the absence of short stature, height velocity less than -2 SDS over 1 year or less than -1.5 SDS over 2 years (this may occur in GHD, presenting in infancy, or in organic acquired GHD), signs indicative of an intracranial lesion, signs of multiple pituitary hormone deficiency, and neonatal symptoms and signs of GHD.

Interpretation of growth data requires recent standards. These standards should be updated every 10-20 years, dependent on the secular trend. Growth data should be expressed as SD scores rather than as percentiles. To correctly evaluate height velocity, there is a need for longitudinal velocity standards. With the increasing use of magnetic resonance imaging (MRI), an abnormality within the hypothalamic-pituitary region may incidentally be detected. This requires clinical evaluation of the child and possibly growth surveillance. In few cases an opthalmological examination may be needed.[9]

Evaluation for genetic disorders

Abnormalities of the growth hormone gene are rare. Pointers to this condition are early onset of growth failure, positive family history and consanguinity, height less than -3 SDS, and extremely low GH response to at least two provocation tests, including GHRH, very low IGF-I and IGF-binding protein-3 (IGFBP-3) levels.

Radiological evaluation

Bone age is usually delayed. Central nervous system imaging by MRI or CT is required, using 22 mm slices with and without contrast. Ideally, pituitary height and/or volume, anatomy of the stalk, and position of the posterior pituitary should be recorded. The resolution of the hypothalamic-pituitary region is inferior on CT scanning but the latter is useful for tumors and bone abnormalities. Intracranial calcification, as often seen in craniopharyngioma, can be detected on skull radiograms.[3,9]

GH provocation tests and IGF-I/IGFBP-3 measurements

Provocative agents should be used after an overnight fast in a well-standardized protocol. Among these agents are arginine, clonidine, glucagon, insulin and L-dopa. Great care should be exercised in using insulin or glucagon in a young child because the risk of hypoglycemia.

Two GH-stimulation tests are required. Growth hormone level >10 Fg/l in one of the tests does exclude GHD. For IGF-I and IGFBP-3, reference ranges, standardized for age and sex, are mandatory. Values less than –2 SD for IGF-I and/or IGFBP-3 suggest an abnormality in the GH axis if other causes of low IGF have been excluded. Nevertheless, in GHD, values of IGF-I and IGFBP-3 can be within the normal range. It is important to integrate all available data (clinical, auxological, radiological, and biochemical) when establishing a diagnosis.[9]

Sex steroid priming

It is difficult to diagnose GHD during the immediate peripubertal period. Low GH levels in provocation tests frequently occur. Therefore, priming is required in boys >10 years and girls >8.5 years.[5]

Testing in the neonate

GH levels should be measured in neonatal hypoglycemia in the absence of metabolic disorders. Random GH measurement less than 20mug/L suggests GHD in the newborn.[9]

Evaluation of the GH-IGF axis

In a child with suspected GHD, testing for GH/IGF-I deficiency requires IGF-I, IGFBP-3 levels and GH provocation tests after hypothyroidism has been excluded. In suspected isolated GHD, two GH provocation tests (sequential or on separate days) are required. In those with defined central nervous system pathology or a history of irradiation, one GH test will suffice. An evaluation of other pituitary function is then required. In patients who have had cranial irradiation or malformations of the hypothalamic-pituitary unit, GHD may evolve over years. Establishing the diagnosis may require repeated testing of the GH-IGF axis. A MRI (or CT scan) of the brain with particular attention to the hypothalamic-pituitary region should be carried out in any child diagnosed as having GHD.[3,9]

Treatment of GHD in children

Patients with proven GHD should be treated with recombinant hGH. The primary objectives of the therapy of GHD are normalization of height during childhood and attainment of normal adult height.[1,3,9]

Dosing of GH

GH should be administered subcutaneously in the evening on a daily basis. The dosage of GH should be expressed in mg/m^2/day. GH is routinely used in the range of 2 IU/m^2/day or 0.7 mg/m^2/day (1mg = 3 IU).[5] A dose-response relationship in terms of height velocity in the first 2 years of treatment has been clearly demonstrated within this range. Under special circumstances, higher doses may be required. Prediction models of growth response might be useful for determination of the optimal individual dose and are currently being investigated.[10]

Monitoring GH therapy

The routine follow-up of pediatric GHD patients should be performed by a pediatric endocrinologist and should be conducted on a 3 to 6-month basis. Increase in height and change in height velocity are used to assess the response to GH therapy. Data should be expressed as the increase in height SDS per year. Bone age should be conducted on a yearly basis. For assurance of compliance and safety, monitoring of serum IGF-I and IGFBP-3 levels is useful, although they do not always correlate well with growth response.[9,10]

Factors affecting the response to GH

Every effort should be made to diagnose and treat children at the youngest possible age. It is important to attain normal height with GH therapy before the onset of puberty. In the MPHD patient in whom puberty does not occur spontaneously, puberty should be initiated at the appropriate time.[9,10]

Management of MPHD

Patients with suspected or proven multiple pituitary hormone deficiencies should be managed similarly to patients with isolated GHD; however, attention should be given to correct clinical recognition, treatment, and monitoring of additional hormonal deficiencies (T4, cortisol, sex steroids, and antidiuretic hormone). In patients with an initial diagnosis of isolated GHD, particularly those with ectopic posterior pituitary or other development abnormalities, the clinician should be alert to the risk of the development of MPHD.[9]

Safety issues

Treatment with GH may unmask underlying hypothyroidism. Significant side effects of GH treatment in children are rare. These include benign intra cranial hypertension, pre pubertal gynecomastia, arthralgia, and edema. A careful history and physical examination are adequate to identify their presence. Management of these side effects may include either transient reduction of dosage or temporary discontinuation of GH. There is no evidence that the risk of leukemia, brain tumor recurrence, slipped capital femoral epiphysis, or diabetes is increased in recipients of long-term GH treatment. Tumor survivors receiving GH should be followed in conjunction with an oncologist and a neurosurgeon when appropriate. There is no evidence that GH replacement needs to be discontinued during inter current illness.[9,10]

Conditions in which GH therapy appears effective in increasing adult height

Therapy with GH is effective in increasing adult height of children with GH deficiency and linear growth velocity of children with chronic renal insufficiency before renal transplantation. Growth hormone safely increased adult height of girls with Turner syndrome.[3,10]

Management

Clinical assessment of the short child

Baseline investigations consists at least two accurate measurements of height are required. Most children will require about a year of observation. Exceptionally slow growth may be manifest over a shorter period. The main historical and physical features that need to be elicited when seeing a short child are shown in **Table 2**.[2]

Additional history and examination should be targeted to any additional symptom or sign that may be found during the consultation. An assessment of the child's appreciation of the problem is an important component of the initial and subsequent consultations.

Investigation for short children

An important question is to decide in which children investigation should be performed, and how extensive these investigations should be. In general, the shorter the child and/or the slower the growth velocity (GV), the more likely it is that an underlying disorder will be detected. Children with height SDS <-2.5 and/or GV under the 3rd centile for age generally require extensive investigation, as well as longitudinal observation, whereas many children >-2.5 SDS will require only a minimum of investigation but do need longitudinal observation of growth rate.[2,5] Suggested investigation are shown in **Table 3**. It is appropriate to perform tests in a stepwise.

Classification of short stature

Classification of short stature is shown in **Table 4.**

Algorithm of evaluation of short stature[5]

Short stature is best detected by the use of standard deviation scores (SDS) instead of percentile lines. As cut-off point for referral SDS referral SDS < -1.3 (<P10) was chosen in order to identify risk groups that need further evaluation.

TABLE 2. HISTORICAL AND PHYSICAL FEATURES FOR CLINICAL ASSESSMENT OF THE SHORT CHILD

History	
Nature of growth problem	Duration; extent; emotional involvement
Psychological factors	
School performance	
Birth size	Weight, length, gestation
Perinatal events	Delivery; drugs, infections; hypoglycemia; jaundice, edema of hands and feet
Family history	Stature; puberty; inherited disease
Systemic symptoms	Raised intracranial pressure; visual field defects and acuity; chest: chronic infection, asthma; abdominal: pain, vomiting and diarrhea; renal: polyuria, polydipsia and infections
Nutritional review	
Development history	
Examination	
Auxology/proportions	Height, sitting height, body proportion, arm span, weight for height
Body composition:	Broad chest; truncal obesity/poor muscle bulk
Dysmorphism	Facial features, midline defects, ears and palate
Hands/feet	Short metacarpal; clinodactily; palmar crease; lymphedema; clubbing
Visual	Field/acuity defects; optic atrophy/papiledema
Genitalia	Small penis; pubertal staging
Systemic signs	Chest; cardiac; abdomen: distension, masses and anal skin tag; renal: hypertension, anemia and renal masses

TABLE 3. SUGGESTED INVESTIGATION FOR ASSESSING THE SHORT CHILD

Investigations	**Clinical disorders**
Bone age	
Karyotype (if female)	Turner syndrome
FSH	
Systemic screen	
Full blood count	Anemia
ESR	Tuberculosis
Albumin, creatinine, Na,K, blood gas	Chronic renal failure, renal tubular acidosis
TSH and Free T_4	Hypothyroidism
Calcium, phosphorus, alkaline phosphatase	Vitamin D-deficient rickets, hypophospataemic rickets
Urine microscopy,culture	Renal infections
GH/IGF-I axis	
IGF-I and IGFBP-3	GHD
GH provocation tests	GHD
Other imaging	
Skeletal survey	Skeletal dysplasia
Cranial ultrasound	Structural defects associated with GHD or MPHD in infants
CT scan and MRI	Etiology of GHD

TABLE 4. CLASSIFICATION OF SHORT STATURE

Normal variant	**Primary growth abnormalities**	**Secondary disorder**	**Endocrine disorder**
FSS	IUGR	Malnutrition	Hypothyroidism
CDGP	Skeletal dysplasias	Cardiovascular	DM
ISS	Chromosomal abnormalities	Renal disease	GHD
	Turner syndrome	Hematological disorders	
	Seckel syndrome	Chronic infection	
	Noonan syndrome		
	Russell-Silver syndrome		
	Progria		
	Prader-Willi syndrome		
	Down syndrome		

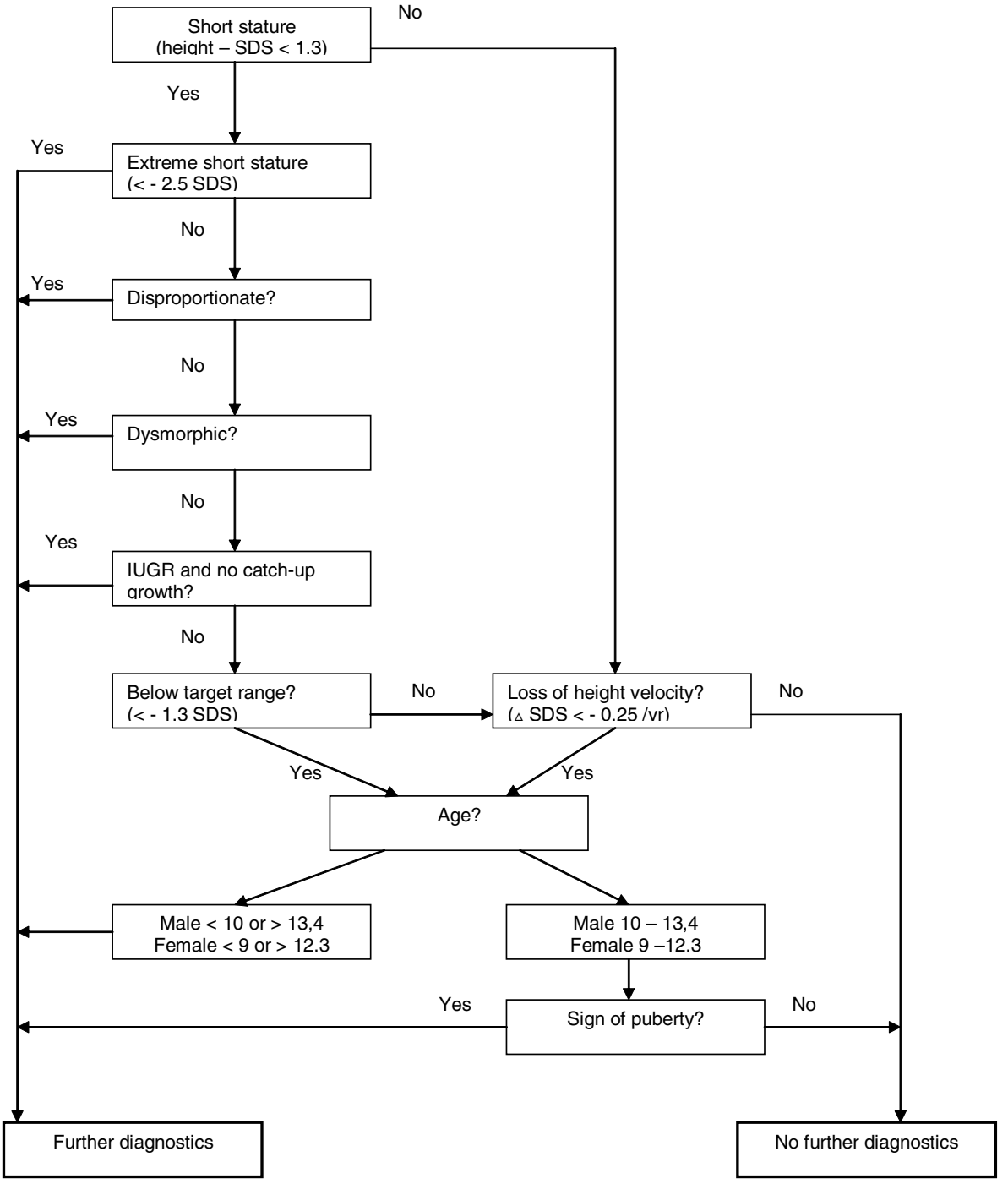

Figure 1. Algorithm of evaluation of short stature.[5]

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