Evaluation of child with short stature

(An overview in reference to hormones)

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Abstract

Short stature, a common pediatric problem, has been variously defined as length/height under third percentile for age (according to international standard), under fifth percentile or below the 3rd standard deviation of mean age (according to ICMR standard) or when the child is small for the mid parental size (a rough statistical measurement of family height). A deceleration in the rate of growth to less than 4 cm/year is often serious and is usually the earliest sign of abnormality of growth.

Keywords: Growth; hormone; short stature; mid parental height.

Normal Growth

Children may grow rapidly over relatively short period of time and physician must be aware of normal standard of growth and development as a function of age. A record of these changes can be utilized as a sensitive indicator of general health. Both longitudinal and cross sectional studies indicate that differences exist in growth among different ethnic groups.

The growth of children can be divided into three components. The infancy component, begins in utero and persists to about 200 days of postnatal life. When growth hormone receptors appear in target tissues the childhood component begins. This lasts until sex steroid secretion brings about the adolescent growth spurt which is responsible for the final difference between adult height of man and woman. Thus the first component of growth is entirely nutrition dependent, the second growth hormone dependent and the third is sex steroid dependent.

In the first year of life, the body length increase by about 50% (from 50 cm to 75 cm). In the second year, another 12-13 cm is added. Thereafter, growth in length/height settles down to a rate of about 5-6 cm every year until adolescence. During the growth spurt, boys add 20 cm in their height and girls gain about 16 cm. The spurt is followed by a rapid slowing of growth. Indian girls reach 98% of the final height on an average by the age of 16 years and boys reach the same stage by the age of about 18 years.

Weight is also an important index of the physical growth and development. Infant born to well fed mother in India weighs about 3.2 kg at birth. A baby usually doubles its birthweight by 5 months of age and triples it by the end of the first year. By the end of the second year, the birthweight gets quadrupled, thereafter the increase is steady at the rate of about 2.25-2.75 kg/years until the adolescent spurt occurs.

The growth spurt starts at the age of 10-11 years in the case of girls and 12-13 years in the case of boys. The growth spurt is maintained for about 2 years in both sexes. During this period, boys gain about 20 kg and girls about 16 kg respectively.

Hormone controlling the growth

1. Growth hormone

Growth hormone plays a central role in the modulation of growth of children from birth until the completion of puberty. In the total absence of growth hormone, Linear growth occurs at about half to third the normal rate. Growth hormone may play a role in control of body anabolism throughout life. Growth hormone secretion is under both positive and negative control. The secretion of Somatostatin and GRH, and hence the release of GH is under the influence of several factors. The secretion of GH is episodic with a relatively short (10-15 minute) has life in plasma. A significant proportion of GH in serum is bound to binding protein that is structurally related to GH receptor. Although small amounts of GH are secreted during waking period, the major secretion of GH occurs during sleep, especially in association with the third and fourth stage of sleep.

2. The somatomedins
Although GH may exert some direct effects on growth, the majority of its growth-promoting actions are mediated by insulin like growth factor or Somatomedin peptidase. These peptides have half lives of hours rather than minutes. Levels are dependent on GH secretion and age with low levels in early childhood, a peak during adolescence and a decline in average values after the age of 50 years.

3. Thyroid hormone

The total absence of thyroid hormone leads to almost complete cessation of linear growth. Thus adequate thyroid hormone appears to be an absolute prerequisite for normal growth. There are several potential mechanisms for this phenomenon. Thyroid hormone exert direct effect on cell metabolism, and thyroid hormone deficiency results in diminished GH secretion in response to stimulation. Finally the action of IGFI on cartilage cells maybe dependent on thyroid hormone.

4. Gonadal steroids

Androgens and estrogens exert their major role in stimulation of growth at the time of puberty. Much of the puberty growth spurt is due to these hormones. Androgens have a direct stimulatory effect on the growth & maturation of bone cartilage and muscle cells. Estrogens appear to have a biphasic action, stimulating growth at low level and inhibiting growth at high levels.

5. Insulin

Insulin has strong anabolic action apart from its effect on carbohydrate metabolism. These actions include stimulation of protein synthesis and cell division. The excessive growth of some of infants of diabetic mothers maybe the consequence of high levels of plasma insulin in the foetus. Insulin may also have growth stimulating actions of its own at low levels in some cell types. The role of insulin in the control of normal growth is still unclear.

6. Other factor

Other factors are nerve growth epidermal growth and platelet derived growth, which have potent actions on the maturation and repair of cells.

Endocrine disorder

In appraisal of a child with short stature, hormonal deficiencies are frequently considered but are less commonly causative than are chronic infections. Deficient secretion of growth hormone or thyroid hormone during childhood or sex steroids at adolescence can lead to a decreased rate of growth and short stature.

a. Human growth hormone deficiency

These children appear normal in height and weight at birth. Delay in growth is observed usually after the age of one year. Growth is regular but slow. These children gain less than 4 cm in height per year. Ratio of the upper to lower segment is normal as anticipated for the chronological age. Bone age is significantly delayed. Gonadal development is infantile or retarded with delay in appearance of secondary sexual characters. Intelligence is usually normal.

Laron's syndrome resembles human growth hormone deficiency clinically but circulating blood GH levels are increased rather than decreased. Somatomedin levels are low in these cases. This is a metabolic disorder with autosomal recessive inheritance. A recently identified cause of growth hormone deficiency has been the syndrome of hypothalamic and adenohypophysis dysfunction, secondary to therapeutic irradiation of central nervous system.

Other causes of growth hormone secretion are neurosecretory dysfunction and bio inactive growth hormone syndrome.

b. Hypothryoidism

The child appears short and stocky. The ratio of the upper and lower segments is immature. Bone age is delayed, sexual development is usually infantile. The abdomen is protuberant with umbilical herna. The face appears puffy and cretinoid. The skin and subcutaneous tissue are thickened with myxedematous appearance. The child appears lethargic and reaction time is increased. The facial expression is dull and children have been seen to put on weight with dextroamphetamine or methylphenidate. Administration of high doses of glucocorticoides particularly synthetic analogues can slow or even stop growth. They are apathetic and are unusually susceptible to cold.
c. Hypogonadism

Adioposogenital dystrophy (Frohlick's syndrome) is associated with moderate growth retardation. The upper and lower segment ratio is normal or slightly delayed.

d. Diabetes mellitus

Short stature is common in children with diabetes, although a normal adult height is usually attained. Somatomedin levels are decreased with poor glycemic control despite elevated concentration of serum growth hormone.

e. Cushing syndrome

In Cushing syndrome, the growth retardation is an early feature of excessive secretion of glucocorticoides by adrenal cortex. Other features of Cushing syndrome are obesity with plethoric moon-shaped faces, abdominal stria, hypertension and glucose tolerance.

Management of child with short stature

A detailed history and a thorough examination are a must. All measurements must be scrupulously accurate, otherwise they may be a source of considerable error, whether observer or instrumental. Till the age of 2 years, supine length is measured rather than standing height because the latter maybe as much as 2 cm less than former, and growth standard for infants and children less than 2 years of age is based on recumbent length. Measurement is done using an infant metre in children less than a year and standiometre in older children. The child stands bare foot with heels, buttocks and shoulders touching the vertical surface and head in the Frankfurt plane. slight upward pressure below the mandibles helps straighten the child and reduces diurnal variation.

Measurement of lower segment, upper segment, span and head circumference are often helpful. Weight must be recorded with a minimum clothing on beam balance. Pubertal staging is done by Tanner's method of pubic hair and breast development for girls and pubic hair and genital development for boys.

General physical and systemic examination for subtle signs like swollen appearance, wide spaced nipples or short neck. Mongoloid faces may give pointers to the cause. Stature of family members is best measured by the doctor, as judgement by relatives maybe highly inacurable.

It's advisable to follow ICMR charts as they are the only all India based data, which also give values for the 5th and 95th percentiles and standard deviations. The measurements are compared with the mean values for that age to see the extent of deviation.

A crude way to assess the genetic component is to plot the parents' height at the end of the height line. For boys the father's height and the mother's height +13 cm. For girls the mother's height and the father's height – 13. The mean of two values is known as mid parental height and gives the target height for the child and the percentile line the child is likely to follow. Careful assessment of the growth velocity is absolutely essential if proper decisions are to be made regarding its management. If the child has a normal velocity and is growing along his centile, the family can be reassured and expensive investigations avoided.

A growth velocity of less than 4 cm per year between the age of 5 years to adolescence is indicative of pathological state. A normal growth rate between birth and 6 months of age below is 15 cm, between 6-12 months of age below 7 cm., in 1-2 years of age below is 10 cm and between 2-5 years of age below is 5 cm per year. For proper assessment of growth velocity, the child should be followed for a minimum of 6 months but better for a year.

Abnormal head circumferences maybe part of a genetic syndromes. Weight disproportionately lower than height suggests nutritional deprivation, while the conserve often occurs in endocrine disorders such as hypothyroidism, growth hormone deficiency and hypercortisolism. Height and weight at any given age be roughly calculated by the following formula:

Height in centimeters 2-12 year = Age x 6+77
In inches Age x 2.5+30

Weight in kilogram in pounds
3-12 month age in months+9/2 age in months+11
1-6 year age in years x 2+8 age in years x 5+17
7-12 years age in years x 7–5/2 age in yrs. x 7+5
Prediction of adult height can be predicted by the following formula:

**Tanner’s formula**

\[ \text{Height at 2 yrs} \times 2 \]
\[ \text{Height at 3 yrs} \times 1.87 \]

**Weech’s formula**

\[ 0.545H^3 + 0.544A + 14.84 \] (boys)
\[ 0.545H^3 + 0.544A + 10.09 \] (girls)

\( H^3 \) = height at 3 years in inches

\( A \) = mid parental height

Proportional linear growth is measured by comparing the crown to rump (CR) length with total length or height.

At birth - 70% of total length
At 3 yr 57% of total length
At puberty 52% of total length

Alternatively one can determine the proportion of crown-rump length with rump heel length ratio.

At birth 1.7:1.0
At 2 yrs 1.4:1.0
At 4 yrs 1.0:1.0

**Span** is a distance measured between the tips of the middle fingers of both arms extended at right angles of the body:

- Under 5 years of age – less by 1-2 cm of the total body length
- At 10-12 years of age – equal to total height
- Over 12 years of age – more than height by 2 cm

**Investigations**

The thoroughness of diagnostic work up may differ from centre to centre, depending on the facilities available and the interest of doctor. Keeping cost effectiveness in mind, a pragmatic approach would be as follows:

- Height between 5th and 50th percentile – Bone age and other basic investigations & follow-up for velocity of growth.

- Height more than up to 2SD below mean – Complete work up is essential.

After the first assessment, it is advisable to routinely deworm the child and advise an adequate diet with plenty of proteins and green vegetables as well as supplement iron for 3-4 months. During the next few months of follow-up, growth velocity is measured, and other investigations are planned according to clinical clues.

**Basic investigations for short stature are:**

- **Haemo gram** – Haemoglobin, total and differential leukocyte count, blood smear, ESR.
- **Radiology** – X-ray films of the left wrist and elbow for bone age, X-ray skull for size of sella turcica and X-ray chest.
- **Urine**-Routine and microscopic examination, specific gravity, pH.
- **Stool examination** – Infestation, malabsorption.
Blood examination – Urea, Creatine, Calcium, Phosphorus, alkaline phosphate, total proteins, albumin, electrolyte, sugar etc.

Buccal smears in cases of girls for study of barr bodies.

Growth hormone estimation is done in all children who do not present with systemic, orthopaedic and metabolic cause e.g. Familial, constitutional, and isolated growth hormone deficiency. Conventionally a variety of provocative tests have been devised; these include a 20-minute strenuous exercise or administration of L dopa, insulin, Arginine, Clonodine or glucagons. In recent years, it has become popular to evaluate the spontaneous secretion of growth hormone by measuring its level every 30 minute from 8pm-8am. This mode of evaluation appears to offer advantages over traditional provocative tests.

Somatomedin levels reflect those of GH and are often used to indicate GH deficiency. Diagnostic use of I-IGF levels requires comparison with age and sex matched controls.

In addition to establishing the diagnosis of GH deficiency it is necessary to examine other pituitary functions. Levels of TSH, and T4, ACTH, Cortisol, dehydroepiandrosterone may provide evidence of other pituitary hormonal deficiencies.

Thyroid functions like T4, TSH, Radioiodine uptake and scan, if necessary, to be done in suspected cases of hypo thyroidism.

Urinary free of cortisol and serum cortisol level (early morning & evening) is necessary for the diagnosis of Adrennocortical insufficiency or Hyder functions.

Gliadin antibodies, intestinal biopsy, dxyllose absorption test maybe done for malabsorption syndrome.

Skeletal survey and scan maybe needed in cases of skeletal disorders.

Renal acidification tests are required in case of vitamin D resistant rickets.

Urinary aminoacidogram required in case of aminoacid metabolism disorder and mucopoly saccharidoses.

Complete karyotype study is required in all dwarf girls and suspected chromosomal disorders like Turners and Down syndrome.

Imaging studies 3D ultrasound and CT scan maybe required in cases of tumours of pituitary, adrenals and pelvic organs.

Treatment of short stature

It comprises 3 element:

• Careful anthropometrical assessment of the situation and an understanding of how to handle the data required.

• Investigation targeted according to the control of the different components which comprises childhood growth.

• Targeted treatment is the exhibition of a treatment designed to augment growth in the childhood component without effect, on either the infancy or the pubertal component of growth. Treatment depends basically on the cause of short stature. No specific treatment is required for familial and genetic (including chromosomal) causes, constitution delay and primordial dwarfsisms.

• Hypothyroidism due to any cause treated with thyroxine in the dose of 4-8 up/Kg/day as a single daily dose. Therapy is monitored by height, bone age and TSH; T4 and T3 levels when necessary. In infancy the dose required is usually 8-9 Ug/Kg/day, as the grows up the dose comes down gradually till in adults 2-3 Ug/kg/day sis sufficient.

For treatment with growth hormone, two categories of patients must be considered for a long-term hormone therapy. Because on the one hand, there is biochemical evidence of growth hormone deficiency combined with slow linear growth. On the other, there is a slow growth but apparently normal secretion. Nearly all of the first category will respond to growth hormone therapy and proportion of the second will grow faster if given growth hormone. Acland et al have suggested that short stature without classic growth hormone insufficiency respond well to exogeneous growth hormone in short term and returns to pretreatment heights velocities afterwards. Consequently, it may be possible to enhance final adult height in these children by growth hormone therapy.
In children with growth hormone deficiency, the growth hormone has to be given by subcutaneous injection daily to be effective. A dose of 15 U/m^2/week is recommended, earlier reports had suggested that subcutaneous or intramuscularly routes could be employed 2-3 times a week. However, the results are better with daily injection.

The backbone of the diagnosis of child who will benefit from growth hormone therapy is anthropometry. Laboratory tests come second. At present growth hormone replacement is expensive. The cost of treating a 10 kg child for one year comes to over 1,00,000 Rs.

The doses of GH used to treat children with classic GH deficiency, usually enhances growth of many non-GH deficient children as well. Therefore, intensive investigation is in progress to determine the full spectrum of short children with intrauterine growth retardation, chronic renal failure. Noonan syndrome, Turner syndrome and others, they experience short-term increased growth velocity following GH treatment, which increased their final height, and treatment of such patients should be confined to prospective clinical trials until further data establishes the validity of this expensive chronic form of therapy.

Replacement should also be directed at other hormonal deficiencies when, in corticortropin deficient patients, the dose of hydrocortisone should not exceed 10-15 mg/m^2 day and therapy can often be deferred until growth has been completed if the deficiency is partial. In patients with a deficiency of gonadotropins, gonadal steroids are given when the bone age reaches the age when puberty usually takes place.

Cushing syndrome is due to exogenous administration of steroids. All that is needed is their gradual and careful tapering off. If a tumour is responsible, surgical removal is indicated. Since the hypothalmo pituitary adrenal axis has been suppressed, cortisone may have to be given in periods of stress till the axis recovers completely.

In Turner syndrome, low dose estrogen (Premarin 0-625 mg/day initially) has been shown to promote growth without closing epiphyses, and should be begun after the age of 12-13 years, gradually increasing to adult dose over 4-5 years. Recently anabolic steroids such as OXAN DROLONE have been used with success. Replacement hormone therapy estrogens and progesterone will be required after about 10 years of age.

Gluten induced enteropathy treated with gluten-free diet will show dramatic increase in growth velocity. Renal tubular acidosis responds well to adequate alkali therapy.

Malnutrition will be treated with adequate calories, vitamins and minerals. Orthopaedic disorders, chronic diseases and other metabolic disease should be treated accordingly.

The emotional derivational dwarf/s has to be kept in convalescent home or suitable foster home. When these children receive emotional warmth and security they show a catch up growth without any treatment.

**Prognosis** depends on the cause and duration of illness. The later the presentation and diagnosis, the less the catch-up growth. Hence it is important to routinely maintain height and weight records. Prognosis for adult height is best in hypothyroidism and constitutional growth delay, intermediate with growth hormone deficiency, celiac disease and malnutrition and relatively poor in familial and genetic causes. Once the epiphyses close, little benefit can be expected with any form of treatment. Prognosis is worsened by inappropriate androgen administration as epiphyses close prematurely.

**References**