Management of Childhood Short Stature

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"The boy lives next to us is much taller than my son although they are in the same class. What happened to my son, doctor?" This is not an uncommon complaint from parents.

Short stature is actually not a disease by itself. It is only a statistically defined height threshold. It can be broadly defined as real or perceived impairment of linear growth which may result in physical, psychological or social difficulties. Medically, it is defined as height less than the 3rd percentile for age on the growth chart derived from local data.

Physiology of growth

Normal linear growth can be divided into three phases after birth: infancy, childhood and pubertal growth. They are under different regulatory mechanisms. During infancy, the growth is rapid, approximately 25cm gain in body length is achieved in the first year. However the growth rate shows a marked decrease during this period from 38cm/year in the first 2 months to 28cm/year at 4 months of age and 12cm/year at 1 year of age. In this period, nutrition plays an important role. In the second year, the height velocity is about 10cm/year. It drops to 7cm/year at 3-4 years and 6cm/year at 5-6 years. It then remains at 4-6cm/year until puberty occurs. 1,2 During childhood period, nutrition becomes less important and hormonal changes, especially growth hormone, becomes the principal regulating factor. Normal thyroid status is also important to maintain growth.

The growth accelerates again in puberty. Girls have their peak height velocity at early puberty, 9cm/year. Boys reach their peak height velocity during mid-puberty, with growth rate of about 10cm/year. 2 Activation of the hypothalamic-pituitary-gonadal axis, especially a significant increase in growth hormone secretion, is responsible for the pubertal growth spurt.

Causes of short stature

In general practice, most short stature patients have familial short stature, constitutional growth delay or a combination of both. Some have short stature following intrauterine growth retardation. Other important differential diagnoses include dysmorphic syndromes, endocrine disorders, chronic diseases and psychosocial deprivation. (Table 1)

Genetic short stature/Familial short stature

This is probably the most common cause of short stature. These patients are short throughout life and are short as adults. However, they characteristically grow at normal rates in their own percentile. It is usually obvious that one or both parents or occasionally, a more distant relative is short. Their bone age is normal, and there is no endocrine abnormalities.

Constitutional growth delay

This is characterised by a retarded linear growth occurring during the first 3 years of life, followed by normal growth that parallels the normal curve throughout the rest of the prepubertal years and a catch-up growth or growth spurt after the usual expected time of pubertal spurt. It usually occurs in boys, only occasionally in girls. Late menarche of mother or delayed pubertal spurt in father occurs in 60-90% of the cases. 3 They are normal on examination apart from slight delay in pubertal development. The bone age is characteristically delayed. The mechanism of the delay is unclear. In most patients with constitutional growth delay, there are no abnormalities in endocrine function. 4 It is easy to diagnose when there is positive family history or when the pubertal spurt starts. But it may lead to extensive investigations in some cases.

Short stature following small for gestational age (SGA)

Small for gestational age can result from foetal, placental or maternal aetiologies. Usually the symmetrical foetal growth retardation is related to early growth failure while the asymmetrical growth failure, with preservation of head growth, occurs because of late deprivation of nutrients related to placental insufficiency. For the latter group, potential for postnatal catch-up growth is reduced. Follow up studies on non-dysmorphic SGA infants indicate that all but 10-15% show catch-up growth by the age of approximately 5 years. 5 There is increasing evidence to suggest that there is an association between metabolic syndromes, adult cardiovascular disease and small for gestational age. The definition of SGA can be variable. Most people use birth weight less than 10th centile for gestation, but some would use less than the 3rd centile. Unless there is obvious reason for their low birth weight, such as chromosomal abnormalities or intrauterine infection etc, they are usually endocrinologically normal.

Dysmorphic syndromes

Every now and then, we might encounter short child
with dysmorphic features. The most common ones are Turner and Noonan Syndrome, others include Russell-Silver, Williams Syndrome etc. Children with other dysmorphic syndromes such as Down’s Syndrome may also have short stature. They are often diagnosed prior to referral for short stature.

For Turner Syndrome, it is caused by complete or partial absence of one of the X chromosomes. It occurs in about 1 in 2500 liveborn girls. It is characterised by three main features: abnormal external and abnormality of certain internal organs, ovarian failure and short stature. Among the three, short stature is always present, irrespective of the karotype and may be the only clinical feature. The following dysmorphic features are helpful for picking up Turner Syndrome: low hairline, web neck, wide carrying angle of arms, short 4th /5th metacarpals, and nail hyperconvexity. The diagnosis is made by karyotyping and in girls of pubertal age, elevated FSH and LH will give a clue.

Noonan Syndrome can occur in both boys and girls. It shows some of the dysmorphic features of Turner Syndrome together with ptosis, hypertelorism and low-set ears. The diagnosis is usually made clinically but about 50% showed mutation in PTPN 11 gene. Studies have shown that growth hormone injections can increase the final height of about 2 inches in Turner patients on average. It also increases growth velocity in cases of Noonan Syndrome.

Endocrine disorders
Growth hormone insufficiency is the most common endocrine disorder presenting with short stature. It can be congenital due to structural defects such as septo-optic dysplasia, genetic due to GH-1 mutation or acquired secondary to CNS tumors, head injury or even transient due to psychosocial deprivation. For severe GH deficiency, it can present before 3 years old with hypoglycaemia, micropenis and obvious short stature. Usually, what we see in clinic are those mild cases who present as short stature in early primary school age. They are short with subnormal growth velocity. They typically have delayed bone age and growth hormone stimulation test showed peak GH value of <15mIU/l. One needs to be aware that GH deficiency can be isolated but it can be part of panhypopituitarism. Therefore, other hormonal axis need to be assessed before starting growth hormone therapy.

Hypothyroidism if untreated may lead to severe stunting of growth. But because of the introduction of neonatal screening, we seldom see short stature due to hypothyroidism only.

Other causes
Cushing’s Syndrome is another cause of short stature. The patient is usually obese and short. There might be history of chronic illness and steroid intake. There might be physical signs such as moon face, buffalo humps, skin striae and hypertension. An overnight dexamethasone test is a useful screening test for cortisol excess.

Skeletal dysplasias such as achondroplasia, hypochondroplasia can present as short stature. Chronic paediatric diseases such as SLE, congenital cyanotic heart disease, chronic renal failure are often associated with short stature. These patients are usually managed by paediatric specialist or even followed in hospitals. One important factor needs to be considered is psychosocial deprivation. Although it is not a common cause for short stature and it is seldom severe enough to cause short stature alone, one should bear in mind during history taking because it is a reversible condition once the underlying psychological stress is removed.

Management of children with short stature
Clinical assessment of growth
Accurate measurement is of crucial importance for growth assessment. For measurement of height, a stable wall-mounted device that has been accurately installed and is regularly calibrated should be used by a well-trained person. The patient is asked to stand with heels (without shoes and socks), buttocks and shoulder blades against the backplate. The measurer then applies pressure on the mastoid processes and the reading is taken at maximum extension without the heels losing contact with the baseboard. For neonates and toddlers, the measurement is often difficult. The use of supine table and neonatometer, consisting of a flat surface with a fixed headboard and moving baseplate can reduce the measurement error. Two people are necessary to get a reliable measurement. The shoulders should be pinned down and the legs are straightened. The measurement is taken when the head is still in contact with the headboard. Weight should also be taken with the subject wearing the minimum of clothing with the use of electronic bathroom-type scales.

In assessment of children with short stature, it is important to also measure the height of both parents with stadiometer. After the initial measurement, the height and weight of patient are plotted on the local growth charts using decimal age. Both parents’ heights are plotted on the chart as well.

History and Examination
Birth history should be asked in details including prenatal events, birth weight, gestation and any perinatal events. Parents should be asked when and how they notice their kid is short, any other family members are short and any past medical history. Family history, consanguinity, social history and school performance should be asked too, Mother’s menarche and father’s growth if he can remember is very important in diagnosing constitutional growth delay. Sometimes the height and pubertal history of extended family members are of help. It is then followed by systematic inquiry.

After the history, the patient should be examined for any dysmorphic features, any disproportion of body height with the help of sitting height or lower segment measurement. Neck should be examined for goitre. Pubertal development should be examined in details. Last but not least is the systematic examination.

Initial investigations
Various biochemical investigations can be performed depending on the history and examination. FSH and LH will be helpful in a girl at pubertal age to screen for ovarian failure which might be secondary to Turner syndrome. Renal function and blood count can be done if
chronic disease is suspected. Thyroid function should also be assessed. IGF-1 or growth hormone profile is usually performed once abnormal growth velocity is documented. Two growth hormone stimulation tests are required for the diagnosis of growth hormone deficiency unless there is obvious reason to account for it, such as post cranial irradiation, or post intracranial surgery in hypothalamic-pituitary region. Other dynamic tests are usually indicated when suspicion of a specific endocrine disease is strong. Bone age is essential for diagnosis of constitutional delay and growth hormone deficiency. MRI pituitary is mandatory if there are signs of hypopituitarism or confirmed growth hormone deficiency. Procedures to assess a child with short stature are summarised in Table 2.

**Treatment**

Most cases of short stature are due to genetic short stature and constitutional delay. Generally, they do not require any treatment unless their psychological well-being is affected. Detailed explanation and reassurance is usually enough for the patients and parents. Lots of attention is paid in paediatric endocrinology to treatment of short stature with different hormonal preparations. However, we have very limited choices of growth promoting therapies, namely growth hormones and sex hormones. And they need to be used properly to minimise their potential side effects.

In cases of severe constitutional delay, a short course of low dose of sex hormone can be used to promote pubertal development. It works well in both boys and girls. Nowadays, growth hormone is licensed for treatment of GH deficiency, Turner Syndrome, Prader-Willi Syndrome, short SGA children, short children with renal failure and lately idiopathic short stature. Before starting the treatment, detailed auxological assessment is essential to make sure that the child still has growth potential. The family must be fully committed after a detailed discussion. Growth hormone is given as a daily subcutaneous injection, usually in the evening. The dosage varies depending on the condition. For a growth hormone deficient patient, 0.5 units/kg/week of growth hormone would be started initially and titrated clinically and biochemically with IGF-1 and IGFBP3. Higher dosage, 1 unit/kg/week is usually enough for the patients and parents. Lots of detailed explanation and reassurance are required for the diagnosis of constitutional growth delay and bone age.

Regular assessment of height and bone age is essential for the timing of discontinuation of the treatment. After the use of recombinant GH, the complication of Creutzfeld-Jakob disease has been wiped out. Leukaemia, once has been reported in association with growth hormone, has been demonstrated in number of epidemiological studies to have no greater incidence than general population. Furthermore, there is no evidence that GH therapy stimulates tumour regrowth in children with cancer.

Overall, the use of human growth hormone therapy in the management of short stature is safe with regular monitoring under a paediatric endocrine specialist.

Short stature is a common problem in our daily practice. Most of these cases need no therapy. If endocrine abnormalities are suspected, referrals to a paediatric specialist would be recommended.

### References


### Table 1. Causes of short stature

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<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Genetic short stature</td>
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<tr>
<td>Constitutional growth delay</td>
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<tr>
<td>Combined genetic short stature and constitutional growth delay</td>
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<tr>
<td>Short stature following small for gestational age</td>
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<tr>
<td>Dysmorphic syndromes</td>
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<tr>
<td>Endocrine disorders</td>
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<tr>
<td>Skeletal dysplasia</td>
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<td>Chronic diseases</td>
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<td>Psychosocial deprivation</td>
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### Table 2. Assessment of short stature

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<td>Blood test if necessary ((CBC, TSH, RFT, LFT))</td>
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<td>Radiological examination if necessary ((bone age))</td>
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<td>Endocrine assessment (if indicated)</td>
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