

## Why Evaluate Short Stature? Perhaps to Save a Life! (A Clinical Perspective)



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Are we just indulging parental anxieties and cosmetic dreams? Why spend time and money to evaluate the “short child”? After 30 years of evaluating and treating children with short stature, I believe the most important answer is “to save lives.”

Having recently presented this perspective at conferences and grand rounds, the audience response is frequently one of uncertainty. Allow me, therefore to present the case of a 9-year-old girl as an example. This patient was referred to me by an attendee at a conference at which I had lectured. The girl had been  $-3$  standard deviations (SDS) for height most of her life, but had not been previously evaluated for short stature. Spurred on by the pediatrician’s new knowledge, the child’s karyotype was obtained and revealed a Turner (XO) pattern, which was a surprise both to her parents and the pediatrician. No cardiac murmurs were heard on physical examination, but because of the known association between heart malformation and Turner syndrome, an echocardiogram was performed and revealed an extremely large hole in the heart, necessitating surgery the following day. Dilated calyces were noted on imaging studies of the patient’s kidneys and surgical intervention has been scheduled for the future. Thus, the lecture set in motion an algorithm not only to improve ultimate target height, but more importantly to “save a life”.

Questions commonly asked by residents, fellows, general pediatricians and even endocrinologists include:

- What are the criteria for the work-up of the short child?
- When do you begin?
- Who is excluded?
- Who is short?
- What tests are preferred for the evaluation?
- How extensive should the work-up be?
- What are the treatment options?

### How is short stature defined?

Despite years of clinical research and over half a century of clinical experience, pediatric endocrinologists are still not in complete agreement on the exact criteria. Growth patterns reflect the general state of health in childhood. Deceleration of growth may emanate from underlying pathological processes that ultimately cause more serious problems than affecting ultimate height attainment. Delineation of the reasons for poor growth is obviously of great importance in order to reverse or eliminate the causative disorder(s).

Assessment of growth is therefore essential in pediatric care. Accurate measurements of growth velocity and critical analysis of growth data allow the attending physician to determine whether further assessment is warranted. Among the multitude of questions that can be asked are “How is ‘short’ defined?” and “Who should be evaluated?” Again, there is no uniform consensus amongst the experts. Short stature, defined as stature more than two standard deviations below the mean, related to age and gender and adjusted for population standards, affects 2% of the population. (Table 1)

### Table 1. NON-ENDOCRINE CAUSES OF SHORT STATURE

**Familial Short Stature** - Bone age is appropriate for chronological age with normal growth velocity and predicted adult height is appropriate to the family pattern. [3, 4]

**Constitutional Growth Delay** - Characterized by delayed bone age, normal growth velocity and predicted adult height appropriate to the family pattern. The subject will usually have a first or second degree relative with a similar growth pattern. [3, 4]

**Nutrition** - Malnutrition is the most common cause of growth failure worldwide.

**Race** - Aside from normal variations in stature, the major causes of short stature are not race-specific.

**Sex** - Boys are more likely to undergo evaluation for short stature, but are also more likely to manifest idiopathic short stature or constitutional delay of growth and development.

### Table 2. GENETIC DISORDERS [5]

- Turner Syndrome
- Noonan Syndrome
- Prader-Willi Syndrome
- *SHOX* (pseudo autosomal dominant) encodes a transcription factor that affects bone growth through regulation of chondrocyte development in the growth plate. An abnormality or reduction in *SHOX* may therefore lead to abnormal bone growth because of atypical proliferation of chondrocytes, as well as defective differentiation. Loss, inactivation, or mutation of one *SHOX* gene copy contributes to the short stature in girls with 45X Turner syndrome, and boys and girls with Leri-Weill dyschondrosteosis (an inherited skeletal dysplasia that affects bone growth development in both sexes and is manifested by short stature, wrist deformity, and mesomelia)
- Other gene defects in short stature: A specific diagnosis of the etiology of short stature may impact treatment and management of the patient [6]. Genes that may be affected include:
  - *GH* (autosomal dominant or recessive)
  - *GHRH* receptor (autosomal dominant or recessive)
  - *GH* receptor (autosomal dominant or recessive)
  - *PTPN11* (autosomal dominant)
  - *POU1F1* (autosomal dominant recessive)
  - *PROP1* (autosomal recessive)

### Table 3. CHRONIC ILLNESSES

- Congenital Heart Disease: Height and weight velocity retardation is evident in children with severe congenital heart defects.
- Asthma: No study found evidence that a sustained decrease in linear growth velocity can be used as a marker of severe asthma.
- Diabetes Mellitus Type 1: Studies show mixed results of severe diabetes mellitus affecting linear growth.
- Beta Thalassemia: There is no clear evidence that this disorder affects growth.
- Inflammatory Bowel Disease: disease severity in some studies was associated with height velocity.
- Juvenile Rheumatoid Arthritis: Studies indicate an association between decreased growth velocity and increased severity of the disease.
- Chronic Kidney Disease: Most studies found a positive relationship between increased severity of kidney failure and decreased height or height velocity.
- HIV: Linear growth deceleration may precede the onset of symptoms of active disease.
- Atopic dermatitis: There were conflicting results in two studies.
- Cerebral Palsy: Decreased growth velocity was prevalent in all studies.
- Sickle Cell Disease: Most studies found a positive association between severe sickle cell disease and decreased height percentile compared with controls.

GH: growth hormone; GHRH: growth hormone releasing hormone; PTPN11: protein tyrosine phosphatase, non-receptor type 11; SHOX: Short stature homeobox-containing gene on chromosome X

## Who should be evaluated?

From a personal perspective, I recommend evaluating the majority of children presenting with short stature. It is not always obvious where normalcy ends and pathology begins, and endocrinologists must use an individualized approach and consider all aspects of the patient's clinical presentation. Clearly there are many causes of short stature and the etiology must be diligently sought in each individual case and the following questions asked:

- Is there an underlying chronic illness such as celiac, heart, or kidney disease?
- Is an underlying genetic disorder or environmental factors or toxins responsible?
- Are there suggestive signs and symptoms, for example recurrent vomiting and/or diarrhea, weight loss or gain, decrease in appetite, poor nutrition, headaches, delayed puberty, disproportionate short stature and/or a slow-down in growth velocity?

Normal variants such as constitutional growth delay, familial short stature or a desire to be taller, should of course be excluded. Children who are growing normally will follow their growth curve fairly closely; thus, even if they are in the 5<sup>th</sup> percentile for height, they are probably growing normally if that is the percentile in which they have always been. Perhaps more important than absolute height in terms of underlying pathology is the change in growth velocity, even if the initial height (e.g. 90<sup>th</sup> percentile) and the current height (e.g. 50<sup>th</sup> or 25<sup>th</sup> percentile) are in the "absolute" normal range.

Some common non-endocrine and endocrine causes of short stature are shown in **Tables 1, 2, 3 and 4.**

<b>Table 4. ENDOCRINE CAUSES OF SHORT STATURE</b>	
Hypothyroidism	Insulin-like growth factor-1 deficiency
Diabetes mellitus (poorly controlled)	Cushing's syndrome
Growth hormone deficiency	Precocious puberty
Growth hormone resistance	

## Specific evaluation of children with short stature

Testing to reveal the pathology underlying abnormal short stature is critical. This must at least include a bone age X-ray, complete blood count, chemistry panel, thyroid function tests, celiac screen, erythrocyte sedimentation rate and a screening test for growth hormone (GH), e.g. analyzing insulin-like growth factor-1 (IGF-1) and often IGF binding protein 3 levels. Additional tests may be ordered depending on the outcomes of the clinical assessment, such as karyotyping for a girl of short stature to rule out Turner (XO) syndrome. Tests for certain genetic causes of short stature are now available, (for example, for pituitary transcription factor abnormalities) and can be ordered in selective cases. (Table 2)

If levels of IGF-1 are determined to be low, a GH stimulation test should be performed to confirm or rule out a diagnosis of GH deficiency [5]. If the result of the GH stimulation test reveals low GH levels, GH deficiency can be confirmed. If the GH values are high, then consider a separate etiology known as Primary IGF-1 deficiency requiring a different type of growth hormone (e.g. Increlex). Additionally, a magnetic resonance imaging scan may be performed to evaluate for the presence of a pituitary or extra pituitary tumor. Furthermore, if such a tumor is present, other pituitary hormones may also be deficient or absent. Replacement of these hormones will subsequently lessen morbidity and mortality.

In conclusion, short stature may indicate an underlying pathology that, if identified and treated, may indeed save a life.

## References

1. Sultan M, Afzal M, Qureshi SM et al. Etiology of short stature in children. *J Coll Physicians Surg Pak* 2008; 18(8):493–7
2. Laron Z, Bidlingmaier M, Strasburger CJ. Indications, limitations and pitfalls in the determination of human growth hormone, IGF-I and their binding proteins. *Pediatr Endocrinol Rev.* 2007 Oct;5 Suppl 1:555–69.
3. Lanes R, Lee PA, Plotnick LP et al. Are constitutional delay of growth and familial short stature different conditions? *Clin Pediatr (Phila)* 1980;19:31-3
4. Ali O, Cohen P. Growth in Children in *Manual of Endocrinology and Metabolism*. Lippincott 2009:95–9
5. Seaver LH, Irons M; American College of Medical Genetics (ACMG) Professional Practice and Guidelines Committee. ACMG practice guideline: genetic evaluation of short stature. *Genet Med* 2009;11:465-70
6. Walenkamp MJ, Wit JM. Genetic disorders in the growth hormone - insulin-like growth factor-I axis. *Horm Res* 2006;66:221–30.