

Management of Short Stature in Childhood and Adolescence

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Abstract

Background: Short stature (SS) in childhood is a frequent reason for referral to pediatric endocrinologists. Normal height is determined according to age, sex and ethnic group as well as the family context. Short stature is a term applied to a child who is two standard deviations or more below the mean height for children of that gender and chronologic age (and ideally of the same racial-ethnic group).

Aim: In this review, we will look into the management of short stature in childhood and adolescence.

Methodology: The review is comprehensive research of PUBMED since the year 1982 to 2019.

Conclusion: Future research should be directed at evaluating which diagnostic tests are valuable in assessing children with short stature, understanding the physical and psychosocial concerns of specific groups with short stature and the ethical implications of attempting to increase adult height, and testing proposed therapeutic interventions such as human growth hormone by controlled trials with well-defined clinical outcomes.

Keywords: Short Stature; Children and Adolescents; Management of Short Stature

Introduction

Short stature is a term applied to a child who is two standard deviations or more below the mean height for children of that gender and chronologic age (and ideally of the same racial-ethnic group) [1]. Short stature (SS) in childhood is a frequent reason for referral to pediatric endocrinologists. Normal height is determined according to age, sex and ethnic group as well as the family context [2].

Some children with short stature are healthy, some have a medical condition known to be associated with short stature and in some short stature is the result of an undiagnosed illness. Parents and children who consult a physician about short stature may be concerned about either the possibility of an underlying disease or perceived social discrimination because of short stature, including teasing or bullying in school or decreased future socioeconomic success [3].

Familial (genetic) and constitutional are by far the most common causes of short stature and delay, which are benign, but the workup is done to identify those at risk of other more severe and probably treatable diseases (GH deficiency or idiopathic short stature (ISS). Early in childhood one of the most common causes is FFT [4].

A pediatric patient with short stature and no clinically evident reason generally requires referral to an endocrine specialist to identify the cause. The subsequent diagnosis may include one of several conditions in which GH therapy has been approved for use [5].

Young patients with short stature were reported to be at increased risk for psychosocial distress due to stigmatization, bullying, social isolation, juvenilization and low self-esteem. Studies examining the behavior profile of short statured children reported higher levels of behavioral problems, compared to a control sample of normal-statured children [6] and a representative population sample [7].

Etiology

Short stature can be due to various etiologies and the cause may be a primary or secondary growth disorder, or idiopathic. Primary growth disorders are intrinsic to the growth plate and include clinically defined syndromes, factors that result in being born small for gestational age (SGA), and skeletal dysplasias. Secondary growth disorders are believed to change the milieu of the growth plate and include GH deficiency, disorders of the GH-insulin-like growth factor (IGF)-I axis including IGF-I deficiency or resistance, endocrine and metabolic disorders, organ system disorders, malnutrition, psychosocial disorders, and iatrogenic conditions [8].

Growth delay and familial short stature are the most common cause of short stature, which means, the child is growing at his/her normal rate and will eventually catch up to the curve if dealing with constitutional delay. In the second disease, familial short stature, the infant has a constant growth rate, but one or both parents are short. This situation typically occurs in parents whom mothers are below 152 cm and fathers 160 cm respectively [9].

Patients with idiopathic short stature (ISS) have no discernible cause; the condition is very heterogeneous and may be either familial or non-familial. In all cases, an early diagnosis is important and therefore, height screening programs must be sufficiently sensitive and specific to ensure timely detection and treatment [8].

Familial short stature: Familial or genetic short stature is most often a normal variant. For most children with genetic short stature, the specific molecular causes remain unknown, but with advances in exome/genome sequencing and bioinformatics approaches, new genetic causes of growth disorders have been identified, contributing to the understanding of the underlying molecular mechanisms of longitudinal bone growth and growth failure [10].

Constitutional delay of growth and puberty: Approximately 1 in 3500 children in the US is diagnosed with growth hormone deficiency (GHD) [11]. Only 20% of these children have organic GHD. Organic causes include central nervous system tumors, radiation, infection, and traumatic brain injury. Approximately 80% of children do not have a readily identifiable cause of GHD. These patients are classified as having idiopathic GHD. Optimal dosing of GH during puberty is also controversial. In normal children, pubertal sex-steroid production independently stimulates growth and increases GH secretion, resulting in the pubertal growth spurt. Studies suggest that GHD patients may achieve greater pubertal growth if treated with GH doses higher than those used in pre-pubertal children [12,13].

Since the replacement of human pituitary-derived GH with recombinant human GH, much experience has been gained with the use of GH therapy. The Food and Drug Administration (FDA) had expanded GH use for the following conditions for children [14]:

1. GH deficiency/insufficiency
2. Chronic renal insufficiency (pre-transplantation)

3. Turner syndrome
4. SHOX haploinsufficiency
5. Short stature from Prader-Willi Syndrome (PWS)
6. Children with a history of fetal growth restriction (SGA, IUGR) who have not caught up to a normal height range by age 2 years
7. Children with idiopathic short stature (ISS): height > 2.25 SD below the mean in height and unlikely to catch up in height.
8. Noonan Syndrome
9. Short Bowel Syndrome

Idiopathic short stature: A practical definition of idiopathic short stature (ISS) is a height below 2 standard deviations (SD) of the mean for age, in the absence of any endocrine, metabolic, or other diagnosis. These children have normal (often at the lower limit) height velocity and no biochemical or other evidence for a specific growth retarding condition, which implies normal results for endocrine screening tests, including those for growth hormone deficiency. It appears that epigenetic changes may play a role in some cases of ISS. In one study, ISS was associated with increased methylation of two promoter regions for the insulin-like growth factor 1 (IGF-1) gene; these epigenetic changes are predicted to reduce the individual's sensitivity to growth hormone [15,16].

Diagnosis

The approach to short stature must involve a thorough medical history, physical examination, and appropriate screening laboratory investigation. Specific tests must then be aimed at suspected illnesses.

The medical history must include such details as the birth weight of the child, the birth length of the child (if known), the gestational age of the baby at birth, and any noted congenital anomalies. Family trauma, emotional trauma, and psychosocial status should be assessed. The family history, as it pertains to any potential inherited or genetic disease, is very important [17].

Physical examination should initially consist of accurate measurements of both height and weight, correctly plotted on a growth chart. Certainly, this is the basis for the diagnosis of short stature. A complete physical examination should be performed, with a determination of the body habitus, beginning with the derivation of the proportion of upper to lower body and the arm span to height value [18].

Laboratory testing investigations would include a complete blood cell count to exclude anemia, leukemia, chronic infection, or malabsorption; an erythrocyte sedimentation rate measurement to screen for chronic inflammation; tests of serum electrolytes, blood urea nitrogen, and creatinine, as well as urinalysis and a urinary pH determination to exclude renal disease; serum calcium, phosphorus, and alkaline phosphatase measurements to rule out rickets; and a serum thyroxine and tri-iodothyronine resin up take and thyroid stimulating hormone assessment to rule out hypothyroidism.

Genetic testing for specific syndromes may be indicated by physical findings or simply a growth pattern and height projection differing significantly from the family. Assessment of the GH-IGF axis begins with a serum IGF-1 level, but, since levels rise rapidly with puberty onset, results must be interpreted relative to skeletal rather than chronological age. Testing GH levels following provocation with various agents is the classic method for assessing GHD, but the interpretation of results is complicated by variation in testing procedures and unclear sensitivity/specificity (and variation among countries) of cut-offs used for diagnosis [19].

Management

In many cases, SS does not require treatment and a conversation with the parents and child would be the most important medical action. To wait and see the patient every 6 months is the correct action. Management decisions often evolve from primary care physicians' threshold for specialist consultation to rule out pathologic causes of shortness, pediatric endocrinologists' perspective about use of growth-promoting medications, insurance, and parents concerned that their child is "noticeably shorter than the other kids" or "teased because of his/her size" [20,21].

Management options for non-GH deficient short stature: Children with non-GHD short stature may receive markedly different recommendations that vary in complexity and costs and for which relative benefits and risks are uncertain. Increases in growth rate and height resulting from androgen or hGH treatment (including one single double-blind, placebo-controlled trial) have not predictably improved psychosocial well-being, even when the surrogate measure of final height is increased [22,23].

Management options for patients with GHD: Efficacy of GH treatment is better when started at a young age, and diagnosis should, therefore, be made as early as possible. Long-term hrGH therapy appears to be effective and safe in patients with GHD. The future will delineate the indications of its use, including new diseases and other skeletal dysplasia. In general, GH therapy is not indicated in SGA during adolescence due to the reduced growth potential remaining after entering puberty. However, combined therapy with GH and gonadotropin releasing hormone analogs (administered for two years) has recently been reported to be safe and effective in improving adult height in SGA children with more severe growth retardation at the onset of puberty [24,25].

The efficacy of GH treatment has been investigated in children whose height has been compromised due to chronic illnesses such as Crohn's disease, cystic fibrosis, glucocorticoid-induced suppression of growth in other disorders (asthma and juvenile idiopathic arthritis (JIA), also known as juvenile rheumatoid arthritis (JRA)), and adrenal steroid disorders such as congenital adrenal hyperplasia (CAH). Studies have shown both anabolic effects and improvement of growth velocity after GH treatment in children with glucocorticoid dependent Crohn's disease.

Conclusion

Future research should be directed at evaluating which diagnostic tests are valuable in assessing children with short stature, understanding the physical and psychosocial concerns of specific groups with short stature and the ethical implications of attempting to increase adult height, and testing proposed therapeutic interventions such as human growth hormone by controlled trials with well-defined clinical outcomes.

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