A Child With Short Stature

ACGME Sub-competencies / Developmental Milestones Addressed

Patient Care: Gather essential and accurate information about the patient; Make informed diagnostic and therapeutic decisions; Develop and carry out management plans
Practice-based Learning and Improvement: Identify strengths, deficiencies, and limits of one's knowledge
Professionalism: Develop awareness of limitations to engage in help-seeking behaviors; Recognize ambiguity in clinical medicine and respond appropriately
Systems-based Care: Coordinate patient care within the health system

Overview

Monitoring growth and development is a primary objective of routine health supervision visits. Height, weight, and head circumference are measured at every health supervision visit for children under age 2; and height, weight, and body mass index are measured for children and young adults older than 2. These parameters are plotted against normative values on standardized growth charts established by the World Health Organization and adopted by the Centers for Disease Control and Prevention. A child's expected growth depends on inherited growth patterns as well as on the child's health and environmental influences. Society generally values height, and parents are highly vested in the growth and development of their child as a measure of his or her overall wellness.

Learning Objectives

Upon completion of A Child With Short Stature, residents should be able to

- identify healthy patterns of growth within the context of the family,
- recognize the influence of family history on growth, accounting for medical, ethnic, and cultural influences on height, and
- describe the signs and symptoms of genetic conditions that may affect a child's growth outside of the expected parameters of his or her parents.

Case Presentation

Initial Presentation

Sophia is a 3-year-old girl who presents for her routine health supervision visit. Her parents note that she is the smallest child in her new preschool class and are concerned that her height reflects an underlying medical problem.

Question 1. Which of the following factors would not be consistent with a pathological cause of short stature?

(A) The child's growth curve falls below the 3rd percentile.
(B) The child's height is consistent with the parents' height.
(C) The child has dysmorphic features and a developmental delay.
(D) The child's growth velocity is decreasing.
(E) The child has disproportionately short arms and legs.

In assessing a child for short stature, the pediatrician must first decide whether the child is truly short. Short stature is clinically defined as being 2 standard deviations below the mean, or below the 3rd percentile on standardized growth charts. However, patterns of growth within the child's family must be taken into account. Is the child short within the context of his or her family?

There are several algorithmic methods for predicting adult height. For example, the midparental height method is a simple calculation that provides a rough estimate of predicted adult height based on parental heights, without the need for a bone-age X-ray.

- For boys, add 13 cm (5 inches) to the mother's height and average the result with the father's height.
- For girls, subtract 13 cm (5 inches) from the father's height, and average the result with the mother's height.

Six and one-half centimeters (2.5 inches) above and below the mean represents the 3rd and 97th percentiles, respectively, or 2 standard deviations from the mean. A child whose predicted height is consistent with the parents' heights most likely has benign familial short stature, which is not pathologic. However, an undiagnosed inherited condition could be the cause of short stature in either parent, and thus a pathologic cause for short stature cannot be completely ruled out. In addition, the accuracy of the various formulas used to predict adult height varies widely, and caution must be used in basing treatment decisions on these predictions.

Growth velocity during the first 2 years of life is about 30–35 cm. Infants often cross percentile lines in the first 24 months, as they grow toward their genetic height potential. During childhood, growth is relatively constant at about 5–7 cm per year in both sexes, although there is often a slight slowing later in childhood. Growth during puberty is approximately 8–14 cm per year. Although a child may cross percentile lines in the first few years of life, most children with familial short stature or constitutional growth delay will have a normal growth velocity by age 3. Continued decrease in growth velocity beyond age 3 suggests underlying pathology.

Dysmorphic features and developmental delays suggest an underlying genetic etiology for short stature. Disproportionate short stature suggests an inherited condition or a metabolic bone disease such as rickets.

Question 2. Which of the following would most likely not present with dysmorphic features?

(A) Chromosomal abnormalities
(B) Nonchromosomal genetic abnormalities
(C) Disproportionate short stature
(D) Intrauterine infection
(E) Maternal exposures or systemic illness
(F) Constitutional growth delay

Constitutional growth delay presents with a downward shift in the growth rate at 3–6 months. Physical appearance and development are typically unremarkable and do not suggest underlying pathology.

Chromosomal abnormalities such as Turner syndrome (45,X) and Down syndrome (47,+ 21) are common chromosomal causes of short stature, and Noonan syndrome and Russell-Silver syndrome are nonchromosomal genetic conditions that present with short stature. All of these syndromes present with dysmorphic features, and therefore, the presence of dysmorphic features might suggest an underlying genetic condition as a cause of a child's short stature. In disproportionate short stature, the limbs are disproportionately short for the trunk or the trunk is disproportionately short for the limbs. The presence of disproportionate short stature suggests a skeletal dysplasia, rickets, or hypothyroidism. Intrauterine infections, such as congenital rubella, cause severe intrauterine growth retardation. Maternal exposures to alcohol or tobacco, poor maternal nutrition, or a systemic illness can all affect the growth of the child and may or may not result in dysmorphic features.

Past Medical History

Sophia was the product of a full-term pregnancy without complications. She was delivered by spontaneous vaginal delivery with a birth weight of 8 pounds 4 ounces (3.74 kg) and a length of 20 inches. Her newborn screen was normal for 52 conditions. She tracked along the 75th percentile for weight and 25th percentile for height until she was 18 months old. Then her growth decelerated, and by her 3-year visit, her height was at the 2nd percentile. Her weight had adjusted downward slightly to the 50 percentile. She is otherwise in good health and has been reaching developmental milestones appropriately. Her diet is generally appropriate for age. Her bowel movements are described as normal: 1–2 times daily, without blood. There have been no hospitalizations or surgeries. She does not take any medication. There are no known allergies. Her immunizations are up to date. Both parents are attorneys, although the mother now stays home to be with Sophia. The mother denies alcohol or tobacco use during pregnancy.

Question 3. On the basis of the past medical history, which of the following potential causes of short stature is most likely?

(A) Idiopathic short stature
(B) Gastrointestinal disorder
(C) Chronic illness or nutritional disorder
(D) Medication-related poor growth
(E) Social or maternal deprivation

The differential diagnosis for short stature is broad and includes genetic causes, chronic illnesses, gastrointestinal disorders, endocrinologic and metabolic disorders, renal disorders, cardiac and pulmonary disorders, immunologic disorders, medications, nutrition, and social-emotional conditions. Sophia's past medical history is quite unremarkable, with no signs or symptoms of systemic illness. Nutritional intake is appropriate for age. Bowel patterns do not suggest a gastrointestinal disorder such as celiac disease or inflammatory bowel disease. She does not take medications, such as glucocorticoids, that could influence growth. The child appears well cared for.

Idiopathic short stature is the diagnosis for moderately to severely short children who do not meet the criteria for familial short stature or constitutional growth delay and for whom, after extensive testing, no other cause for poor growth is found.

Question 4. Which of the following genetic syndromes known to cause short stature is most likely to result in an infant being small for gestational age at birth?

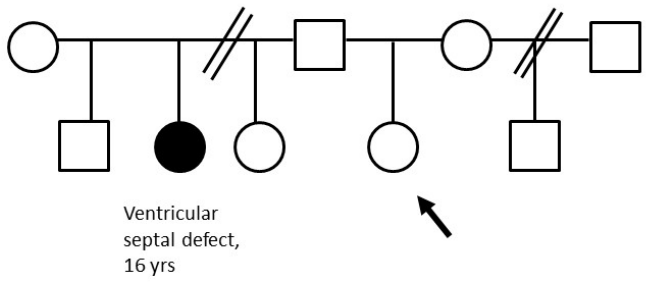
(A) Turner syndrome
(B) Noonan syndrome
(C) Down syndrome
(D) Russell-Silver syndrome
(E) Prader-Willi syndrome

All of the genetic syndromes listed above can result in distinctive dysmorphic features that suggest a genetic condition as a cause of growth failure. Individuals with small-for-gestational-age height and weight are most likely to be Russell-Silver syndrome, which presents with intrauterine growth retardation and smallness for gestational age. Although infants with Turner, Noonan, or Down syndrome may be born small, they may also be appropriate-for-gestational-age size at birth. Therefore, growth parameters alone cannot be used to rule out these syndromes. Prader-Willi syndrome is the most common syndromic form of obesity; short stature is common in Prader-Willi syndrome but may not develop until late childhood.

Family History

Sophia's father is Caucasian of northern European descent. His height is 5'11'', and his weight is 185 pounds. The patient's mother is also Caucasian of northern European descent. Her height is 5' 7'', and her weight is 118 pounds. The mother has a son from a previous marriage who is in good health. The father has 3 children from a previous marriage: a son and 2 daughters. All are of above-average height. The second daughter, who is now 16 years old, was born with a ventricular septal defect requiring surgical repair. There is no history of known genetic syndromes, cognitive or developmental disabilities, or early deaths or miscarriages in the family. The parents are not related.

Pedigree



Question 5. Which of the following elements of the family history might point to a genetic etiology for short stature, triggering a genetics referral?

(A) Reproductive or prenatal history issues
(B) Early or unexpected death in a family member
(C) Cognitive or behavior issues
(D) Growth and stature disorders
(E) Consanguinity
(F) All of the above

Attention should be paid to the possibility of reproductive problems such as infertility, miscarriages, and birth defects, all of which may suggest a chromosomal disorder. A family history of developmental or cognitive delays, such as autism, or a history of early onset disease or early death could suggest an underlying, or genetic, abnormality inherited through the family and would prompt genetic testing and possibly referral to a geneticist. A history of a known disorder of growth and stature within a family would necessitate evaluation for that disorder. A family history of consanguinity might suggest a possible autosomal recessive condition.

Question 6. Which of the following important historical elements in the evaluation of short stature in this family is the least significant?

(A) The heights of close family members
(B) The ages of puberty in the mother and father
(C) The family's ethnicity
(D) The child's weight and head circumference measurements
(E) The absence of a positive family history

Although one might argue that all of the above information contributes to the evaluation, the least significant element is the absence of medical problems in the family. The presence of medical problems in the family would call for collection of detailed family history information, such as celiac disease and other gastrointestinal problems, kidney disease, and endocrinologic disease such as growth hormone deficiency or hypothyroidism.

Family history is a significant resource for clues pertaining to a possible diagnosis of the cause of Sophia's short stature. As previously discussed, the father's and mother's heights are essential in defining the expected height of the child. The ages of puberty in the father and menarche in the mother are important when evaluating an adolescent for constitutional growth delay. In a 3-generation family history, the heights of siblings, grandparents, uncles and aunts, and 1st-degree cousins are all important in understanding familial growth patterns. The family's ethnicity may suggest familial short stature.

In this case, however, the family history is noncontributory. There are no red flags for genetic or systemic disease, and familial heights are average to above average. The family history information is nevertheless still important in any subsequent evaluation of the patient.

Physical Examination

Physical exam reveals a small but well-nourished blond Caucasian child without obvious dysmorphology. HEENT exams reveal eyes and ears normally placed. The neck is supple without masses. Cardiac exam shows a regular rate and rhythm without murmurs or gallops. Chest exam is unremarkable with normally spaced nipples. The lungs are clear. The abdomen is soft and nontender without masses or hepatosplenomegaly. The skin is without distinguishing lesions. The extremities show no clubbing, cyanosis, or edema and are well-proportioned to the child's body. Neurologically, the child is active, moves all extremities equally, and shows age-appropriate coordination.

Question 7. In the two most common causes of short stature—familial short stature and constitutional growth delay—which of the following physical findings is most likely?

(A) Cardiac murmur
(B) Obesity and hypogonadism
(C) Triangular face, hypertelorism, and pectus excavatum

(D) Normal physical exam
(E) Macrocephaly, rhizomelia, and bowed legs

A cardiac murmur may be an incidental finding or a clue to an underlying diagnosis. Cardiac abnormalities are common in a host of genetic conditions; pulmonary stenosis is the most common cardiac defect in Noonan syndrome, coarctation of the aorta in Turner syndrome, and atrioventricular canal defect and ventricular septal defect in Down syndrome. Isolated congenital heart disease can also lead to growth failure secondary to increased metabolic demands.

Obesity and hypogonadism might suggest Prader-Willi syndrome. Triangular face, hypertelorism, and pectus excavatum are typical of Noonan syndrome. Macrocephaly, rhizomelia (proximal shortening of the long bones), and bowed legs are consistent with achondroplasia, the most common condition associated with severe disproportionate short stature. Being aware of the significance of major or minor physical findings can be an important clue in the evaluation of short stature.

The most common genetic causes of short stature—familial short stature and constitutional growth delay—will most likely not have any unusual physical findings at all. That is, even the lack of physical signs is significant in the evaluation.

Question 8. Which of the following physical findings might direct the work-up toward a genetic etiology for Sophia's short stature?

(A) Webbed neck and widely spaced nipples
(B) Palpable thyroid gland
(C) Abdominal striae
(D) Clubbing of the finger tips
(E) Decreased subcutaneous fat

A webbed neck and widely spaced nipples in a girl with short stature suggest Turner syndrome and may also be found in Noonan syndrome. Of course, findings on physical exam can lead to nongenetic pathologies as well. A palpable thyroid, abdominal striae, or clubbed fingers, although not likely to be seen in a 3 year old, would suggest systemic disease in an older child. Chronic gastrointestinal, endocrinologic, pulmonary, renal, and immune conditions can be associated with short stature. Decreased subcutaneous fat, with weight affected more than height, suggests malnutrition, gastrointestinal disease, or other chronic illness.

Diagnostic Testing

Sophia's medical history, family history, and physical exam were not contributory for an underlying diagnosis. Preliminary screening laboratory tests were subsequently performed in search of an etiology for her short stature.

Question 9. Of the following, which would not be an appropriate preliminary test in the evaluation of short stature in the primary care office?

(A) Complete blood count and sedimentation rate
(B) Growth hormone level
(C) Thyroid function testing
(D) Celiac screening and complete metabolic profile
(E) Chromosome analysis

In general, diagnostic testing without clinical suspicion has a low yield in determining why a child is short. If clinical signs point to a diagnosis of familial short stature or constitutional growth delay, it is appropriate to do no testing at all. However, with severe short stature, growth failure, or prior to a referral to a specialist, screening for an underlying condition may be useful. CBC, ESR, and comprehensive metabolic profile are appropriate for ruling out renal, liver, and metabolic etiologies. Celiac disease and hypothyroidism are common conditions that can present with short stature. In a female, chromosome analysis to rule out Turner syndrome should be considered.

A random growth hormone level is not helpful in screening for short stature. Owing to the pulsatile secretion patterns of growth hormones, a low level does not necessarily mean the child is growth hormone deficient. If growth hormone deficiency is suspected, measurement of the level of insulin-like growth factor 1 (IGF-1) is probably the best screening test, although the level can be borderline low in constitutional growth delay. IGP binding protein 3 testing is also often ordered, but it may not be as effective as IGF-1 testing in predicting growth hormone deficiency.

Question 10. Of the following, which is the most appropriate diagnostic test to add to the initial evaluation of isolated short stature?

(A) MRI of the pituitary
(B) Skeletal survey
(C) Bone-age X-ray
(D) Growth hormone stimulation test
(E) Chromosomal microarray

A bone-age X-ray is the only radiographic test that is routinely ordered in the evaluation of isolated short stature. Although it is not diagnostic, because most conditions with short stature will result in a delayed bone age, the test does provide information about future growth potential. Bone age is typically consistent with chronological age in familial short stature.

An MRI of the pituitary may be useful if there is an indication of hypopituitarism and growth hormone deficiency but would not be a first-line test in the evaluation of isolated short stature. A skeletal survey would be helpful if a skeletal dysplasia were suspected as a cause of the short stature. Growth hormone stimulation test is the diagnostic test for evaluation of growth hormone deficiency. Its administration and interpretation require the expertise of a trained endocrinologist and would not be part of a primary care physician's initial work-up.

Chromosomal microarray testing compares the patient's DNA to normal controls to detect submicroscopic deletions and duplications (also called copy number variations). Microarray testing is appropriate in screening for a genetic disorder when there is a clear dysmorphology, developmental delay, or both but the phenotype is nondiagnostic. If Noonan syndrome is suspected, molecular sequencing for specific associated gene mutations, such as mutations of the *PTPN11* gene, is recommended.

The Role of "Genetic Thinking" in Diagnosis, Prevention, and Treatment

Diagnosis

Preliminary laboratory evaluation, including chromosomal analysis showing a normal 46,XX karyotype, and the celiac screen, thyroid function tests, and blood chemistry profile were all within normal limits. Bone age was delayed by 9 months. Physical exam did not show any particular dysmorphology that might suggest a genetic condition. Family history was negative for familial patterns of short stature.

Question 11. Which of the following is the least likely cause of Sophia's short stature?

(A) Idiopathic short stature
(B) Familial short stature
(C) Constitutional growth delay
(D) Growth hormone deficiency
(E) Turner syndrome

The lack of presenting comorbid symptoms or dysmorphology, positive laboratory findings, or positive family history for short stature point to the diagnosis of idiopathic short stature, which is the term used to classify the growth of individuals with stature below the 3rd percentile for whom no medical, skeletal, hormonal, chromosomal, or genetic etiology is identified. Sophia's growth is not consistent with her parents' heights or family history; therefore, the child's presentation is not consistent with familial short stature. Delayed bone age is consistent with constitutional growth delay; however, bone age is often delayed in other causes of short stature as well. Despite Sophia's normal IGF-1 level, growth hormone deficiency cannot be ruled out. Although some of the above diagnoses remain in consideration, a normal chromosomal analysis rules out Turner syndrome in this patient.

Prevention and Treatment

Question 12. All of the following could be considered in the ongoing management of this child except

(A) Reassurance to the family that the child is healthy and that no further evaluation is necessary,
(B) Referral to an endocrinologist for further growth hormone testing,
(C) Ongoing surveillance of the child's growth parameters to ensure that she continues to track along her predicted percentile curves,
(D) Genetic testing for the short stature homeobox (*SHOX*) gene, or
(E) Referral to a behavioral psychologist for therapy and treatment related to the psychological stress of being short.

Most patients with short stature have normal psychosocial functioning. Short stature appears to have minimal detectable impact on peer perceptions, social behavior, friendships, and acceptance. If a child has social-emotional difficulties, then a referral to psychology may be appropriate, but factors other than stature should be considered as a potential etiology. Preemptive referral to psychology is not warranted.

Now that obvious and manageable causes of short stature have been ruled out, it is reasonable to reassure the family that this is a normal variant for their child and that, although Sophia may be short, she is otherwise in good health. The child will require continued surveillance of her growth at yearly intervals to assure that she is progressing appropriately on her growth curves and at an appropriate velocity. Timing of puberty would be delayed in constitutional growth delay. If growth velocity continues to decrease, falling further off the growth curve, referral to an endocrinologist for growth hormone stimulation testing may be appropriate.

The *SHOX* gene is a transcription-factor gene on the pseudoautosomal region of the X and Y chromosomes and is important in regulating skeletal maturation. It is responsible for the short stature associated with Turner syndrome and Léri-Weill dyschondrosteosis. Growth hormone treatment is effective in increasing linear growth in children with these conditions. A mutation in

the *SHOX* gene may be present in up to 4% of children with idiopathic short stature, and growth hormone treatment is likely to be effective in these children. An endocrinologist may consider molecular genetic testing of the *SHOX* gene to determine the potential efficacy of growth hormone therapy.

Summary

The differential diagnosis for short stature is quite broad and can be affected by conditions of almost all major organ systems. Height is, at its essence, a familial condition. Although we define short stature in terms of normative population-based values, a "normal" expected height for an individual is determined by that individual's family history and ethnicity and is influenced by his or her general health and environment. Genetic height potential must be considered before short stature can be defined as a problem. The history and physical examination should assess for associated dysmorphic features, anomalies, and evidence of systemic disease. For a child who is otherwise healthy without systemic symptoms and who is growing at a normal rate, extensive laboratory evaluation is not necessary. A thorough family history may provide clues about genetic conditions that run in the family as well as systemic conditions that have an increased prevalence in families. For a short girl, chromosomal analysis to rule out Turner syndrome may be of some value, but other genetic testing is usually not warranted, unless indicated by findings on history and exam.

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