Growth Matters:

Early Identification & Referral in Pediatric Endocrinology

Recognize early… Refer timely!

START EXPLORING

Understanding the disease area

- SGA
- NS
- ISS
- TS

Why should you refer early?

- Importance of Early Referral

Referral guidelines for growth disorders

- Referral Guidelines

SMALL FOR GESTATIONAL AGE (1/2)

NEXT

Definition, epidemiology & etiology

Definition:

Birth weight and/or length < -2 SD for gestational age[1,2]

~90% of infants born SGA achieve appropriate catch-up growth by 2 years of age[3]

Epidemiology:

- Global prevalence in infants: **2.3 - 10%**[3]
- Prevalence is higher in premature infants[4]; varies significantly by region and ethnicity[4,5]

Etiology:

Attributable to[6]:

- Maternal factors (~50%)
- Fetal abnormalities (~5%)
- Placental insufficiency (<5%)
- No identifiable pathology (40%)

Genetic causes:

- IGF-I (mutation)[1]
- IGF-I receptor1 (partial mutation/ deletion)[1]
- ALS (deficiency)[1]
- PAPP-A2 (mutation)[1]
- Genes involved in diabetes/obesity[1]
- Angiotensin-converting enzyme 2 genes[7]

Signs & symptoms*[8]

- Low birth weight and/or short birth length
- Inadequate catch-up growth within the first 2 years
- Lack of interest in eating
- Lack of muscle mass and/or poor muscle tone
- Persistently low weight-for-height proportion
- Fasting hypoglycemia and mild metabolic acidosis
- Generalized intestinal movement abnormalities
- Late closure of the anterior fontanelle (soft spot)
- Frequent ear infections or chronic fluid in ears
- Early delayed bone age; later fast advancement
- Early puberty or (rarely) true precocious puberty
- ADD (known now as ADHD) and specific learning disabilities
- Hypospadias (abnormal opening of the penis)
- Cryptorchidism (undescended testicles)

*List is not all-inclusive. ALS, acid-labile subunit; ADD, Attention Deficit Disorder; ADHG, (Attention-Deficit/Hyperactivity Disorder); IGF, insulin-like growth factor; PAPP-A2, pregnancy-associated plasma protein A2); SD, standard deviation; SGA, small for gestational age

1. Finken MJJ et al. Endocr Rev. 2018;39(6):851-894. 2. Clayton PE et al. J Clin Endocrinol Metab. 2007;92(3):804-810. 3. Saenger P et al. Endocr Rev. 2007;28(2):219-251; 4. Fujita K, et al. Pediatr Int. 2016;58:372–6. 6. Lee ACC, et al. BMJ. 2017;358:j3677. 5. Ewing AC, et al. Matern Child Health J. 2017;21:786–96; 6. Houk CP, Lee PA. Int J Pediatr Endocrinol. 2012;2012(1):11; 7. He J, et al. Kidney Blood Press Res. 2018;43:1596–606; 8. Magic Foundation. https://www.magicfoundation.org/Growth-Disorders/Small-for-Gestational-Age/.

SMALL FOR GESTATIONAL AGE (2/2)

Diagnosis

Diagnosis of SGA requires[1]:

Accurate gestational age
(Preferably via first trimester ultrasound)

Accurate measurements at birth
(Weight, length, head circumference)

Assessment[2]:

Confirm short stature and SGA status

- History (Maternal, fetal, or placental factors)
- Physical exam (weight, length, head circumference)
- Growth pattern
- Bone age

Rule-out growth disorders or genetic disorders

- Laboratory screening for specific parameters (e.g., bone age), hormone levels (e.g., IGF-1), and genetic mutations.

If no clues for primary disorder, diagnose as SGA of unknown origin.

IGF-1, insulin like growth factor; SGA, small for gestational age. . 1. Clayton PE et al. J Clin Endocrinol Metab. 2007;92(3):804-810.; 2. Finken MJJ et al. Endocr Rev. 2018;39(6):851-894.

NOONAN SYNDROME (1/2)

NEXT

Definition, epidemiology & etiology

Definition[1]

- Genetic disorder (*de novo* mutation or autosomal inheritance)
- No sex predominance

Epidemiology:

Occurs in

~1:1000 - 1:2500

live births[1]

Etiology:

Mutations in RAS/MAPK pathway genes[1] (PTPN11, SOS1, RAF1, KRAS, RIT1, MAP2K1, BRAF, NRAS)

Consequences[2,3]:

- GH deficiency¶
- Neurosecretory dysfunction
- GH resistance
- Low levels of IGF-I

Occurs in familial and sporadic form[1]

Clinical signs & symptoms

Short stature[1]

~Approximately 50% to 70% of patients have short stature

Characteristic facial features[4]

- Broad, high forehead
- Hypertelorism
- Low-set, posteriorly rotated ears with a thick helix
- High-arched palate
- Micrognathia
- Short neck with excess nuchal skin
- Epicanthal folds
- Downward-slanting palpebral fissures
- Low posterior hairline

Congenital heart defects[4]

- Pulmonary valve stenosis
- Hypertrophic obstructive cardiomyopathy
- Atrial and ventricular septal defects
- Persistent ductus arteriosus

Other clinical manifestations[2,4]

- Pectus carinatum, pectus excavatum
- Thoracic scoliosis
- Cryptorchidism
- Lymphatic abnormalities
- Coagulopathy
- Cognitive/learning disabilities
- Ophthalmologic issues
- Seizures

GH, growth hormone; IGF-I, insulin like growth factor 1. ¶ reports of GH-secretory dynamics are inconsistent, and some patients have normal GH levels

1. Bhambhani V, Muenke M. Am Fam Physician. 2014;89(1):37-43; 2. Romano A, et al. Pediatrics. 2010;126:746–59; 3. Binder G et al, J Clin Endocrinol Metab. 2005;90(9):5377–5381; 4. van der Burgt I. Orphanet J Rare Dis. 2007;2:4.

NOONAN SYNDROME (2/2)

Diagnosis

Based on clinical features[1]

Combination of major and minor criteria. If the patient has[2]:

- Typical facial dysmorphology + one major feature or two minor features; or
- Suggestive facial dysmorphology + two major features or three minor features

Clinical geneticist referral aids in diagnosis and management[1]

Van der Burgt criteria for diagnosing Noonan syndrome[2]

Feature	A = Major	B = Minor
Facial	Typical dysmorphology (evolves with age)	Suggestive dysmorphology
Cardiac	Pulmonary valve stenosis, hypertrophic cardiomyopathy, and/or NS-specific ECG	Other defect
Height	<3rd percentile	<10th percentile
Chest wall	Pectus carinatum/excavatum	Broad thorax
Family history	First-degree relative with confirmed diagnosis	First-degree relative with suggestive Noonan syndrome
Other	All: intellectual disability, cryptorchidism, and lymphatic vessel dysplasia	≥1: intellectual disability, cryptorchidism, or lymphatic vessel dysplasia

ECG=electrocardiogram; NS=Noonan syndrome. ***1.*** *Bhambhani V, Muenke M. Am Fam Physician. 2014;89(1):37-43; 2. Van der Burgt I. Orphanet J Rare Dis. 2007, 2:4 doi:10.1186/1750-1172-2-4..*

IDIOPATHIC SHORT STATURE (1/2)

Definition, epidemiology & etiology

Definition:

Height >2 SD, below the corresponding mean height for a given age, sex, and population group for unknown reason[1]

Epidemiology:

60 - 80% of children presenting with short stature to an endocrinologist have ISS[1]

Etiology:[2]

Idiopathic indicates unknown causes, but recent research shows it could be due to monogenic variants affecting:

- The GH–IGF-1 axis
- ECM
- Growth plate signaling pathways

Signs & symptoms*

- Short stature with variable phenotypes and genotypes[3]
- Normal birth weight & body proportions, GH sufficient[1]
- No identifiable cause: systemic, endocrine, nutritional, or chromosomal[1]
- Categories[2]:
  - Familial short stature (FSS)
  - Constitutional delay of growth and puberty (CDGP)
  - Children with subtle or unidentified syndromic features

ECM, Extracellular matrix components; GH, growth hormone; GH-IGF-1, growth hormone-insulin like growth factor-1; ISS, idiopathic short stature; SD, standard deviation.

1. Cohen P, et al. J Clin Endocrinol Metab. 2008;93:4210-4217; 2. Paparella R et al, Children 2025, 12(7), 855; 3. Inzaghi E et al. Horm Res Paediatr. 2019;92(2):71-83.

IDIOPATHIC SHORT STATURE (2/2)

Diagnosis

STEP 1: MEDICAL HISTORY, EXAMINATION[1,2]

- History: Birth, growth, and family history, chronic illness or psychosocial/ cognitive development.
- Physical examination: Height velocity, body proportions, head circumference, any dysmorphic features.

STEP 2: SCREENING & IMAGING[1,2]

- Bone age X-ray (left hand).
- Routine labs: TSH, Free T4, IGF-1, IGFBP-3, celiac screen, etc.
- Rule out systemic conditions (renal, liver, GI, etc.).
- Consider if syndromic features or GH insensitivity suspected.

STEP 3: GENETIC TESTING[3]

- Common genetic defects: SHOX, NPR2, ACAN, FGFR3.
- Karyotype in females to rule out Turner syndrome.

CAN, aggrecan gene; FGFR3, fibroblast growth factor receptor 3GH, growth hormone; GI, gastrointestinal; IGF-1, insulin like growth factor 1; IGFBP-3, insulin like growth factor 3; ISS, idiopathic short stature; NPR2, natriuretic peptide recptor 2; SHOX, short stature homeobox gene; TSH, thyroid stimulating hormone

1. Cohen P, et al. J Clin Endocrinol Metab. 2008;93:4210-4217; 2. Pedicelli S, et al. J Clin Res Pediatric Endocrinol. 2009;1:105-115; 3. Inzaghi E et al. Horm Res Paediatr. 2019;92(2):71-83..

TURNER SYNDROME (1/2)

NEXT

Definition, epidemiology & etiology

Definition:

Most common sex chromosome abnormality in phenotypic females[1]

Epidemiology[1]:

- Female fetuses: **3%**
- **1 in 2500** live female births
- **1.5 million** women worldwide
- Overall mortality: **3-fold increase**
- Life expectancy: **Reduced by ~13 years**

Etiology:

- Complete or partial monosomy of the X chromosome (missing or structurally altered)[1]
- Structural abnormalities include[3]:
  - Deletion (all or partial)
  - Isochromosome Xq
  - Ring X chromosome

Clinical signs & symptoms

Most common feature[1,2]: short stature

Average final height deficit[2]: 20 cm[2]

Growth velocity[2]: <10th percentile for age

Short stature[3]
~95%-100% prevalence

Characteristic facial features[3]
- Ear malformations (including hearing defects) (~15%-30%)
- Micrognathia (~60%)

Cardiovascular system[3]
- Aortic coarctation (~7%-14%)
- Bicuspid aortic valve (~14%-34%)
- Hypertension (~50%)

Genitourinary system[3]
- Ovarian failure (>90%)
- Horseshoe kidney (~10%)

Other clinical manifestations[3]
- Webbed neck (~40%)
- Broad chest (~30%)
- Low posterior hairline (~40%)

1. Elsheikh M et al. Endocr Rev. 2002;23(1):120-140. 2. Bondy CA; Turner Syndrome Study Group. J Clin Endocrinol Metab. 2007;92(1):10-25; 3. Gravholt CH et al. Nat Rev Endocrinol. 2019;15(10):601-614. .

TURNER SYNDROME (2/2)

Diagnosis

Indications for Chromosome Analysis to Diagnose TS[1]

As the only clinical feature:
• Fetal cystic hygroma, or hydrops, especially when severe
• Idiopathic short stature
• Obstructive left-sided congenital heart defect[a]
• Unexplained delayed puberty/menarche
• Couple with infertility
• Characteristic facial features in a female[b]

At least two of the following:
• Renal anomaly (horseshoe, absence or hypoplasia)
• Madelung deformity
• Neuropsychologic problems and/or psychiatric issues
• Multiple typical or melanocytic nevi
• Dysplastic or hyperconvex nails
• Other congenital heart defects[c]
• Hearing impairment <40 years of age together with short stature

Karyotyping is the gold standard test to diagnose TS

Prenatal:

- Primary analysis: Abnormal ultrasound findings or a high-risk result on non-invasive prenatal testing (NIPT).
- Confirmation: Invasive genetic testing and, if parents decline, by postnatal karyotyping on newborn blood. Fetal ECG is recommended if TS is diagnosed prenatally.

Postnatal:

- Karyotyping on peripheral blood (minimum 30 metaphases, which can detect approximately 10% mosaicism with 95% CI).
- If mosaicism is suspected, additional metaphases or tissue samples (e.g., skin, buccal) may be analyzed.

Karyotyping should be repeated, particularly if initially performed prenatally

Adapted from Gravholt CH et al. European Journal of Endocrinology, 2024, 190, G53–G151
a, Typically bicuspid aortic valve, coarctation, aortic stenosis (with/without bicuspid aortic valve), mitral valve anomalies and hypoplastic left heart syndrome; b, Down-slanted palpebral fissures, epicanthal folds, low-set anomalous pinnae, micrognathia, narrow palate, short broad neck, and webbing; c, Partial anomalous pulmonary venous return; atrial septal defect, secundum type; and ventricular septal defects, muscular or membranous. CI, confidence interval; TS, Turner's syndrome

THE IMPORTANCE OF EARLY REFERRAL, DIAGNOSIS AND TREATMENT

Poor growth can indicate an underlying health issue[1]

Short stature is often the sole symptom of disorders like GHD, TS, and SGA without catch-up growth[2,3]

Starting treatment at ages 2–4 greatly enhances growth velocity, prepubertal height normalization, and adult height outcomes[4]

Reaching heights similar to peers reduces social stigma and emotional distress in children[5]

Early referral ensures that the “window of opportunity” for medical intervention is not missed, particularly before puberty when growth potential is highest[3]

GHD, growth hormone disorder; SGA, small for gestational age, TS, Turner’s syndrome. 1. Haymond et al. Acta Paed 2013;102:787–94; 2. Grote F K et al, BMC Public Health 2007, 7:77; 3. Mavinkurve M et al, Malaysian Family Physician 2021; Volume 16, Number 3; 4. Houk and Lee, International Journal of Pediatric Endocrinology 2012, 2012:11; 5. Abd El-Aziz A W et al, 2735-3540, 76-2, June 2025

CLINICAL & PSYCHOSOCIAL IMPLICATIONS OF Llate REFERRAL

Consequences of late referral and treatment

- Impaired physical and cognitive development[1,2]
- Suboptimal management of comorbidities such as renal, hematological, and metabolic disorders[3]
- Long-term consequences include[4]:
  - Lower academic achievement
  - Reduced adult income
  - Poor muscle strength (e.g., hand grip)

Psychosocial impact of short stature

Psychosocial consequences of short stature:

- Impaired HQoL[5]
- Increased risk of bullying[6]
- Emotional distress and reduced self-esteem[7]
- Greater social isolation, stigmatization and exclusion[8]

Gain in height has been reported to be associated with gain in self-esteem[7]

Poor growth might be the first sign of an underlying condition[9]

- A cross-sectional observational study of 104 consecutive patients shows:
  - 23.08% had chronic medical illnesses such as:
    - Renal, hematological, diabetes mellitus and celiac diseases
- Conditions were not primarily growth-related, but poor growth was the presenting symptom.

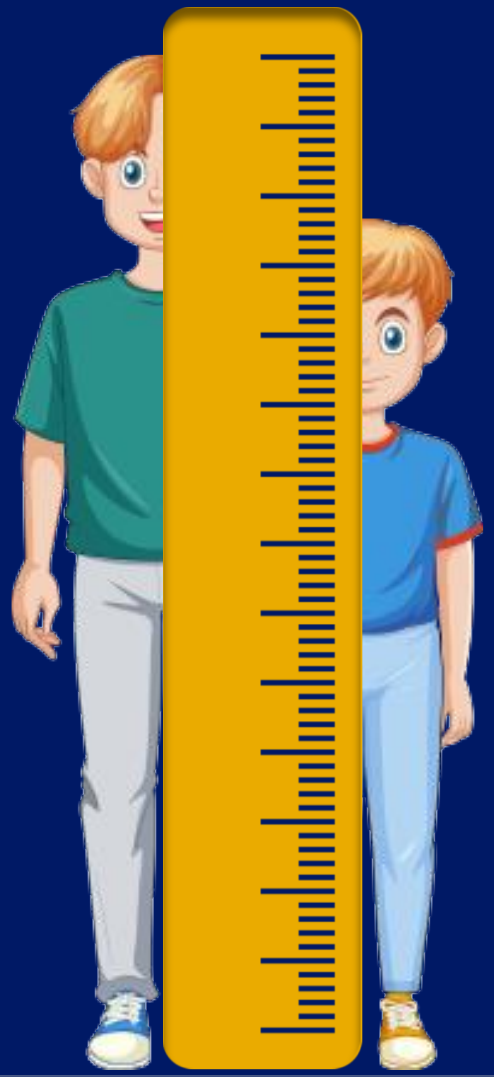
Short stature requires thorough evaluation to identify treatable causes for timely intervention and optimal growth

HQoL, health related quality of life. *1. Adair et al. Lancet 2013;38:525–34. 2. Victora et al. Lancet 2008;371(9609):340-57 3. Choudhury et al. J Evid Based Med Healthc 2016;3(54):2770–2; 4. Hoddinott et al. Am J Clin Nutr 2013;98(5):1170–8; 5. Quitmann et al. PLoS One 2016;11(4)e0153953; 6. Voss and Mulligan BMJ 2000;320(7235)612–3; 7. Chaplin et al. Horm Res Paediatr 2011;75 291–303; 8. Usubini A G et al J. Clin. Med. 205, 14, 538; 9. Choudhury et al. J Evid Based Med Healthc 2016;3(54),2770–2.*

IMPACT OF EARLY VS LATE REFERRAL

Early referral:

- Improved final adult height due to timely GH therapy initiation[1]
- Better psychosocial outcomes[2,3]
- Optimized management of comorbidities[4]
- Higher likelihood of achieving genetic height potential[1]
- Improved bone density, sexual function, and overall health[5]
- Earlier pubertal induction and better uterine development[6]



Late referral:

- Reduced adult height due to missed growth window[7]
- Delayed diagnosis of underlying conditions (e.g., TS, NS, GHD, SGA)[7]
- Suboptimal management of chronic illnesses[4]
- Impaired cognitive and academic development[8,9]
- Lower bone density, poor sexual development, and social isolation[5]

GH, growth hormone; GHD, growth hormone disorder; NS, Noonan syndrome; SGA, small for gestational age, TS, Turner's syndrome. *1. Polak M et al, European Journal of Endocrinology (2017) 177, 421-429.; 2. Chaplin et al. Horm Res Paediatr 2011;75:291–303.; 3. Quitmann et al. PLoS One 2016;11(4):e0153953 doi:10.1371/journal.pone.0153953; 4. Choudhury et al. J Evid Based Med Healthc 2016;3(54):2770–2; 5. Lee and Conway. Lancet Diabetes Endocrinol 2014;2:333–8.; 6. Bannink E M N et al, Clinical Endocrinology (2009) 70, 265–273; 7.* Krishnamoorthy P et al, Paediatrics & Child Health, 2024, 29, 306–310; *8. Victora et al. Lancet 2008;371(9609):340-57; 9. Hoddinott et al. Am J Clin Nutr2013;98(5):1170–8*

ALGORITHM FOR THE EVALUATION AND REFERRAL OF SHORT STATURE

Initial indication: Child with short stature
(Height <3rd percentile, decreasing growth velocity after 3 years of age; height below genetic potential; Intrauterine growth restriction without catch-up growth by age 2; Syndromic appearance, abnormal body proportions)

Are there any gastrointestinal or endocrine symptoms?

Yes

Evaluate for celiac disease/ inflammatory bowel disease/ hypothyroidism/cortisol excess

Refer to Pediatric Gastroenterologist or Endocrinologist

No

Does the patient exhibit any dysmorphic feature?

Yes

Do they exhibit proportionate features?

Yes

Assess for genetic syndromes

Male

Refer to Genetics

Female

Consider Karyotype then refer to Genetics

No

Assess for chondrodystrophy

No

Evaluate the growth velocity, bone age and predicted height & weight,

If the patient has:-
Growth velocity: ≥ 5 cm/year
Bone age: delayed

Case of constitutional delay of growth and puberty

If the patient has:-
Growth velocity: ≥ 5 cm/year
Estimated height: aligned with mid-parental height
Bone age: normal

Likely familial short stature

If the patient has:-
Growth velocity: < 5 cm/year
Estimated weight: normal/increased
Bone age: delayed

Refer to Pediatric Endocrinologist

Adapted from 1. PES referral guidelines for children with suspected short stature, 2020, Available at: Suggestive history and physical findings, Accessed on: 12 Sept, 2025; 2. Barstow C et al, Am Fam Physician. 2015;92(1):43-50; 3. Children's Wisconsin Growth Pathway, Available at: GROWTH PATHWAY, Accessed on: 12 Sept, 2025.

REFERRAL GUIDELINE FOR SHORT STATURE

When to refer your patient to Pediatric Endocrinologist?

Urgent indications[1]:

- Headaches or vision changes
- Suspected multiple hormone deficiencies

Routine indications[1,2]:

- Poor growth
- Height below 3rd percentile
- Intrauterine growth retardation, no catch-up growth by age 2 years
- Slow growth velocity: < 5 cm/year
- Delayed puberty (14 years of age for boys or 13 years of age for girls)
- Height prediction > 2 SD (10 cm) below the mid-parental height
- Bone age > 2 SD below chronologic age

Useful details for consulting with Pediatric Endocrinologist[1]

Previous growth data/growth charts

Blood tests for:

- Total or free T4 and TSH
- Comprehensive metabolic panel
- Complete blood count
- ESR or CRP
- IGF-1
- IGFBP-3
- Tissue transglutaminase IgA
- Total serum IgA
- Chromosome analysis if female child has features of Turner's syndrome

Bone age X-ray of left hand and wrist

Adapted from 1. PES referral guidelines for children with suspected short stature, 2020, Available at: Suggestive history and physical findings, Accessed on: 12 Sept, 2025; 2. Barstow C et al, Am Fam Physician. 2015;92(1):43-50