

Interactive Pediatric Endocrine Grand Round on Growth Hormone Deficiency Diagnosis

Case-based diagnostic reasoning: true GHD, mimics, false positives & false negatives

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Learning objectives

Build a defensible pre-test probability of GHD from auxology and clinical context.

Recognize when IGF-1, bone age, GH stimulation testing, MRI, and genetics add—or do not add—diagnostic value.

Identify common pathways to false-positive GHD: obesity, peripubertal status, undernutrition, hypothyroidism, and low pre-test probability.

Identify false-negative or “borderline” situations where a rigid GH peak cutoff can mislead.

Apply a practical diagnosis-first algorithm before prescribing recombinant GH.

How the round works

VOTE → DATA → RE-VOTE → DIAGNOSIS

Each case begins with only the history and growth chart.

Ask yourself: “What is my pre-test probability?”

Then we reveal the physical examination, laboratory data, bone age and/or MRI.

Do not diagnose from the GH stimulation test alone.

At the end of each case: state the single most important diagnostic error to avoid.

The central idea: GHD is a clinical diagnosis supported by biochemistry

A LOW PEAK GH $\neq$ GHD

A NORMAL PEAK GH $\neq$ “NO GHD”

CONTEXT CHANGES THE MEANING OF THE TEST

Auxology is the anchor: height SDS, height velocity, crossing of percentiles, and distance from genetic target.

Biochemical tests modify probability; they do not replace the growth phenotype.

MRI can move probability dramatically when a structural hypothalamic–pituitary abnormality is present.

Genetics becomes important when the phenotype is familial, syndromic, discordant, or unexplained.

Step 1: read the growth chart before ordering a GH test

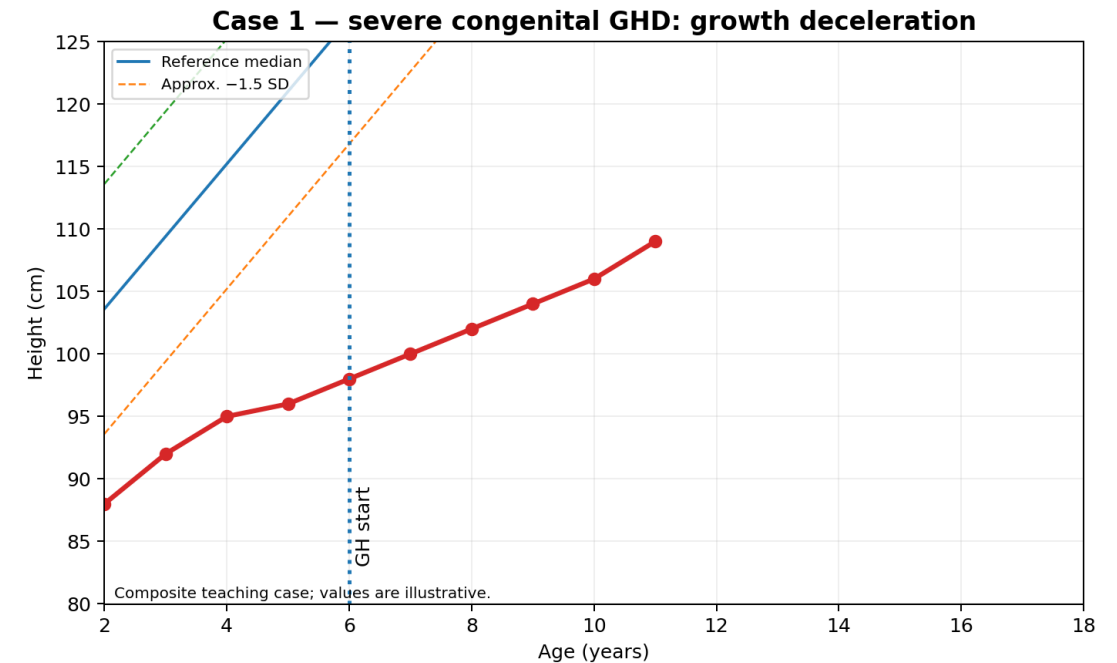
Measure accurately and calculate height SDS and height velocity from reliable serial measurements.

Ask whether the trajectory is abnormal—not simply whether the child is short.

Compare with mid-parental target height and the child's previous trajectory.

Weight pattern matters: disproportionate weight-for-height can support severe GHD; weight faltering suggests systemic disease.

Pubertal timing and bone age can change the interpretation of growth velocity.



Question: What is more informative—the current height SDS or the velocity?

Step 2: estimate pre-test probability

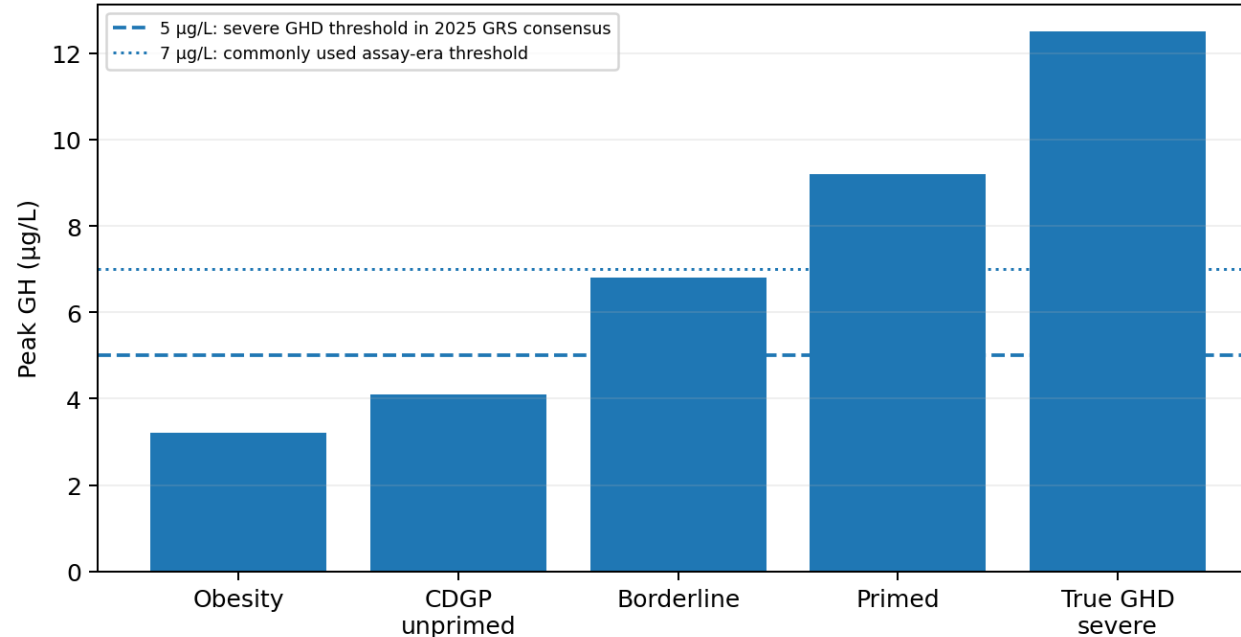
Raises probability	Lowers probability / suggests mimic
Height < -2 to -3 SDS + low velocity	Normal velocity with stable percentile
Downward crossing of height SDS	Short parents / familial pattern
Low IGF-1 + delayed bone age	Normal IGF-1 + normal bone age
Other pituitary hormone deficits	Obesity / hyperphagia
Midline defects, neonatal hypoglycemia, micropenis	Disproportion, Madelung wrist, dysmorphism
Pituitary abnormality on MRI	Systemic disease or untreated hypothyroidism

What each test can—and cannot—tell you

Test	Useful for	Major caveat
IGF-1	Stable screening marker; low value supports GHD	Nutrition, hypothyroidism, liver/renal disease, age
IGFBP-3	Helpful particularly in younger children	Less specific than a structural diagnosis
Bone age	Biologic maturation / context	Not specific for GHD
GH stimulation test	Biochemical support when pre-test probability is appropriate	Nonphysiologic; assay-, BMI-, puberty- and stimulus-dependent
Pituitary MRI	Structural etiology; strongly changes probability	Normal MRI does not exclude isolated/genetic GHD
Genetic testing	Familial/syndromic/discordant cases	Interpret variant in phenotype context

GH stimulation testing: why the cutoff is not the diagnosis

Why peak GH is a probability modifier—not a stand-alone diagnosis



2025 Growth Hormone Research Society pediatric consensus: a stimulated GH peak <5 µg/L is consistent with severe GHD.

Historically, 7 and 10 µg/L thresholds have been widely used; harmonized assays have shifted some practice toward lower thresholds.

Test performance is influenced by BMI, pubertal status/sex steroids, stimulus, assay, and reproducibility.

Use the laboratory's validated assay-specific decision limits—and integrate the entire phenotype.

CASE 1 — Vote before seeing the MRI

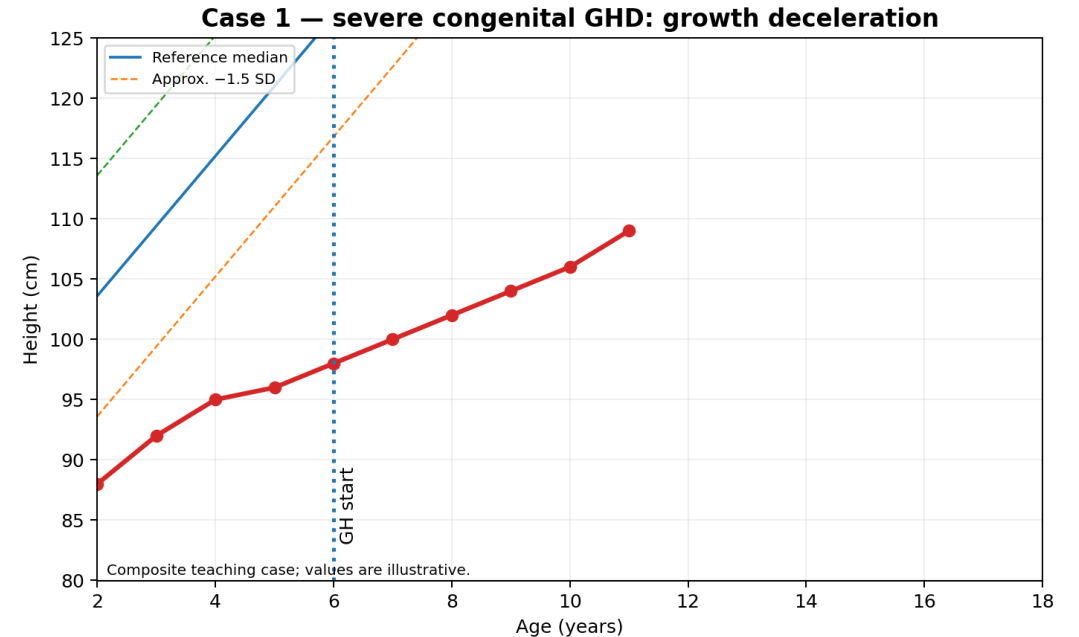
Boy, age 6 years 2 months.

Height SDS -3.6 ; height velocity 3.2 cm/year over the preceding 2 years.

Weight SDS $+0.3$; relatively cherubic facial appearance.

Neonatal history: recurrent hypoglycemia; one episode required IV glucose.

Current: prepubertal; no chronic systemic symptoms.



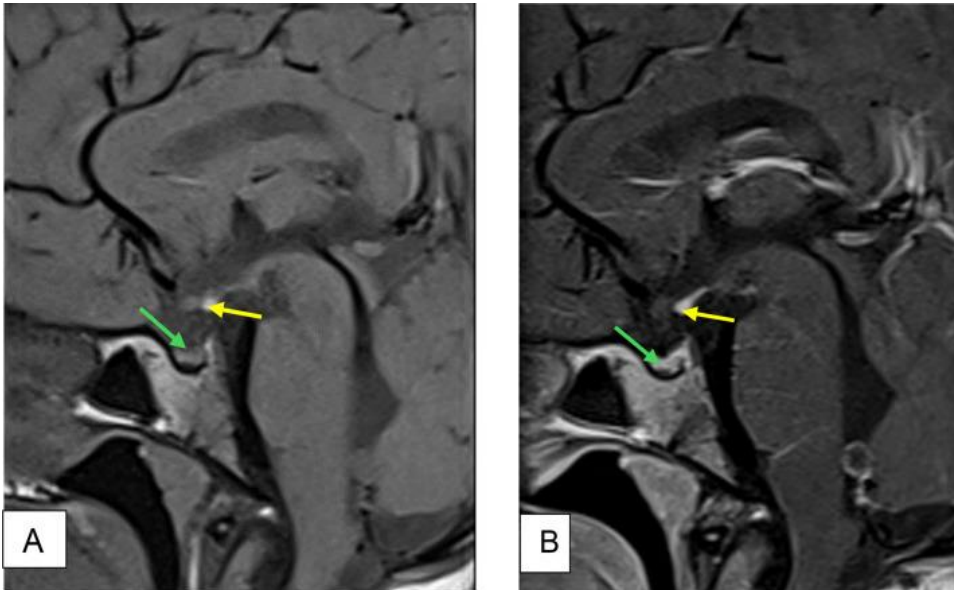
VOTE: GHD / mimic / insufficient data

CASE 1 — The biochemical pattern

Parameter	Result	Interpretation
IGF-1 SDS	−3.1	Strongly supportive
IGFBP-3 SDS	−2.4	Supportive
TSH / free T4	Low FT4 + inappropriately normal TSH	Central hypothyroidism
8 AM cortisol	Low	ACTH deficiency suspected
GH stimulation	Peak 2.1 µg/L	Severely abnormal
Bone age	3 years at CA 6.2 y	Marked delay

This is no longer “isolated short stature.” Think hypothalamic–pituitary disease.

CASE 1 — MRI: the diagnosis becomes anatomical



Classic pituitary stalk interruption pattern:

Absent or markedly thin stalk

Hypoplastic anterior pituitary

Ectopic posterior pituitary bright spot

Structural disease strongly raises the probability that the low GH response is clinically meaningful.

Screen longitudinally for evolving additional pituitary hormone deficiencies.

Diagnosis: congenital GHD as part of hypothalamic–pituitary dysfunction (PSIS phenotype).

CASE 1 — Diagnostic lesson

LOW GH + LOW IGF-1 + SEVERE AUXOLOGY + STRUCTURAL MRI = HIGH-CONFIDENCE GHD

The MRI is not merely confirmatory—it identifies etiology and predicts broader pituitary surveillance needs. A provocative test is not necessary in every high-probability structural case; the diagnostic package matters. Neonatal hypoglycemia, micropenis/cryptorchidism, midline anomalies and central hypothyroidism are high-yield clues.

CASE 2 — The false-positive GHST

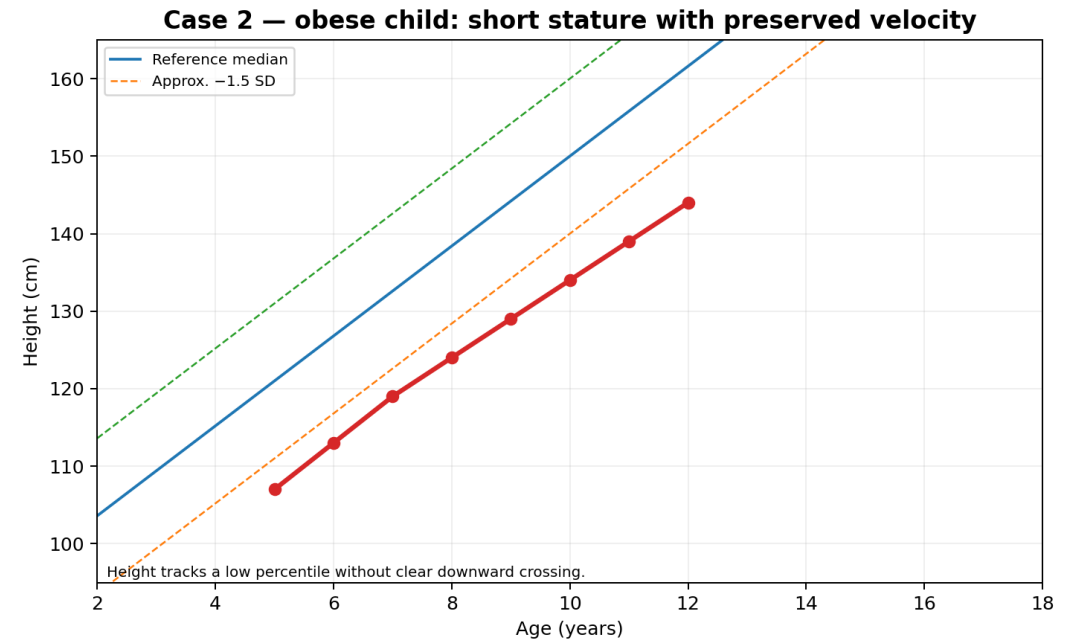
Boy, 11 years 8 months.

Height SDS -2.2 ; height velocity 6.0 cm/year.

BMI SDS $+2.3$; no disproportion or dysmorphic features.

Mid-parental target height: around -1.5 SDS.

IGF-1 SDS: $+0.1$; bone age: approximately concordant with chronological age.



GHST peak: 3.2 $\mu\text{g/L}$. GHD?

CASE 2 — Why obesity can distort the GHST

Obesity is associated with lower spontaneous and stimulated GH secretion.

A low stimulated peak in an obese child with otherwise reassuring auxology and IGF-1 can be a false-positive GHD signal.

The key mismatch is: severe biochemical “GHD” but preserved growth velocity + normal IGF-1 + no supportive MRI phenotype.

Do not let a single provocative test overrule a low clinical pre-test probability.

Reassess auxology, nutrition/metabolic status, puberty, assay and test conditions before labeling GHD.

CASE 2 — Diagnosis: not GHD

FALSE POSITIVE

Most likely: obesity-associated blunting of GH response in a child without convincing auxologic evidence of GHD.

Normal IGF-1 and preserved growth velocity substantially reduce the probability of clinically important GHD.

Management target: treat the child's actual problem and continue longitudinal growth surveillance.

CASE 3 — Peripubertal short stature: unprimed vs primed

Boy, 13 years 1 month; height SDS -2.3.

Growth velocity 5.1 cm/year.

Father reports puberty began at age 15 years.

Testicular volume 3 mL; Tanner G1.

Bone age: 10.8 years.

IGF-1 SDS -0.8.

Unprimed GHST peak = 4.1 µg/L

Would you diagnose GHD now?

What would sex-steroid priming change?

CASE 3 — Priming is a specificity tool, not a magic test

Low sex-steroid exposure in peripuberty can blunt the GH response to pharmacologic stimulation.

Systematic-review evidence shows priming often increases peak GH and reduces the number of children classified as GHD.

Guideline practices vary; priming is particularly relevant when CDGP is plausible and predicted adult height is concerning.

Priming should be interpreted as part of the clinical context—not as a way to “make the test normal.”

Teaching point: avoid diagnosing a lifelong disorder from an unprimed borderline test in a clearly prepubertal adolescent.

CASE 3 — The diagnostic re-frame

Feature	Supports GHD	Supports CDGP
Height SDS	-2.3	-2.3
Growth velocity	Borderline	Compatible
Family history	No	Strong
Bone age	Delayed	Markedly delayed
IGF-1	Mildly low-normal	Compatible
Unprimed GHST	Low	Can be falsely low
Clinical probability	Moderate	High for CDGP

Do not confuse a low pharmacologic response with proof of permanent GH deficiency.

CASE 4 — Short girl with “possible GHD”

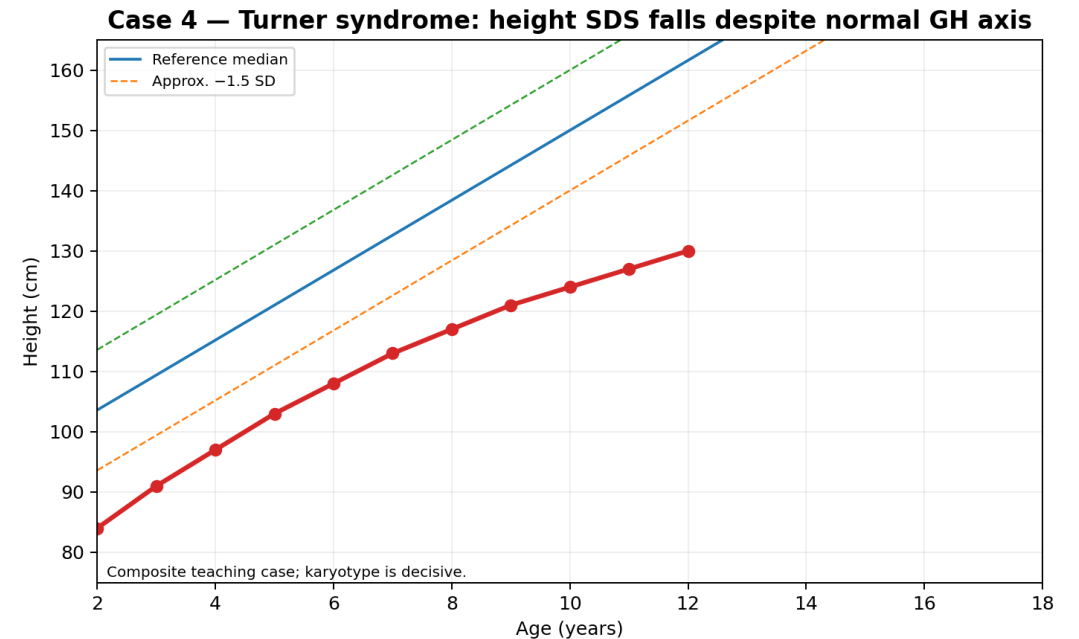
Girl, 10 years 4 months; height SDS -2.8 .

Growth velocity 4.5 cm/year.

Broad chest, widely spaced nipples, mild cubitus valgus.

Webbed neck is subtle; no obvious lymphedema.

IGF-1 SDS -1.1 ; GHST peak 5.8 $\mu\text{g/L}$.



Question: Is this a GH test problem—or a phenotype recognition problem?

CASE 4 — The missing test is a karyotype

Turner syndrome can present primarily as short stature, especially when classic dysmorphism is subtle.

Growth failure may be due to SHOX haploinsufficiency and other Turner-related mechanisms—not pituitary GHD.

A borderline GHST does not establish GHD.

Clues that should trigger karyotyping/chromosomal testing: short stature + characteristic body habitus, cubitus valgus, shield chest, webbed neck, delayed puberty or unexplained growth failure.

Diagnosis: Turner syndrome phenotype until proven otherwise; GH therapy is an indication-specific decision, not proof of GHD.

CASE 5 — The wrist that changes the diagnosis

Girl, 10 years 9 months; height SDS -2.4 .

Short forearms and increased sitting-height/height ratio.

Elbows show subtle cubitus valgus.

GHST peak $8.6 \mu\text{g/L}$; IGF-1 SDS -0.5 .

At first glance: “borderline GHD.”



Radiograph clue: Madelung-type distal radius/ulna deformity.

CASE 5 — Disproportion beats the GH cutoff

SHOX deficiency should be considered when short stature is disproportionate or accompanied by Madelung deformity and related skeletal signs.

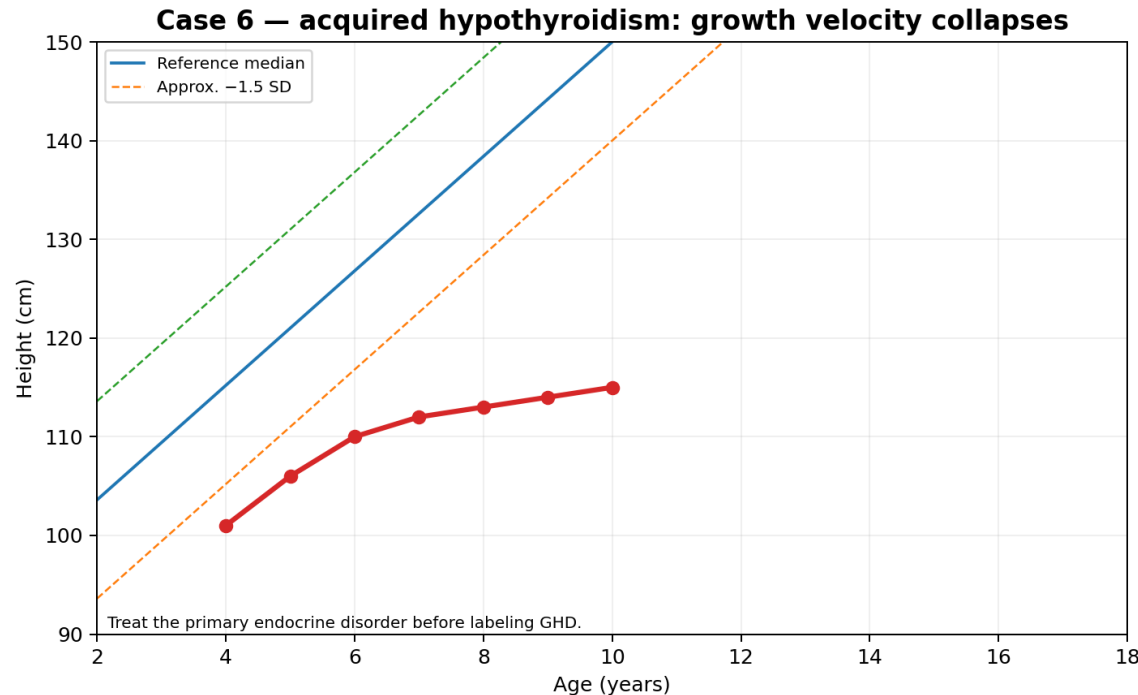
Radiology can be more diagnostically informative than another GH stimulation test.

Genetic testing may identify SHOX deletion/variant and prevent misclassification as idiopathic GHD.

Body proportions are a “bedside genetic test” that should never be skipped in short stature.

If the skeleton looks different, stop and phenotype before repeating the GHST.

CASE 6 — The endocrine mimic hiding in plain sight



Girl, age 8 years 10 months.

Height SDS -2.1; velocity fell to ~1.8 cm/year.

Fatigue, constipation, dry skin; school performance has declined.

IGF-1 SDS -2.2.

GHST peak 5.4 $\mu\text{g/L}$.

What must be corrected before interpreting the GH-IGF-1 axis?

CASE 6 — Treat the thyroid, then reassess growth

Untreated hypothyroidism can suppress linear growth and lower IGF-1.

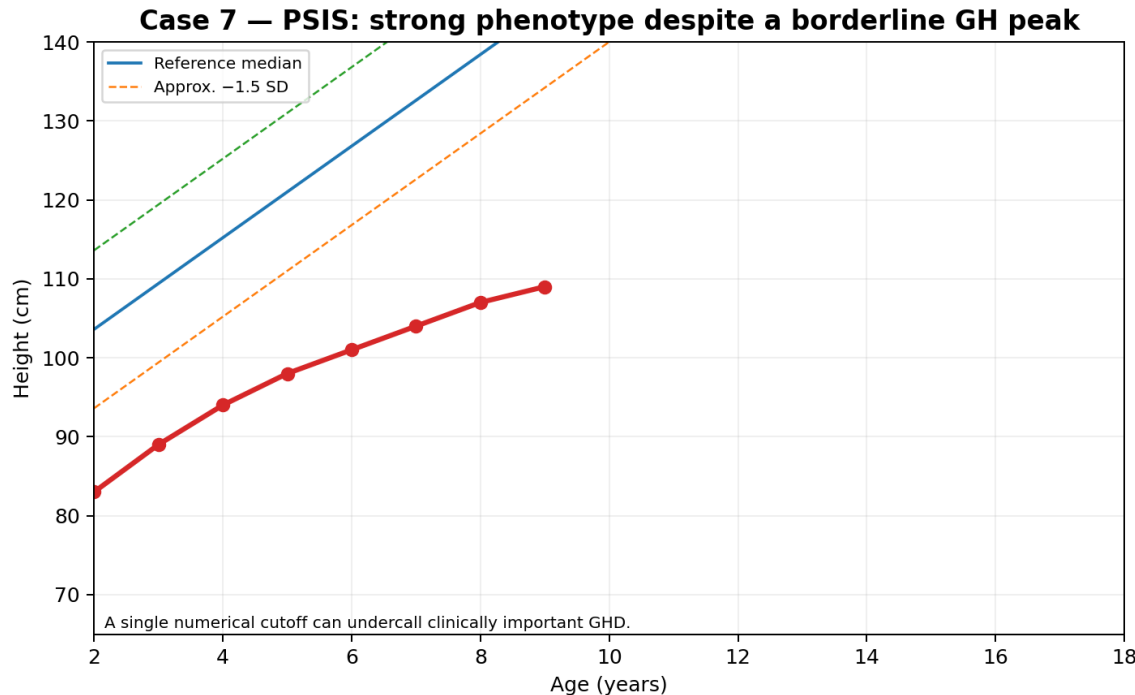
A low IGF-1 is therefore not specific for GHD.

GHST interpretation is also less meaningful when the underlying endocrine milieu is abnormal.

Correct the primary disorder and re-evaluate the growth trajectory before assigning a permanent GHD label.

Diagnostic rule: do not test the GH axis in isolation when another endocrine disorder explains the phenotype.

CASE 7 — When a “normal-ish” GH peak is a false negative



Boy, 8 years 7 months.

Height SDS -3.4; velocity 3.0 cm/year.

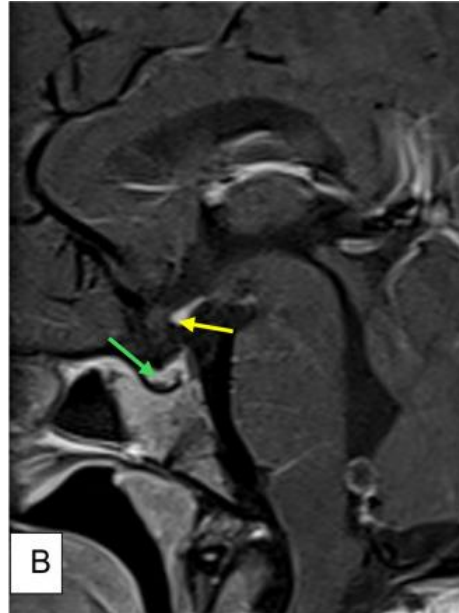
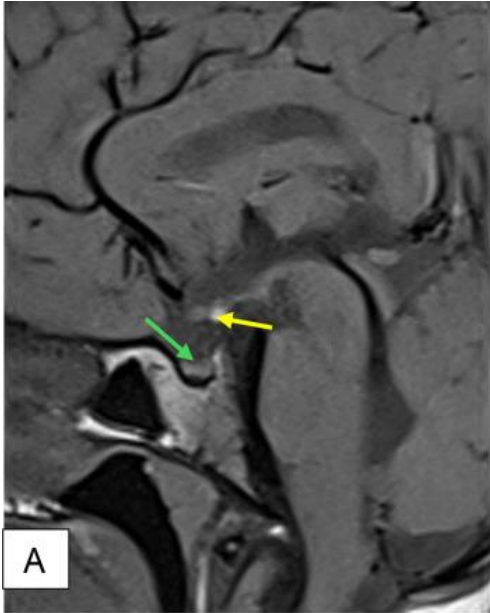
IGF-1 SDS -2.5; bone age delayed 3 years.

GHST peak = 6.2 $\mu\text{g/L}$.

Assay laboratory uses a 5 $\mu\text{g/L}$ severe-GHD threshold.

Would you call the GHST “normal” and stop?

CASE 7 — MRI rescues the diagnosis



Pituitary stalk interruption pattern: absent/thin stalk + hypoplastic anterior pituitary + ectopic posterior pituitary.

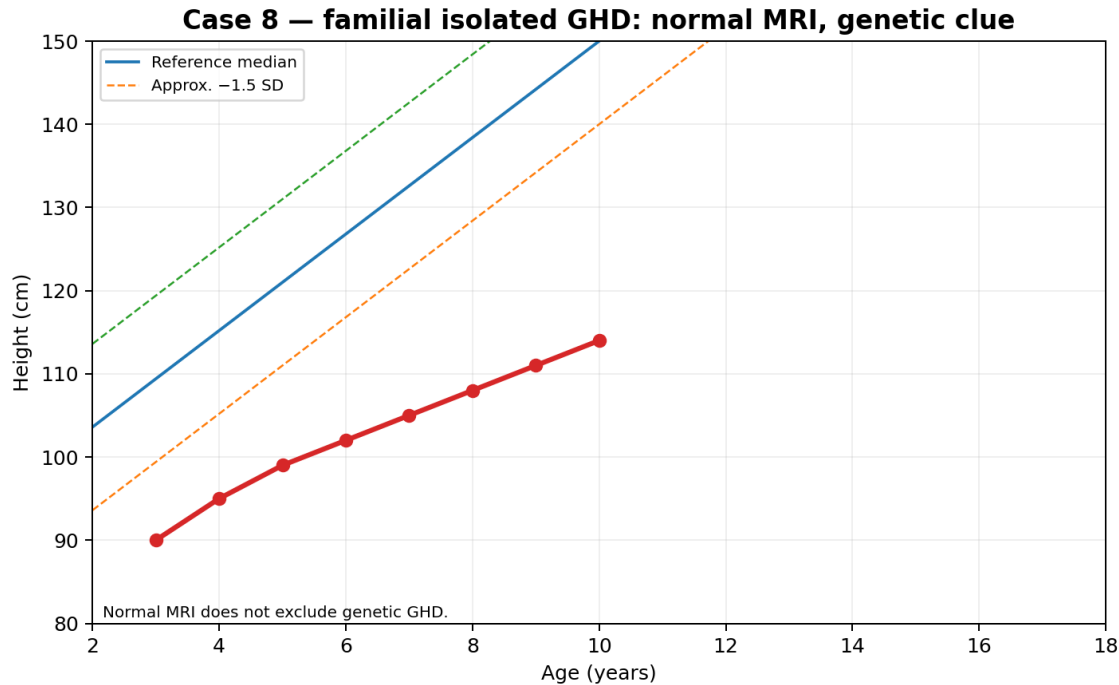
Here, a peak GH of 6.2 $\mu\text{g/L}$ is not enough to erase the high pre-test probability.

The correct interpretation is not “GH sufficient”; it is “borderline biochemical result in a high-probability structural disorder.”

Consider the whole pituitary axis and longitudinal evolution.

False negative = a result that is numerically acceptable but clinically discordant.

CASE 8 — Familial isolated GHD with a normal MRI



Girl, 10 years 2 months; height SDS -3.0 ; velocity 3.4 cm/year.

Mother: short stature and childhood GH treatment.

IGF-1 SDS -2.4 ; IGFBP-3 low.

Two GHSTs: peaks 3.8 and 4.5 $\mu\text{g/L}$.

Pituitary MRI: normal size and stalk anatomy.

Question: does a normal MRI argue against genetic GHD?

CASE 8 — When genetics is the next diagnostic test

Familial isolated GHD with a normal MRI should prompt consideration of genes affecting GH synthesis or hypothalamic signaling.

Examples include GH1 and GHRHR; the molecular phenotype can be more informative than MRI anatomy.

Genetic testing is especially useful when there is recurrence in the family, severe phenotype, unusual response pattern, or discordance between auxology and imaging.

Genetic diagnosis may inform family counseling and expectations for long-term endocrine surveillance.

Normal MRI ≠ normal GH axis.

The diagnostic “triangle”

AUXOLOGY

BIOCHEMISTRY

ETIOLOGY / PHENOTYPE

High confidence comes from convergence—not from any single number.

Discordance should trigger re-evaluation, not reflexive treatment.

Structural MRI and genetics can explain why the GHST is abnormal—or why it is misleading.

Every child deserves a diagnosis that still makes sense when the GH result is removed from the chart.

Two ways we overdiagnose GHD

LOW PRE-TEST PROBABILITY + LOW PEAK

Normal growth velocity or stable percentile

Normal IGF-1 and bone age

Strong familial short stature or CDGP history

Obesity or low BMI affecting GH dynamics

Untreated hypothyroidism / systemic illness

Unrecognized skeletal or chromosomal phenotype

PERIPUBERTAL / OBESITY / SYSTEMIC DISEASE

Two ways we underdiagnose GHD

HIGH PRE-TEST PROBABILITY + BORDERLINE PEAK

Severe height SDS + very low velocity
Low IGF-1 / IGFBP-3 and marked bone-age delay
Multiple pituitary hormone abnormalities
Neonatal hypoglycemia / micropenis / midline clues
Pituitary stalk or anterior pituitary abnormality
Familial or genetic phenotype

NORMAL MRI OR SINGLE “NORMAL” TEST

A practical 7-step diagnostic algorithm

1. Confirm measurement + calculate height velocity

2. Plot family target and assess body proportions

3. Exclude systemic/endocrine/skeletal mimics

4. Measure IGF-1 ± IGFBP-3 in context

5. Decide whether GHST is actually needed

6. Interpret GHST using assay + BMI + puberty + stimulus context

7. Use MRI/genetics when phenotype or GHST is discordant

When should you pause before ordering another GHST?

Height is short but growth velocity is normal.

Height is consistent with familial target.

IGF-1 is normal and bone age is concordant.

The child is obese and the GH peak is unexpectedly low.

The child is peripubertal with strong CDGP features and an unprimed test.

There are disproportion, dysmorphism, wrist abnormalities, or other clues to a genetic/skeletal diagnosis.

Another endocrine or systemic disorder has not yet been corrected.

When should you escalate despite a borderline GH peak?

Height SDS is very low and height velocity is clearly reduced.

IGF-1/IGFBP-3 are repeatedly low without another explanation.

Bone age is substantially delayed.

Other pituitary hormone deficits are present.

Neonatal hypoglycemia, micropenis, midline defects or neurologic history raise suspicion.

MRI shows PSIS, pituitary hypoplasia, tumor, or other hypothalamic–pituitary pathology.

Family history suggests a monogenic disorder.

Five questions to ask before signing the diagnosis

1. Does the growth pattern actually look like GHD?

2. Have I excluded the common mimics?

3. Is the IGF-1 result interpretable in this child?

4. Could BMI, puberty, sex-steroid status, assay or stimulus explain the GHST?

5. Would MRI or genetics change my diagnostic probability?

Take-home messages

1

Auxology creates the pre-test probability; the GHST modifies it.

False-positive GHD is often a problem of context; false-negative GHD is often a problem of rigid thresholds.

2

Phenotyping, MRI and genetics are not “extra tests”—they are diagnostic tools that can resolve discordance.

3

The best GH diagnosis is the one that remains convincing when the peak GH number is hidden.

Selected references & image credits

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