9 year-old Female with Short Stature

Katie O’Sullivan, MD
Fellow, Adult/Pediatric Endocrinology
University of Chicago
ENDORAMA
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History of Present Illness

- 9 and 4/12 year female presenting for evaluation of short stature
- Life-long history of short stature with Ht < 3%
- No recent decline in growth velocity
- Normal weight for height
- Mid-parental height = 57.9 in ~ 4 ft 10in (<3 %)
- “I know I’m short, but it doesn’t bother me.”
Birth/Early Medical History

- Born premature at 26 weeks via NSVD
- Birth Weight: 1 lb 12 oz (= 794 gm = 51%), Birth Length: 11 in (1%)
- Prolonged NICU Course x 5 months:
  - BPD/Respiratory distress, req. resp. support x 6 wks
  - Intraventricular Hemorrhage (IVH) Grade 1
  - Pulmonic stenosis s/p balloon stent
  - Thrombocytopenia req. several plt transfusions
  - GER
  - Retinopathy of Prematurity (ROP)
- Newborn screen: normal
- Karyotype: normal
- Previous evaluation by geneticist: normal
• **Current Medical History:**
  - Pulmonary artery regurgitation
  - Mild Thrombocytopenia
  - Allergic Rhinitis
  - A few hospitalizations for respiratory illness during first 2 years of life
    - No recent recurrent infections

• **Diet/GI History:**
  - Requires G-tube feeds for oral aversion/slow oral feed
    - Pediasure/Carnation Instant Breakfast x 2 servings
  - Regular Diet
  - No food restriction
  - No weight loss, abdominal pain, diarrhea, nausea, vomiting.
**Developmental History:**
- Requires IEP/Special Ed
- Currently in 3rd grade. Reads chapter books.
- Receives OT, PT, ST

**Medications:**
- Allegra PRN
- No frequent steroid use

**Allergies:**
- None

**Surgical History:**
- s/p laser therapy for ROP
- Pulmonary stenosis – balloon stent repair
- G-tube placement
- Tonsillectomy/Adenoidectomy

**Social History:**
- Lives with mother, father, and sister at home.
- No outside caretakers
- Mother – IT coordinator
- Father - accountant
Family History

- No history of growth problems, but “all” of maternal family “short”
- Maternal GM with hypothyroidism. No other endocrine diseases in the family.

- **Mother (Filipino):**
  - 4’7”
  - menarche at 11 yo

- **Father (Caucasian):**
  - 5’6”
  - stopped growing at 18yo, shaved in mid high-school.

- **Sister: 12yo**
  - 4’9”
  - menarche at 11yo
Review of Systems

- General: No weight loss, change in appetite. No sluggishness. No cold intolerance. No fevers. +short.


- Respiratory: Negative for cough or shortness of breath. No choking. No wheezing.

- Cardiovascular: Negative for palpitations or chest pain. No leg swelling. +history of pulmonary stenosis now with regurgitation.

- Gastrointestinal: Negative for abdominal pain, distention, nausea, vomiting, diarrhea, constipation. +Receives G-tube feeds twice/day.

- Genitourinary: Negative for urgency, frequency, hematuria and enuresis.
Review of Systems

- Skin: Negative for acne, rash, dry skin, and birth marks.
- Neurological: Negative for headaches, tremulousness.
- Psychiatric/Behavioral: Negative for behavioral problems. +developmental delay.
Differential Diagnosis
Differential Diagnosis

- **Intrinsic Shortness:**
  - Bone Age = Chronologic Age
  - Normal Growth Rate
    - Genetic- Familial Short Stature
    - Chromosomal/Genetic Syndromes
    - IUGR/SGA
    - Bone development disorders
    - SHOX

- **Delayed Pattern:**
  - Bone Age = Height Age
  - Normal Growth Rate, but shifted
    - Constitutional Growth Delay
    - Undernutrition (low caloric intake, malabsorption incl. Celiac Disease)*
    - Chronic steroids*
    - Chronic Disease*
      - CKD, CHD, CLD, Pulmonary Dx, chronic infections, IBD
    - Negative psychosocial influences

- **Attenuated Growth:**
  - Slow Growth Rate
    - Growth Hormone Deficiency
    - Hypercortisolism
    - Hypothyroidism

* Can be Delayed Pattern or Attenuated Growth Pattern
Differential Diagnosis

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Physical Exam

- Vitals: T 97.6F, P 80, BP 94/60
- Growth Parameters:
  - Height: 107.8 cm (<3%)
  - Weight: 18 kg (0.02%)
  - BMI: 15.5 kg/m² (31%)
Growth Velocity
Physical Exam

- General: She is active, interactive, noticeably short and appears younger than stated age.
- Eyes: PERRL, Uncooperative with fundoscopic exam. No visual field deficits. +hypertelorism. +prominent epicanthal folds. +down-slanting palpebral fissures.
- Hair/Face/Ears: +thick hair, +broad forehead.
- Mouth: +dry mm. +high-arched palate
- Neck: short, webbed neck, low-posterior hairline, mild thyromegaly, no palpable thyroid nodules.
- Cardiovascular: RRR, III/VI systolic murmur greatest at LUSB.
Physical Exam

• Chest: Respiratory effort normal. CTAB. Tanner I breast.
• Axilla: No axillary hair
• Abdomen: Soft, non-tender, non-distended, normal active bs. +G-tube in place in LUQ clean/dry/intact.
• Genitourinary: Tanner 1 genitalia. No pubic hair.
• Musculoskeletal: Normal tone. Normal range of motion.
• Neurological: Normal gait. Patellar reflexes 2+.
• Skin: warm. No rash. No birthmarks.
Work-Up?
Bone Age

- Chron. Age = 9 yrs 4 mos
- Bone Age = 8 yrs 10 mos
- Std Dev = 10.74 mos
Laboratory Studies

- CMP: normal
- ESR: normal
- Anti-Ttg IgA: normal
- Total IgA: normal
- Karyotype: 46, XX
- TSH: 5.71 (0.6-5.5 uU/mL)
- Free T4: 1.9 (0.9-1.67 ng/dL)
- Anti-Tg AB >30, Anti-TPO AB 30
- CBC: Plt 132
- Urinalysis: normal
- IGF-1: 87 (74 – 282 ng/mL)
- IGFBP-3: 3.4 (2-4.8 mg/L)
Genetics Evaluation

- Genetic Testing for Noonan Syndrome:
  - “Heterozygous likely pathologic variant was detected in Exon 3, nucleotide c.181G>A, amino acid p.Asp61Asn (p.D61N).
  - “This likely pathogenic PTPN11 variant is consistent with the Noonan syndrome features observed in this patient. Please note the p.D61N variant has been reported in several patients with a diagnosis of Noonan syndrome. The Aspartic acid (D) residue at position 61 is highly conserved across species and has been shown to be involved in stabilizing the SHP-2 protein encoded by PTPN11... This suggests that the D61N variant is likely pathogenic.”
Clinical Questions

• What are the endocrinopathies associated with Noonan Syndrome?
• What is the etiology of short stature in Noonan Syndrome?
• How effective is growth hormone therapy for patients with Noonan Syndrome?
Noonan Syndrome (NS)

- Autosomal dominant genetic disorder
- 1 in 1000 to 2500 births
- Complete penetrance, variable expressivity
- Phenotype:
  - Facial Abnormalities
  - Short Stature
  - CHD
  - Learning Disabilities
- Gene mutations (61%):
  - Ras/MAPK signal transduction

RAS-MAPK Signaling Pathway

- PTPN11 = most common
- SOS1
- RAF1
- SHOC2
- KRAS
- NRAS
- BRAF

Endocrinopathies of NS

1. Short stature (50-70%)
2. Hypothyroidism?
   - Thyroid antibodies commonly found
   - No more common than general pop’n
3. Pubertal delay and diminished growth spurt
   - Mean onset: 13.5 yr girls, 14 yr boys

Short Stature in Noonan Syndrome

- Birth Length typically normal -> later deceleration
- Delayed Bone Age
- Predicted Adult Height <3% (54.4% of women, 38% men)
- Pathogenesis of Short Stature:
  - GH Deficiency: 37-45%
  - GH neurosecretory dysfunction
  - GH resistance
- PTN11 +: Higher prevalence of short stature
  - Low IGF-1 levels, normal/slightly increased [GH]

Growth Charts: Noonan Syndrome vs. Traditional

Indications for Growth Hormone Therapy

- GH Deficiency
- Idiopathic Short Stature (Ht > 2.25 SDs), 160 cm for men and 150 cm for women
- Short Stature associated with:
  - Turner Syndrome
  - Chronic Kidney Disease
  - Born SGA
  - Prader-Willi Syndrome
  - SHOX gene mutations
  - **Noonan Syndrome** – approved in 2007 by FDA for doses up to 0.066 mg/kg/day
Effectiveness of Growth Hormone in Children with Noonan Syndrome

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients, n (n Female)</th>
<th>Baseline Age, y</th>
<th>Baseline SDS</th>
<th>GH Dose, mg/kg per wk</th>
<th>Duration Therapy, y</th>
<th>Delta Height SDS</th>
<th>Height Gain</th>
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</thead>
<tbody>
<tr>
<td>88</td>
<td>4 (4)</td>
<td>13.5</td>
<td>(−0.6)</td>
<td>0.19 for 1 y, then 0.31</td>
<td>3.5</td>
<td>(0.48)</td>
<td>NA</td>
</tr>
<tr>
<td>84</td>
<td>10 (4)</td>
<td>12</td>
<td>−3.1 (−0.7)</td>
<td>0.30</td>
<td>5.3</td>
<td>3.1 cm</td>
<td>13 cm (boys), 9.8 cm (girls)</td>
</tr>
<tr>
<td>89</td>
<td>18 (11)</td>
<td>8.6 (boys), 7.7 (girls)</td>
<td>−2.9 (−0.3)</td>
<td>0.23 (n = 10), 0.46 (n = 15) for 2 y, then dose titration^b</td>
<td>7.5</td>
<td>1.7</td>
<td>NA</td>
</tr>
<tr>
<td>91</td>
<td>24 (NA)</td>
<td>10.2 (median)</td>
<td>−3.24 (median)</td>
<td>0.24 (median [range: 0.17–0.77])</td>
<td>7.59 (median)</td>
<td>0.61 (0.97)</td>
<td>NA</td>
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<tr>
<td>90</td>
<td>29 (8)</td>
<td>11</td>
<td>−2.8 (0.0)</td>
<td>0.35</td>
<td>6.4 (median)</td>
<td>1.3 (1.3)</td>
<td>9.5 cm (boys), 9.0 cm (girls)</td>
</tr>
<tr>
<td>92</td>
<td>65 (30)</td>
<td>11.6</td>
<td>−3.5</td>
<td>0.33</td>
<td>5.6</td>
<td>1.4</td>
<td>10.9 cm (boys), 9.2 cm (girls)</td>
</tr>
</tbody>
</table>

Results are mean values unless specified otherwise. SDS indicates SD score; NA, not applicable.

^a Height SDS is reported according to population standards and/or (NS standards).

^b Estimated mean: 0.35 mg/kg per week.
Potential Risks of GH Therapy in Noonan Syndrome

- Worsening Cardiomyopathy
- Potential exacerbation of hematologic malignancies
- Other Side Effects:
  - Pseudotumor Cerebri
  - Increased Intraocular Pressure
  - SCFE
  - Worsening scoliosis
  - Theoretic risk of increased glucose intolerance
Back to Our Patient...

- TSH trended up to 13
  - started LT4 50 mcg qd -> TSH improved to 3.69
- Repeat IGF-1 is lower
  - IGF-1: 69 (74-282 ng/mL)
  - IGF-BP3: 3 (2-4.8 mg/L)
- Scheduling GH stimulation test prior to initiation of GH therapy
## Thyroid Function Tests

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<tbody>
<tr>
<td><strong>TSH</strong></td>
<td>5.71</td>
<td>13.17</td>
<td>8.82</td>
<td>3.69</td>
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<tr>
<td>Free T4</td>
<td>1.9</td>
<td>1.8</td>
<td>1.93</td>
<td>1.94</td>
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<tr>
<td>Free T4 by dialysis</td>
<td></td>
<td></td>
<td></td>
<td>2.4</td>
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<tr>
<td>Total T4</td>
<td></td>
<td></td>
<td>10.1</td>
<td>10.6</td>
</tr>
<tr>
<td>Total T3</td>
<td></td>
<td></td>
<td></td>
<td>131</td>
</tr>
<tr>
<td>LT4 dose</td>
<td></td>
<td></td>
<td>50 mcg</td>
<td>50 mcg</td>
</tr>
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</table>
Summary

• Short stature is a common presentation to pediatric endocrinology clinic
• Differential diagnosis of short stature is broad, but can be categorized by growth pattern
• Noonan Syndrome is one of the more common genetic syndromes associated with short stature
• Growth Hormone therapy for short stature in Noonan Syndrome is approved by the FDA, but still controversial and requires close monitoring
Works Cited

Extra Slides