10-year-old female with attenuated growth

Endorama
March 29, 2012
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CC and HPI

- 10-4/12-year old female with 22q deletion syndrome presenting to her Geneticist for follow-up
- Previously seen 2 years earlier with no concerns (height: 113.4 cm, HA= 5-10/12 weight:18.6kg)
- Interval history
  - Echo to follow CHD showed incidental thyroid nodule
  - Dedicated thyroid imaging (MRI) in June 2011 reportedly non-concerning
  - "Kidney issues" based on laboratory evaluation w/o specific f/u recommended
- Previous growth below but parallel to the 3rd percentile
- Physical examination revealed no appreciable linear growth from 8/2009 to 9/2011
  - C/o GH def

PMH

- Born full-term after uncomplicated pregnancy and delivery
  - BW: 7 lb, BL:19 in
- Evaluation for murmur on DOL#2 revealed TOF
- Further evaluation revealed 22q deletion syndrome
- S/p repair of TOF at 5 months old
- Poor dentition s/p complete oral rehabilitation 3/31/2004
- Laryngeal web, villopharyngeal incompetence s/p pharyngeal flap 5/05/2004
- Pneumonia 1/2011 and 5/2011
- Medications: MVI w/ iron NKDA

Review of Systems

- Glasses
- Increased fatigue, intermittent neck swelling, dry skin since summer
- Chronic cold toes and fingers but no cold intolerance
- Chronic thin hair
- Denied constipation
- Denied deterioration of school performance

Family History

- Mother- early puberty w/ menarche at 9 years, asthma
- Father- delayed puberty, BPH, migraine headaches; s/p cholecystectomy, appendectomy, multiple chalazion excisions
- Sisters, 13 and 17 years, healthy, NL puberty, menarche at 12 in both; Brother, 9 years, tall and premature pubarche at 7 years, w/o evaluation
- M cousin- unspecified thyroid abnormality
- Pat GF- prostate cancer
- PGM- hyperthyroidism

Social History

- LAHW parents, 2 older sisters, younger brother
- 5th grade, no educational problems

Physical Examination

- Wt: 23.4 kg (<3rd %) Ht: 115.7 cm (nearly -4 SD; HA: 6-1/12 years) BMI: 17.5 kg/m^2 (58th %)
- T- 98.7 F P-88 BP-97/68
- Skin- yellow-orange hue, dry and coarse
- HEENT: flat face, flat nose; webbed-appearance to the neck; w/o goiter
- EXT: Tapered fingers
- CV: RRR. 3/6 blowing holosystolic murmur
- Pubertal exam: Pubic and axillary: Tanner Stage I; adiposity to chest and question of small breast buds

Differential diagnosis for growth attenuation?

Laboratory analysis?

Differential diagnosis for growth attenuation

Endocrine causes

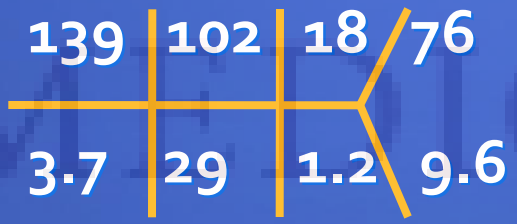
- Hypothyroidism
- Growth hormone deficiency
- Cortisol excess
- Vitamin D deficiency

Non-endocrine causes

- Chronic renal failure
- Metabolic acidosis
- Cancer
- Severe systemic illness

Laboratory data

- Sept 30, 2011- Genetics visit
- TSH- >1000 mcU/mL
- FT4- <0.10 ng/dL T4- <0.5 mcg/dL



Assessment and plan?

Assessment and plan

- Severe hypothyroidism
- Synthroid- 112 mcg (~5 mcg/kg)

Laboratory data

Initial TFTs

- TSH- >1000 mcU/mL
- FT4- <0.10 ng/dL

139	102	18	76
3.7	29	1.2	9.6

8.1	5.1
0.3	0.1
92	34
58	

Repeat TFTs (s/p 2 doses)

- TSH- 830.5 mcU/mL
- FT4- 0.65 ng/dL (0.9-1.7)
- TPO Ab- 80; TG Ab- negative

- CK- 1880 U/L (9-185)
- Urine myoglobin- negative
- Chol- 354; LDL- 272; HDL- 69; TG- 63

Assessment and plan

- Overly rapid correction of hypothyroidism; other lab abnormalities attributable to severe hypothyroidism
- Hold Synthroid x 2 days, then decrease to 50 mcg daily
- Repeat labs in 2 weeks

Laboratory data

- TSH 13.52 mcIU/mL (0.31-4.82); FT4- 1.11 ng/dL (0.59-1.61)
- NL CMP
- Chol- 199 mg/dL (0-200), LDL- 145 (<200), HDL- 35 (40-60), TG- 93 (0-150)
- CK- 282 U/L (26-192)

1-month follow-up visit

- Improved energy
  - More defiant, difficulty concentrating; energetic and loud
- Difficulty w/ sleep initiation
- Declining grades but well-behaved at school
- Denied palpitations, intermittent loose stools w/ BM qod-qd; stable appetite; thinner appearance; thicker hair and growing quickly; less dry skin; warm hands
- Chest hurting and breast buds noted 2 days before clinic visit. Denied BO, acne, sexual hair

Physical Examination at F/U

- Wt: 21.4 kg (-2 kg) Ht: 116.1 cm BMI: 15.9 (29th)
- 96.2 P 95 BP 95/56
- Improvement of yellow-orange hue
- Decreased webbed-appearance to the neck
- 1 cm breast buds B/L, Tanner I AH, PH

Lab Data

- TSH- 1.40 mIU/ml (0.5-4.30)
- T4- 9.5 mcg/dL (4.5-12)
- FT4-1.5 ng/dL (0.9-1.4)
- BMP, lipids, CK WNL

- LH 1.38 mIU/mL (TI </= 0.15, TII </=2.91)
- FSH 1.35 mIU/mL (early pubertal range 0.4-6.50)
- Estradiol- 14 pg/mL (<16)
- DHEA-SO_4 <15mcg/dL

- BA: 6.29 years
- PH of 61.4 (MPH: 64.5)

Interpretation

- Essentially euthyroid by labs
- Inappropriate puberty for skeletal maturation

Questions

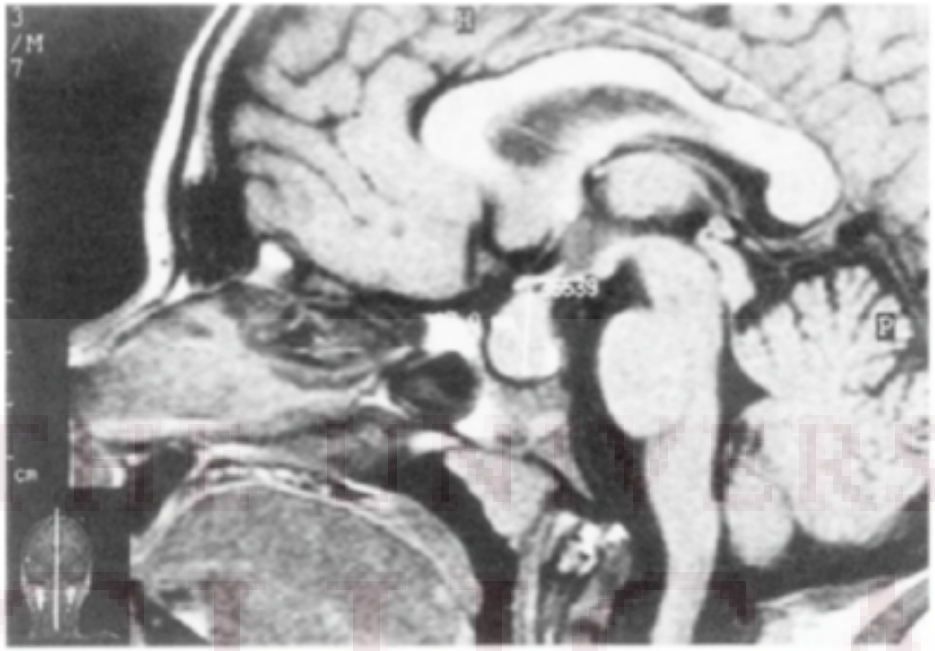
- Is her relative sexual precocity related to her hypothyroidism?
- How should we manage her puberty and growth?

22q.11.2 deletion

- Variable phenotypes even within families
  - DiGeorge, velo-cardio-facial syndrome, conotruncal anomaly face syndrome, Opitz GBBB syndrome
- Endocrine aspects
  - Hypoparathyrodism
  - Growth disorders
    - Growth hormone deficiency
  - Hypothyroidism
  - Hyperthyroidism

Hypothyroidism and puberty

- Prolonged, severe hypothyroidism results in linear arrest and marked delay in skeletal maturation
- Generally, puberty is delayed
- Van Wyk Grumbach Syndrome can occur
  - Sexual precocity in the setting of severe hypothyroidism
  - Thought to be due to TRH increasing FSH
    - FSH is high
    - Prolactin is high
    - LH is low or normal
    - Estradiol is pubertal
  - Features can include pituitary enlargement, ovarian cysts
  - Resolves with LT_4 treatment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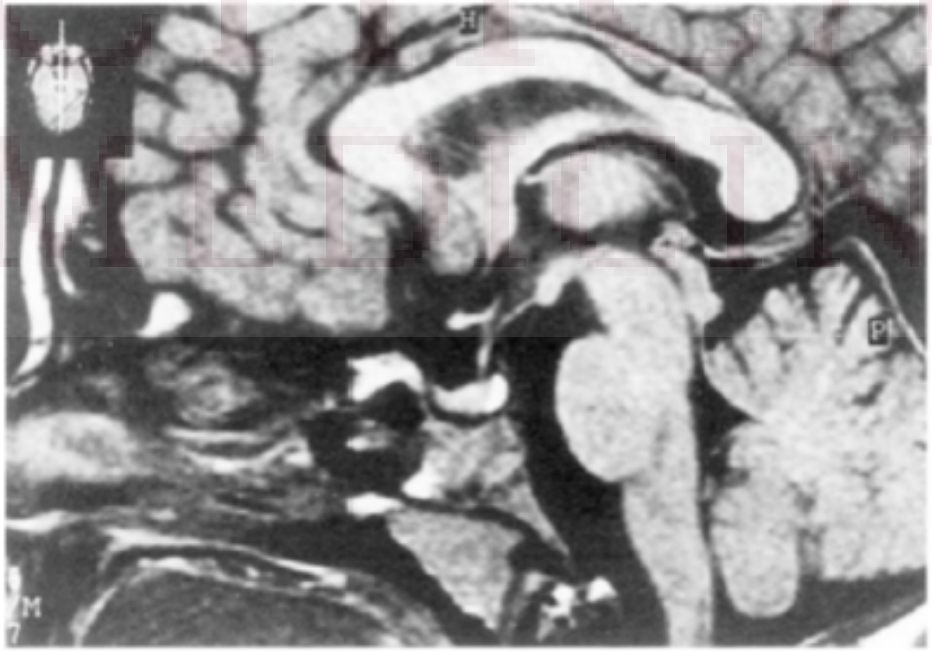
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Hypothyroidism and growth

- Skeletal maturation delay
  - Delayed ossification and mineralization
  - Downregulation of GH, IGF-1
- Treatment results in catch-up growth with the rate of skeletal maturation exceeding gains in height
- Central puberty onset often occurs shortly after treatment and exacerbates short stature

Hypothyroidism and growth

- Conflicting studies on efficacy of treatment for height augmentation
  - Nebesio, Wise, et al. J Pediatr Endocr Met. 2011
    - Retrospective review of 21 children w/ profound hypothyroidism (6 treated with growth-promoting therapies)
      - Time to achieve euthyroid state did not impact rate of skeletal maturation
      - Use of growth-promoting therapies did not effect height outcome
  - Teng et al. J Pediatr Endocr Met
    - Retrospective review- followed 17 tx'd w/ LT_4 and 6 tx'd w/ LT_4 and GnRHa to adult height
    - GnRHa tx'd patients were older, shorter, and more advanced in puberty and bone age
    - Similar improvement in height Z scores, similar height deficits, similar adult heights

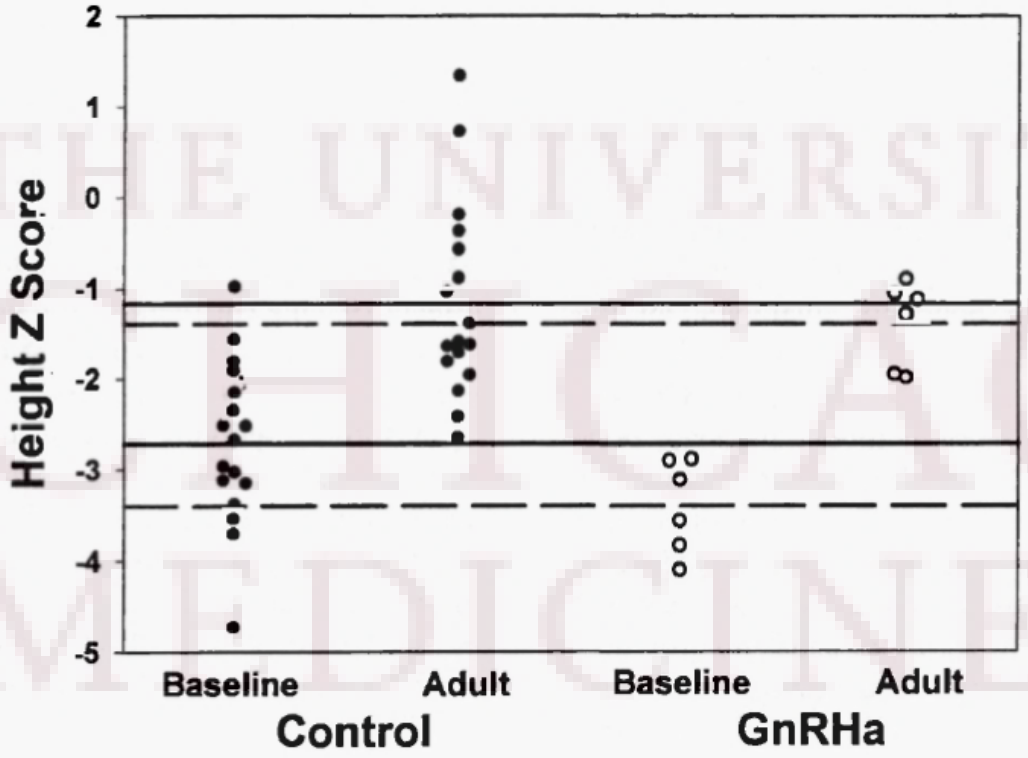


Fig. 1: **Adult height cohort.** Solid circles denote control patients and the continuous lines represent their mean baseline and adult height Z scores. Open circles denote GnRHa patients and the dashed lines represent their mean baseline and adult height Z scores.

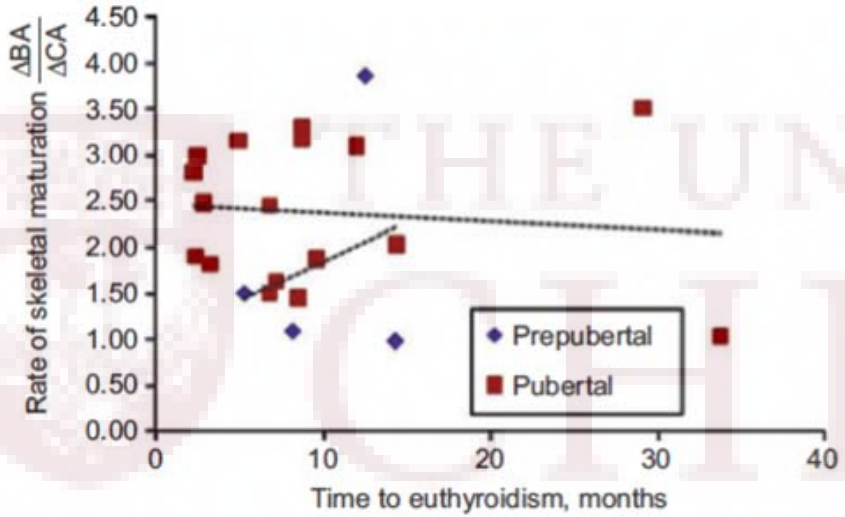


Figure 1 Relationship between the time to euthyroidism and rate of skeletal maturation in prepubertal (n=4, r=0.26, p=0.74) and pubertal (n=17, r=–0.11, p=0.69) children with severe acquired hypothyroidism.

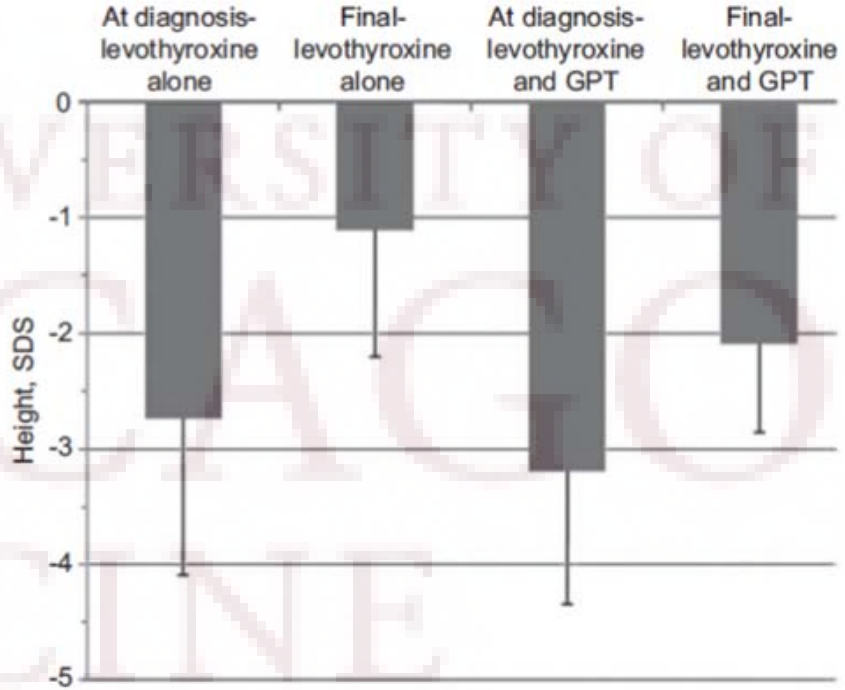
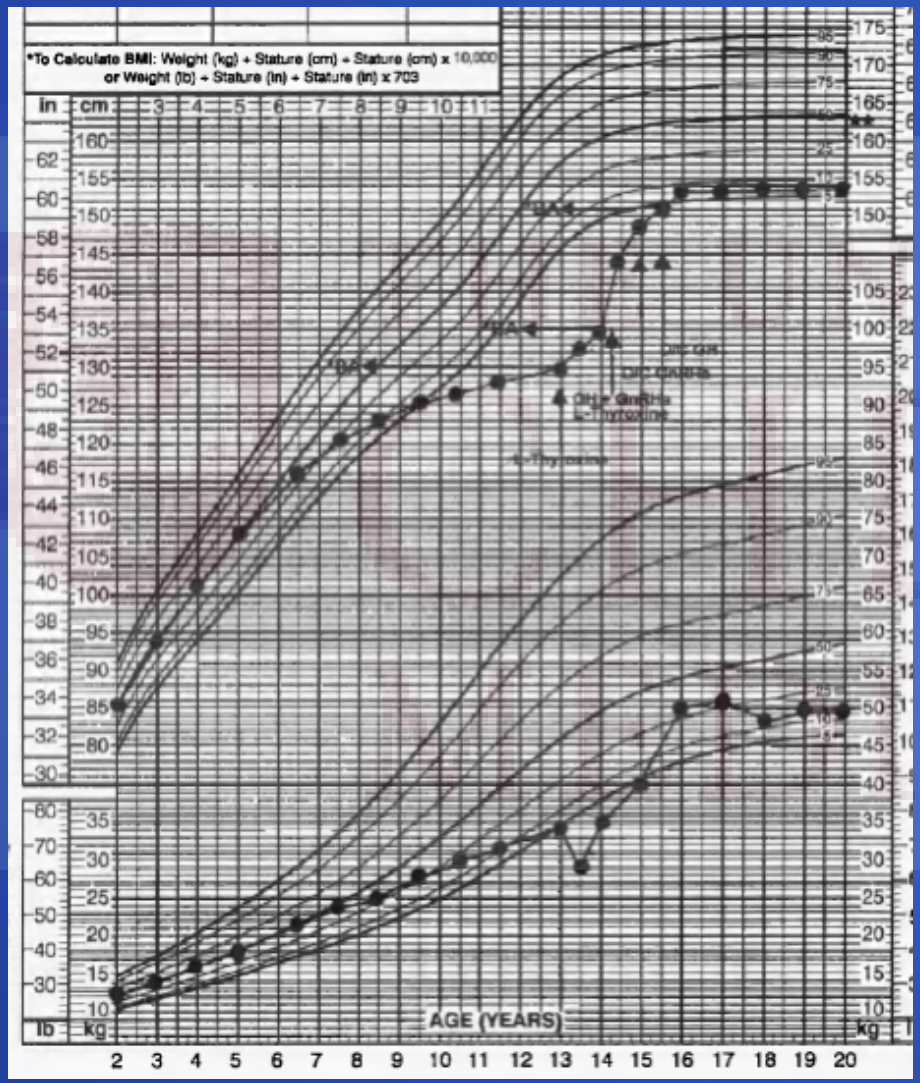


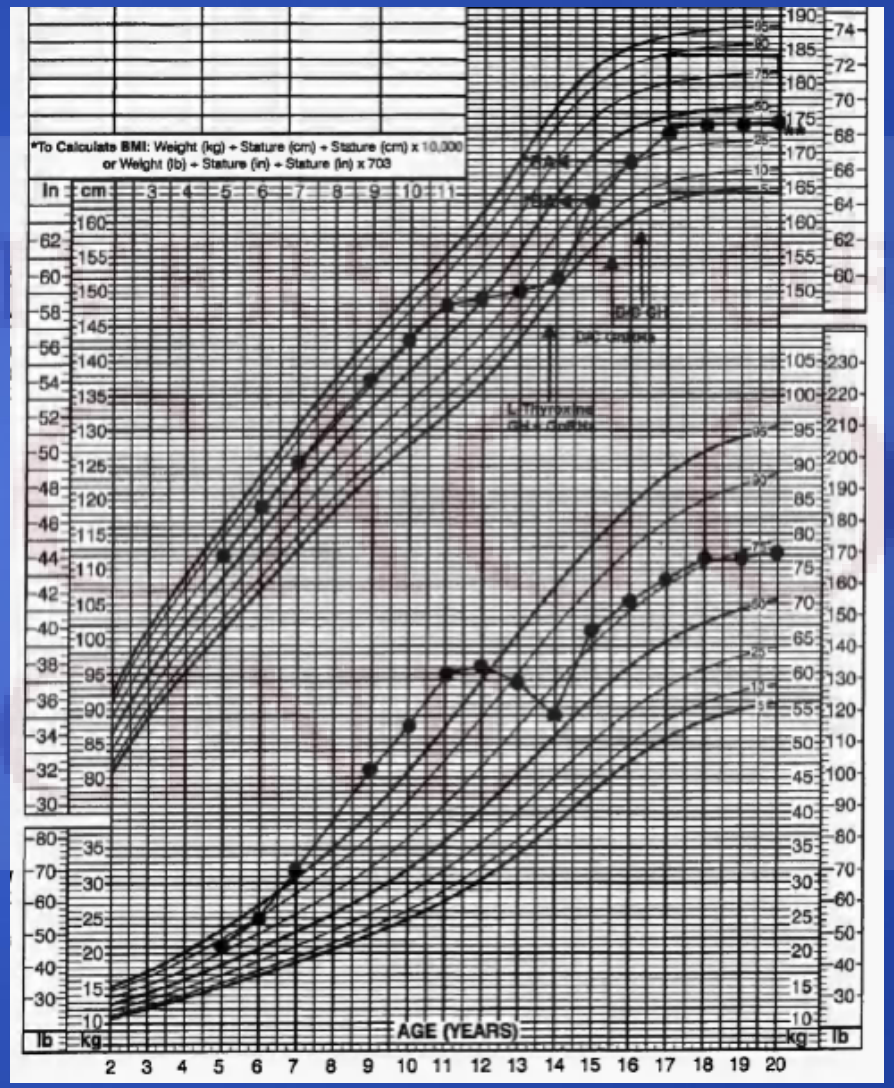
TABLE 1

Comparison of the two patients: baseline characteristics and outcome

	Patient 1	Patient 2
Baseline characteristics		
Chronological age (yr)	13	$13\text{-}^{11}/_{12}$
Height age (yr)	$8\text{-}^{1}/_{2}$	12
Height z-score	-4.0	-1.32
Growth rate (cm/yr)	1.0	1.0
PAH (cm)	144	164
MTH (cm)	163	174
Outcome		
FH (cm)	155	174
Height z-score	-1.4	-0.4
Height gain (cm)	11	10

PAH = predicted adult height; MTH = mid-parental target height; FH = final height.


*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703
in
cm
lb
kg
AGE (YEARS)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in
cm
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AGE (YEARS)

Our patient

- Euthyroid, but continued difficulties with behavior and concentration
- Pubertal progression
- Bone age advancement of 8 months over 4 month interval
- Following growth and puberty closely

Summary

- 22q deletion syndrome has a variable phenotype that can include hypothyroidism
- Severe hypothyroidism in children presents as attenuated growth with or without other features
- Treatment of severe hypothyroidism often exacerbates short stature due to rapid skeletal maturation
  - Efficacy of growth-promoting agents is questionable
- 22q deletion can also cause growth disorders, which may exacerbate final height in our patient

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