DIAGNOSE IT

Case Reports in Pediatric Endocrinology September 2018

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT DIABETES & ENDOCRINOLOGY 2018-19

UPMC CHILDREN'S HOSPITAL OF PITTSBURGH

Case Presentation

A 4-year-old female with complex past medical history was referred to the endocrine clinic for evaluation of short stature and delayed bone age. Her symptoms upon referral consisted of cold intolerance, constipation, and chronic fatigue.

She was born via Caesarean section with APGAR scores of 6 and 9. Birth weight was 3 kg with a length of 48.26 cm (19 inches). She stayed in the neonatal intensive care unit for hypoglycemia with no incidence of jaundice.

Past medical history included:

- Pierre Robin Sequence — s/p cleft palate surgery with revisions
- Sagittal craniosynostosis
- Tethered cord s/p surgery with revision
- Hemangioma of the right upper eyelid that did not affect vision
- Sensorineural hearing loss with hearing aids
- Cerebellar hypoplasia

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DIAGNOSE IT is an ongoing series of case reports presented by Nursen Gurtunca, MD, and Pushpa A. Viswanathan, MD. This publication is designed to educate physicians and allied health care professionals through a discussion of some of the most interesting and complex cases seen within the Division of Endocrinology, Diabetes, and Metabolism at UPMC Children's Hospital of Pittsburgh.

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Family Medical History

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Father's height is 180 cm (5'11"), and mother's height is 175 cm (5'10"). The patient has a healthy younger sister. There is no family history of short stature, genetic disorders, or thyroid disease.

The patient's motor developmental history revealed that she sat independently at 6 months and walked at 18 months. Her speech was delayed with first spoken words at 2½ years. She was toilet trained for micturition at 4 years of age.

Physical Examination

Physical examination revealed the following findings:

- Height 93.8 cm (2nd percentile) (z score= -2.08); arm span 91.4 cm; height velocity 4.5 cm/year
- Weight 18.7 kg (80th percentile)
- BMI 22.5 (99th percentile) (z-score= +2.6); OFC 75th percentile
- Vitals: normal for age
- HEENT: dysmorphic features (retromicrognathia, depressed nasal bridge)
- Neurological: Ataxia
- GU: Prepubertal

The rest of the exam was unremarkable.

Initial Laboratory Values

- TSH mildly elevated at 6.260 uIU/mL (0.700 - 5.700)
- FT4 elevated at 3.60 ng/dL (0.8 - 1.80)
- IGF-1 is normal for age: 83 (IGF-1 Z score female n - 0.7)
- Prolactin is normal at 20 ng/mL
- Bone age markedly delayed at 1 year and 2 months for chronological age of 4 years and 2 months

Next Steps in Diagnosing This Patient

What are the next steps in diagnosing this patient?

1. Total T4, T3 levels along with thyroid antibodies
2. Thyroid uptake and scan
3. Thyroid ultrasound
4. All of the above
5. None of the above

What is your diagnosis?

1. Subclinical hypothyroidism
2. Non-thyroidal illness
3. Assay interference
4. Autoimmune thyroid disease
5. Congenital hypothyroidism/Defect in thyroxine synthesis
6. Defect in thyroxine metabolism/action

Additional Studies

Date	TSH (uIU/mL) (Ref Range [RR] 0.7-5.7)	FT4 (ng/dL) (RR 0.89-1.78)	Total T4 (ug/dL) (RR 6.4-13.3)	Total T3 (ng/dL) (RR 119-218)	Thyroid Antibodies
08/29/2013	6.26	3.6	—	—	—
12/11/13	6.6	3.47	27.8	110	Positive TPO Ab = 70; Tg Ab < 20; TSH Receptor Ab 8.4% (<16%)

TPO = thyroid peroxidase; **Tg** = thyroglobulin; **Ab** = antibodies

Differential Diagnosis

Her thyroid hormone tests show elevated total and Free T4, slightly above upper normal range TSH, and low T3.

This constellation of lab tests is against subclinical hypothyroidism where Free T4 and T4 are usually low-normal, and never elevated, while TSH is elevated. Non-thyroidal illness is also unlikely where TSH, Free T4, and T4 are also low along with total T3. Assay interference is unlikely due to significant changes with multiple hormone values. Although thyroid peroxidase antibody titer is positive, her thyroid hormone profile is not consistent with autoimmune thyroid disease (associated, incidental Hashimoto's thyroiditis is possible). Congenital hypothyroidism/defects in thyroxine synthesis is unlikely as total T4 and Free T4 are high.

High T4 and Free T4 with low T3 suggest problems at the level of thyroxine metabolism, specifically in the conversion of T4 to the active hormone T3. This conversion is mediated by Iodothyronine deiodinases, selenocysteine-dependent membrane proteins which catalyze release of iodine directly from the thyronine hormones.

Due to involvement of multiple systems in addition to clinical features of hypothyroidism, she underwent whole exome sequencing. She was identified to have the following mutations: compound heterozygous for the R770X mutation and the R540W variant-likely pathogenic mutation — in the SECISBP2 gene. This compound heterozygosity causes a selenoprotein deficiency, which impairs the iodothyronine deiodinase responsible for T4 to T3 conversion. The abnormal thyroid hormone metabolism of this condition has been associated with growth retardation and delayed bone maturation. Hearing loss has also been reported.

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Differential Diagnosis

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Interestingly, she also was found to have a variant of unknown significance (M34T variant) in the GJB2 gene (associated with hearing loss). Whether this may have contributed to her hearing deficit is unclear.

Given the patient's hypothyroidism symptoms and delayed bone age, we started Liothyronine 2.5 ug BID, with subsequent dose increase and titration to 7.5 ug in the morning and 5 ug in the evening, with the aim of normalizing T3 levels.

Post-treatment Laboratory Values

Date	TSH uIU/mL Ref Range (RR) (0.700-5.700)	T4 ug/dL (RR 6.4-13.3)	T4 Free x ng/dL (RR 0.89-1.78)	T3 Free, pg/mL (RR 3.3-4.8)	Total T3 ng/dL (RR 110-195)
03/14/16	2.358	15.7	1.26	—	210
10/17/16	3.780	16.3	1.85	5.0	155
05/10/17	0.928	9.7	1.06	5.3	166
02/26/2018	1.53	11.5	1.35	5.3	179

Follow-up

After treatment with T3 initiation:

- Symptoms including chronic fatigue, cold intolerance, and constipation have improved. An improvement in growth velocity has been documented as well.
- TSH normalized
- T4 decreased
- FT4 decreased
- T3 normalized