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Unusual Thyroid Constellation in Down Syndrome: Congenital Hypothyroidism, Graves' Disease, and Hemiagenesis in the Same Child

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Abstract

We report a girl with Down syndrome who was diagnosed with congenital hypothyroidism in the newborn period due to left thyroid hemiagenesis. Unexpectedly, her hypothyroidism resolved at the age of 3 years. After being off thyroid hormone replacement for 7 years and having normal thyroid function, she developed Graves' disease. Although Graves' disease in association with thyroid hemiagenesis has previously been reported, this represents the youngest patient in whom this scenario has been described. Issues pertaining to thyroid hemiagenesis, autoimmune hyperthyroidism, and thyroid disease in children with Down's syndrome are discussed.

Keywords

thyroid hemiagenesis; congenital hypothyroidism; Graves' disease; Down syndrome

INTRODUCTION

Many different forms of thyroid disease are known to occur at increased rates in children with Down syndrome as compared with the general population. Infants with Down syndrome have an increased incidence of congenital hypothyroidism¹, whereas children with Down syndrome have a propensity to develop both hypothyroidism and hyperthyroidism due to autoimmune thyroid disease².

Here, we report an infant with Down syndrome who was diagnosed with congenital hypothyroidism due to thyroid hemiagenesis. She was able to discontinue thyroid hormone replacement at the age of 3 years, and then remained euthyroid for several years. She later developed autoimmune hyperthyroidism isolated to the right lobe of her thyroid. To our knowledge, this is the first report of a child with transient congenital hypothyroidism due to thyroid hemiagenesis who subsequently presented with Graves' disease.

PATIENT REPORT

The patient was diagnosed prenatally with Down syndrome (47,XX,+21). Complications at birth included being born premature at 36 weeks gestation and duodenal atresia, which was repaired on the first day of life. Her initial newborn screen done after 48 hours of life was normal. Due to her prematurity, a repeat newborn screen was done at 17 days of life which revealed increased thyroid stimulating hormone (TSH) of >40 $\mu\text{U/ml}$. Serum studies were then drawn which revealed elevated TSH of 66.2 $\mu\text{U/ml}$, total T4 of 7.56 $\mu\text{g/dl}$ (97.31 nmol/l), and free T4 of 1.3 ng/dl (16.7 pmol/l). Thyroid hormone replacement was started at 3 weeks of life. A technetium scan revealed left hemiagenesis of the thyroid gland.

Starting at 12 months of life, she began to have a persistently low normal to suppressed TSH (<0.1 to 1.0 $\mu\text{U/ml}$) and an intermittently elevated free T4 (2.8 to 4.4 ng/dl ; 36.0 to 56.6 pmol/l). Thyroid hormone supplementation was gradually decreased and was eventually stopped at 3.2 years. Over the next approximately 7 years, she remained off levothyroxine and had normal, annual thyroid function studies.

At the age of 10 years, she developed signs and symptoms of hyperthyroidism, including diarrhea, inattention, and hyperactivity. Thyroid function studies now revealed that she was hyperthyroid with low TSH of 0.081 $\mu\text{U/ml}$, elevated total T4 of 13.0 $\mu\text{g/dl}$ (167.34 nmol/l), elevated free T4 of 4.0 ng/dl (51.5 pmol/l), and positive autoimmune markers suggestive of Graves' disease with a TSH- receptor stimulating antibody (TRAb) of 27% (negative is 16%). Technetium scan (Fig. 1) and thyroid ultrasound (Fig. 2) supported the diagnosis of Graves' disease confined to the right lobe and isthmus of her thyroid. After discussing treatment options with the family, radioactive iodine was administered at 19.52 mCi , and she became permanently hypothyroid 11 weeks later.

DISCUSSION

The etiology of thyroid hemiagenesis is unknown, but there are several thyroid transcription factors and developmental genes that may be involved³. Most cases of thyroid dysgenesis, including hemiagenesis, are thought to occur sporadically⁴. However, there may be some genetic component involved since thyroid hemiagenesis has been discovered in sisters⁵, in monozygotic twins where one twin had an ectopic gland and the other twin had hemiagenesis⁶, as well as in first degree relatives of children with thyroid dysgenesis⁷. The prevalence of thyroid hemiagenesis in normal children is estimated to be between 1 in 500⁸ and 1 in 2,000 children⁹. Although it occurs with a nearly equal predilection for males and females⁹, thyroid hemiagenesis is more commonly found on the left side¹⁰, as is the case with our patient.

The occurrence of Graves' disease in association with thyroid hemiagenesis is rare, and all published cases to date^{11–31} are listed in Table 1. To our knowledge, this is the youngest child ever reported with this unusual combination. In addition, none of the previous reports have occurred in an individual who was initially diagnosed with congenital hypothyroidism. Two cases have occurred in females who developed Graves' disease after initially being diagnosed with Hashimoto's thyroiditis and primary hypothyroidism^{15, 19}. Including the patient reported here, the majority of these cases have occurred in females (83%).

Thyroid hemiagenesis may not be detected on the newborn screen since one lobe of the thyroid is normal and can compensate for the absent lobe. When it does present at birth, however, it is typically considered to be a permanent form of congenital hypothyroidism^{32, 33}. It is unclear why the congenital hypothyroidism in our patient resolved. Since she had normal thyroid function tests for 7 years before the clinical and biochemical detection of Graves' disease, it is unlikely that our patient had subclinical hyperthyroidism resulting in the resolution of her congenital hypothyroidism.

It is also of interest that our patient has trisomy 21 since children with Down syndrome have an increased prevalence of thyroid disorders, including congenital hypothyroidism, compensated hypothyroidism, autoimmune hypothyroidism, and autoimmune hyperthyroidism². Infants with Down syndrome are 28 times more likely to have congenital hypothyroidism¹. After infancy, up to 25% of children with Down syndrome may have compensated hypothyroidism³⁴, in which TSH is elevated but free and total T4 levels are normal and thyroid antibodies are negative. In most cases, this condition resolves spontaneously without any significant compromise in growth or intellectual development^{35, 36}. It is unclear why some children with Down syndrome develop these transient biochemical abnormalities. However, researchers have shown that many children with Down syndrome have an exaggerated TSH response to thyrotropin-releasing hormone (TRH) stimulation, suggesting immaturity or dysfunction of the hypo-thalamic-pituitary-thyroid axis^{37, 38}. Longitudinal studies have revealed that this exaggerated TSH response to TRH resolves after the third year of life³⁷. In all children with Down syndrome, the prevalence of autoimmune hypothyroidism is more common than autoimmune hyperthyroidism^{39, 40}. Markers of autoimmune thyroid disease are often not detected until after the age of 8 years⁴⁰, and the occurrence of autoimmune hyperthyroidism in children with Down syndrome is rare before this age².

Due to various developmental delays, intellectual disabilities, and behavioral problems, it may be difficult to determine clinically whether a child with Down syndrome has a thyroid disorder. Although hypothyroidism is more common and many phenotypic features overlap with those found naturally in Down syndrome, it is important to consider the diagnosis of hyperthyroidism, especially in a child with worsening behavioral problems, irritability, diarrhea, and poor weight gain. Guidelines published by the American Academy of Pediatrics recommend performing thyroid screening tests in children with Down syndrome at birth with the newborn screen, at 6 months of life, and annually thereafter⁴¹.

In conclusion, this case highlights the unpredictable course of thyroid disease which may occur in children with Down syndrome. To our knowledge, our patient represents the first report of a child with transient congenital hypothyroidism that resolved and later evolved into Graves' disease. This atypical case expands the range of thyroid disease which may occur in children with Down syndrome.

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Fig. 1.
 ^{123}I thyroid uptake and scan. 24-hour radioiodine uptake was elevated at 39%. The left lobe of the thyroid is absent.

Fig. 2.
Doppler ultrasonographic image. There is diffuse hypervascularity of the right lobe and isthmus.

TABLE 1

Reports of individuals with thyroid hemiagenesis and Graves' disease

Reference	Year published	Gender	Age at diagnosis of Graves' disease (yr)	Side absent
Harada <i>et al.</i> ¹¹	1972	Female	58	Left
Mikosch <i>et al.</i> ¹²	1999	Female	57	Left
Mirouze <i>et al.</i> ¹³	1967	Male	53	Left
Friedman & Bauman ¹⁴	1979	Male	52	Left
Ruchala <i>et al.</i> ¹⁵	2008	Female	51	Left
Ozaki <i>et al.</i> ¹⁶	1994	Female	47	Right
Hervas Benito <i>et al.</i> ¹⁷	2001	Male	45	Right
Lee <i>et al.</i> ¹⁸	2003	Female	44	Left
Ozaki <i>et al.</i> ¹⁶	1994	Female	43	Left
Bando <i>et al.</i> ¹⁹	1999	Female	42	Right
Burman <i>et al.</i> ²⁰	1975	Female	41	Left
Baldini <i>et al.</i> ²¹	2005	Female	41	Left
Harada <i>et al.</i> ¹¹	1972	Female	39	Left
Matsumura <i>et al.</i> ²²	1982	Female	35	Left
Shechner <i>et al.</i> ²³	1992	Female	35	Left
Veliz & Pineda <i>et al.</i> ²⁴	2000	Female	35	Left
Levy ²⁵	1989	Female	34	Left
Shechner <i>et al.</i> ²³	1992	Female	33	Right
McHenry <i>et al.</i> ²⁶	1995	Male	31	Left
Zangeneh <i>et al.</i> ²⁷	2001	Female	31	Left
Rashid <i>et al.</i> ²⁸	1998	Female	29	Left
Ozgen <i>et al.</i> ²⁹	2004	Female	29	Left
Harada <i>et al.</i> ¹¹	1972	Female	28	Right
Harada <i>et al.</i> ¹¹	1972	Female	28	Left
Sasaki <i>et al.</i> ³⁰	1991	Female	28	Right
Harada <i>et al.</i> ¹¹	1972	Female	21	Left
Mortimer <i>et al.</i> ³¹	1981	Female	20	Left
McHenry <i>et al.</i> ²⁶	1995	Male	17	Left
Ozaki <i>et al.</i> ¹⁶	1994	Female	16	Left
Present report	2009	Female	10	Left