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Congenital hypothyroidism and thyroid dyshormonogenesis: a case report of siblings with a newly identified mutation in thyroperoxidase

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Abstract

Background—Thyroid dyshormonogenesis continues to be a significant cause of congenital hypothyroidism. Over time, forms of thyroid dyshormonogenesis can result in goiter, which can lead to difficult management decisions as the pathologic changes can both mimic or lead to thyroid cancer.

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Methods—Herein we describe the cases of two brothers diagnosed with congenital hypothyroidism, with initial findings consistent with thyroid dyshormonogenesis. One brother eventually developed multinodular goiter with complex pathology on biopsy, resulting in thyroidectomy.

Results—Whole exome sequencing revealed the brothers carry a novel frameshift mutation in thyroperoxidase; the mutation, while not previously described, was likely both deleterious and pathogenic.

Conlcusions—These cases highlight the complex pathology that can occur within thyroid dyshormonogenesis, with similar appearance to possible thyroid cancer, leading to complex management decisions. They also highlight the role that a genetic diagnosis can play in interpreting the impact of dyshormonogenesis on nodular thyroid development, and the need for long-term follow-up in these patients.

Keywords

congenital hypothyroidism; multinodular goiter; thyroid dyshormonogenesis; thyroperoxidase; whole-exome sequencing

Introduction

Congenital hypothyroidism (CH) is one of the most common causes of preventable neuro-developmental retardation and has an incidence of approximately 1 in every 3500 live-births [1]. New avenues for determining the root cause of thyroid dysfunction have identified the potential of genetic inheritability of several forms of CH [2, 3]. While CH can result from agenesis of the gland itself, thyroid dyshormonogenesis is known to be an important cause of decreased thyroid levels in the newborn period. In the setting of thyroid dyshormonogenesis and elevated thyrotropin levels, significant goiter can occur. This can lead to a difficult diagnostic dilemma later in life with concern for cancer. In this report we describe the cases of two brothers with congenital hypothyroidism identified via newborn screening who were diagnosed with thyroid dyshormonogenesis, and subsequently developed multinodular goiter. Their cases highlight both the complex pathology that can arise in a dyshormonogenetic goiter, as well as the role of genetic testing in these diagnoses that can aid in management and possible surgical treatment decisions.

Genetic testing plays an expanding role in the diagnosis of thyroid disorders. The majority of cases of CH are due to defects in organogenesis of the thyroid gland itself (70–85%), either by complete agenesis (30%), thyroid ectopia (48%), or a hypoplastic eutopic gland (5%) [1, 4]. Mouse models and genetics studies have helped to identify several candidate genes responsible for these etiologies of CH. These genetic links can be associated with both syndromic (e.g. *FOXE1*, *NKX2-1* and *NKX2-5* mutations) and non-syndromic (*TSHR* and *PAX8* mutations) presentations [4]. Multiple genetic causes of dyshormonogenesis have also been described. For example, Pendred syndrome (from mutations in the *SLC26A4* gene encoding the anion transporter) is a well-characterized cause of impaired thyroid hormone production; mutations in the genes coding the sodium-iodine symporter, the oxidase proteins DUOX2 and DUOXA2, thyroglobulin, and DHAL1 also result in symptomatic loss of

thyroid hormone production with autosomal recessive inheritance [5–9]. However, mutations in thyroid peroxidase (TPO), the heme peroxidase required for iodination of thyroglobulin tyrosyl residues, seem to be the most common cause of inherited CH [10, 11]. Multiple mutations have been implicated in loss of TPO function; in the studied siblings, we found a novel mutation in TPO extending into the final intron/exon junction of the gene, associated with their presentations of congenital hypothyroidism developing into multinodular goiter.

Case presentation

Case 1

Patient 1 was admitted to the hospital at 8 days of life due to failure to thrive, poor feeding, and decreased activity with a concern for sepsis. During his admission his state-mandated thyroid newborn screen revealed an undetectable T4 level and a thyroid-stimulating hormone (TSH) of 592 mIU/mL. No palpable thyroid gland was noted on initial physical exam, although a thyroid ultrasound at that time did identify thyroid tissue, raising thyroid dyshormonogenesis as a possible diagnosis in light of the absence of demonstrable thyroid function. Family history was significant for consanguinity; the patient's parents are first cousins. He was started on levothyroxine replacement, with his doses gradually increased as needed to maintain a euthyroid state. His developmental history has been significant for delays in both gross motor and speech function, first sitting without support at age 8 months, walking at 18 months, and a delay in first words to preschool age. As a result, early intervention services were initiated at 10 months of age. At 10 years of age, a thyroid ultrasound revealed a right thyroid lobe measuring 7.6×3.2×3.2 cm, with hypoechoic nodules measuring 3.6×2.3×3.2 cm and 3.9×2.9×2.9 cm, and a left lobe measuring 4.5×1.9×1.9 cm with 1.2×1.1×1.2 cm and 0.8×0.6×0.67 cm hypoechoic nodules. A thyroid uptake and scan with 311 μCu was significant for a 2 h uptake of I^{123} of 32.9% (nl = 6–18%), and a 24 h uptake of 11.5% (nl = 10–35%) interpreted as low given the high uptake at 2 h and suggestive of a defect in thyroid hormone organification. Serial ultrasounds demonstrated a gradual increase in size of the nodules over the next year, with TSH values that gradually fell from a peak of 23.16 mIU/mL 3 weeks after the uptake and scan, to 8.9 mIU/mL after 1 month, then 6.71 mIU/mL after another 3 months, and then 4.12 mIU/mL 1 month following. A TSH nadir of 1.29 mIU/mL was reached 1 year after the uptake and scan, with a slight rise to 2.5 mIU/mL after 3 months. Due to the increase in size that was felt to be out of proportion to TSH values, an ultrasound-guided needle biopsy was performed that demonstrated cellular proliferation of follicular cells with a micro follicular architecture, with scant colloid. There was strong PAX8 immunoreactivity and the sections were negative for parathyroid hormone, consistent with concern for follicular neoplasm. Therefore shortly thereafter a total thyroidectomy was performed, and the right and left lobes were received separately, weighing 184.0 g on the right side (including isthmus) and 34.0 g for the left lobe. The thyroid lobes were remarkable grossly for several nodules. The three largest nodules measured 5.6 cm in the right upper lobe, 5.3 cm in the right lower lobe and 3.5 cm in the left lower pole. Histologic sections showed a background thyroid with atrophic lobules, surrounded by pronounced fibrous septae, with loss of luminal colloid and exhibiting occasional hyperchromatic enlarged nuclei with irregular nuclear contour. The nodules were relatively hypercellular and showed a wide range of histologic findings. Some

were composed of variably sized follicles, while others showed a solid to microfollicular architecture, a finding which is commonly seen in this condition and referred to as follicular adenoma like hypercellular nodules. Two of the remaining nodules exhibited enlarged vesicular nuclei with irregular nuclear contours, nuclear grooves and occasional nuclear overlapping. The first nodule measured 1.4 cm in greatest dimension from the right lobe and the second nodule measured 2.0 cm from the left lobe. Both nodules were well circumscribed and did not show an infiltrative border. However, the nuclear features raised the possibility of papillary carcinoma within these nodules. The presence of a spectrum of nuclear changes similar to these foci in the remaining thyroid, as well as the lack of classical papillary nuclear features preempted the diagnosis of carcinoma in these nodules. The histologic changes are part of the spectrum of changes that is seen in dyshormonogenetic goiter [12]. Since thyroidectomy, the patient has been stable, with levothyroxine doses adjusted as needed to maintain a euthyroid state.

Case 2

Patient 2 is the brother of patient 1 and was born via cesarean section for breech presentation after a uncomplicated pregnancy. His family asked that thyroid levels be sent immediately along with the state newborn screen. His TSH was greater than the upper limit of detection for the state mandated screen, and he was started on levothyroxine replacement with doses adjusted as needed. Patient 2 had normal growth and development, and had also been followed with serial thyroid ultrasounds. An ultrasound performed at 5 years of age was significant for a right lobe measuring 5.1×1.2×1.2 cm with a 0.6×0.9×0.6 hypoechoic nodule, and a left lobe measuring 3.4×1.2×1.2 cm. A thyroid uptake and scan was significant for a 24 h uptake of 37.7%. A hypoechoic nodule has been noted on all subsequent thyroid ultrasounds, and over the next 2 years despite maintaining a TSH in the range of 0.16–2.15 mIU/mL, the gland and nodule have enlarged slightly. Due to the similar presentations of these two brothers coupled with the history of consanguinity, the family was referred for genetic counseling. Whole exome sequencing was performed from peripheral blood on the brothers to determine a possible genetic cause for their thyroid disorder. Briefly, exome sequencing libraries were prepared from genomic DNA from the probands using Agilent SureSelect XT Human All Exome v5fl UTRs kit (Agilent Technologies, Santa Clara, CA, USA) according to the manufacturers' protocol. Paired-end sequencing was performed on the Illumina HiSeq 2500 platform to provide a mean sequence coverage of more than 150×, with more than 99% of the target bases having at least 10× coverage. The data were analyzed and annotated using Nextgene (Softgenetics LLC, State College, PA, USA) software, an in-house developed "pipeline" for variant filtration and prioritization. Variants were filtered for quality, leaving only the ones that passed the quality metrics. Nonsynonymous, splice, stop-gain, and stop-loss variants with a minor allele frequency <0.01 in the 1000 Genomes Project and Exome Variant Server (EVS) were prioritized, including the novel variants that were not present in either the 1000 Genomes Project, EVS data sets, or in the database of Single Nucleotide Polymorphisms (dbSNP). In addition, evolutionary conservation and computational predictions using SIFT [13] and PolyPhen [14] were also included in the variant analysis. Finally, the variants considered to be clinically relevant were classified accordingly to American College of Medical Genetics guidelines [15]. Both Case 1 and Case 2 were found to be homozygous for the frameshift mutation: c.

2738_2748+5del; p.D913fs on chromosome 2p25 in the *TPO* gene (a frameshift mutation at aspartate 913 crossing into the intron-exon junction, described using the standard Human Genome Variation Society (HGVS) nomenclature (http://www.hgvs.org/mutnomen/). Patient 2 continues to have regularly scheduled screening ultrasounds to follow the progression of the noted thyroid nodules.

Discussion

Newborn screening for thyroid disease continues to play a significant role in preventive medicine, likely preventing up to 160 cases of intellectual developmental disability a year in the US [16]. While changes in cutoff values for screening labs such as TSH may affect the false positive rate of detection on newborn screen, any positive screen should be rapidly evaluated with confirmatory testing and physical exam [17]. It has been suggested that in high risk cases that include affected siblings as in the cases above, cord blood should be sampled (as well as later confirmatory tests due to the TSH surge at birth) [18]. This can lead to more rapid treatment, which can improve intellectual outcomes in these patients [18]. During the initial workup of CH, identification of a thyroid gland on ultrasound prior to or immediately following initiation of treatment is suggestive of a dyshormonogenetic goiter. It has been suggested that if a gland is detected in this early timeframe, DNA should be collected for future use in mutational analysis [18]. Rapid genetic diagnosis has been suggested to allow for changes in management, as certain defects could possibly be treated with iodide supplementation rather than thyroid replacement [10], though thyroid replacement remains the standard of care.

TPO is a 933 amino-acid type 1 glycosylated heme-binding protein with a single transmembrane domain that catalyzes the iodination of tyrosine residues to form monoiodostyrosine and diiodotyrosine and the coupling of iodotyrosine residues on thyroglobulin [19]. It spans >150 kilobases of chromosome 2p25 and is comprised of 17 exons, alternative splicing of which can lead to multiple active and inactive splice variants [19, 20]. While well characterized as one of the primary thyroid autoantigens, mutations in TPO are also the leading cause of congenital dyshormonogenesis [21]. Algorithms have been suggested for the analysis of dyshormonogenesis, which include gene-specific testing as well as broader sequencing of a panel of genes known to cause thyroid dyshormonogenesis [11, 18]. While tests for known mutations causing thyroid dyshormonogenesis exist, they will miss mutations in genes that previously have not been associated with thyroid dyshormonogenesis. It has been estimated that at least 25% of patients with previously undiagnosed genetic disorders can receive a diagnosis from whole exome sequencing [22]. The frameshift mutation in these cases (c.2738_2748+5del; p.D913fs on chromosome 2 in the *TPO* gene) is hypothesized to result in a nonfunctional protein as the mutation crosses an intron/exon junction at the C-terminus of the enzyme. The identified variant has not been previously described in the literature to cause disease; however, the frameshift mutation is a disruptive mutation and this homozygous variant is considered likely pathogenic in this family. This is consistent with the diagnosis of familial dyshormonogenetic goiter in these two brothers. Whole exome sequencing has therefore played an important role in diagnosis and management of these two patients. We suggest that whole exome sequencing should be included as another tool for specific diagnosis in the

setting of strong clinical suspicion of thyroid-specific inherited disorders, especially as the cost of sequencing and analysis continues to decrease [23]. We posit that in the case of thyroid dyshormonogenesis, in which multiple genes may lead to the phenotype, whole-exome sequencing can be an avenue for both rapid screening of multiple genes as well as provide new data into deleterious mutations existing in the population.

Ultimately, these cases demonstrate the sometimes difficult management decisions associated with multinodular goiter in children. Clinical progression to multinodular goiter without a genetic diagnosis can lead to need for surgical excision, since approximately 25% of nodules in pediatric cases are thought to be at risk for thyroid neoplasia, compared to the 5% rate in adults [24]. While discovery of a mutation in TPO as the cause of multinodular goiter may diminish that risk, it does not exclude the possibility of cancer. Most imporatantly, as exemplified in both these and previous cases, multinodular goiters in the setting of thyroid dyshormonogenesis can appear malignant, or may actually progress to true malignancy, complicating the workup and subsequent treatment [25, 26]. Therefore, going forward it would be of interest to determine the correlation, if any, between specific known and new mutations in TPO or any other step in thyroid hormone production and their relative risk of development of cancer. Given the potential for confusion between neoplastic change and nuclear atypia of dyshormonogenetic glands, these cases highlight the benefit of rapid genetic diagnosis of patients with suspected thyroid dyshormonogenesis, and the need for frequent follow-up over time to monitor for nodular changes, and allow for workup as per established standards of care for pediatric thyroid nodules [27].

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