Novel DICER1 mutation as cause of multinodular goiter in children

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Accepted 9 January 2013
Published online 1 June 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/hed.23250

ABSTRACT: Background. The aim of this report was to present a rare case of an adolescent with multinodular goiter (MNG) found to have a DICER1 mutation.

Methods and Results. The methodology includes a presentation and discussion of a chart review including endocrine hormone tests, thyroid ultrasound, and genetic testing for DICER1. A 12-year-old girl presented with a diffusely enlarged thyroid gland. Family history revealed an older sister with a history of bilateral ovarian Sertoli-Leydig cell tumors and MNG. Thyroid function tests were normal. Serial thyroid ultrasounds showed enlarging multiple bilateral nodules. Fine-needle aspiration suggested MNG. Genetic testing revealed a novel heterozygous premature termination mutation (c.1525G>T p.R509X) in the DICER1 gene.

Conclusions. Thyroid nodules are rare in children but carry a higher risk for malignancy. It is essential to inquire about family history and refer for genetic evaluation with a family history of MNG. In patients with DICER1 mutations, tumor surveillance is critical due to the increased risk of multiple tumors, including ovarian tumors and pleuropulmonary blastoma.


KEY WORDS: DICER1, multinodular goiter, ovarian Sertoli-Leydig cell tumors, tumor surveillance, family history

INTRODUCTION

Multinodular goiter (MNG) is a common disorder characterized by non-neoplastic enlargement of the thyroid gland due to the development of multiple nodules. MNG is noted to have a greater incidence in females (5:1 ratio of females:males) and in low iodine intake regions. However, the incidence of MNG is still quite common in regions of sufficient iodine intake, supporting the notion of a possible genetic basis for this disorder. Two loci for familial MNG have been identified: MNG1 on chromosome 14q and MNG2 on chromosome X. Germline mutations in DICER1, on chromosome 14q32, have been linked to familial MNG with and without ovarian Sertoli-Leydig cell tumors (SLCTs). DICER1 is a member of the ribonuclease III (RNase III) family of genes involved in the generation of micro-RNAs (miRNAs). miRNAs are a class of short, double-stranded, noncoding regulatory RNAs that modulate gene expression post-transcriptionally. A global downregulation of miRNAs has been shown to promote tumorigenesis. DICER1 and other miRNAs have been implicated as having a critical role(s) in the molecular regulation of multiple organ systems. The importance of DICER1 was emphasized in a study of Dicer1 knockout mice, which showed that a null mutation of Dicer1 is embryologically lethal. Tissue-specific conditional knockout experiments have demonstrated the essential organogenetic role of Dicer1 in multiple organ systems, including the lung, adrenal cortex and testis, female reproductive system, retina, glomerulus, limb, and skeletal muscle. Jacks and colleagues found that heterozygous loss of Dicer1 accelerated tumor formation in Kras-induced mouse models of cancer and provided evidence for an active selection against complete loss of Dicer1 during tumor progression in these tumors, implicating Dicer1 as a haploinsufficient tumor suppressor gene. Germline mutations of DICER1 have not only been reported in MNG with and without Sertoli-Leydig cell tumors, but also in pleuropulmonary blastoma (PPB), cystic nephroma (CN), cervix embryonal rhabdomyosarcoma (cERMS), primitive neuroectodermal tumor (cPNET), and Wilms...
tumor.18–22 DICER1 mutations exhibit low penetrance in PPB and CN, but high penetrance in MNG.3 We report 2 siblings with MNG and a germline DICER1 mutation, in which the older sibling also manifested bilateral SLCTs.

CASE REPORTS

This study was approved by the University of Michigan Institutional Review Board committee. A chart review was performed for both siblings.

The otolaryngology, genetic, and endocrinology evaluations as well as the CT scan, thyroid ultrasound, and endocrine hormone tests were performed at the University of Michigan (Ann Arbor, MI). The gynecologic evaluation, pelvic ultrasound, chest CT, and CA-125 laboratory tests were performed at the National Institutes of Health (Bethesda, MD). DICER1 sequence analysis was performed at Ambry Genetics Laboratory (Aliso Viejo, CA).

Sibling 1

A 12-year-old girl was noticed to have an enlarged thyroid earlier in January 2011. History was negative for symptoms of hypothyroidism or hyperthyroidism, including palpitation, sweating, nervousness, tremor, diarrhea, insomnia, cold or heat intolerance, fatigue, constipation, or hair loss. She reported a recent 4-pound weight loss attributed to increased physical activity. She had no signs of hyperandrogenism such as hirsutism, excessive acne, or excessive hair loss. She had regular menses. The patient was evaluated by a pediatric otolaryngologist, a pediatric endocrinologist, and a pediatric geneticist.

Her birth history was unremarkable without teratogenic exposures. Her past medical history was significant for eustachian tube dysfunction and right tympanic membrane perforation status post right paper patch myringoplasty. She also underwent surgical excision of a midline neck mass at age 6; pathologic examination was consistent with dermoid cyst.

Family history was significant for colon cancer in a paternal grandfather, esophageal cancer in a paternal great uncle, and possible thyroid disorders in a grandmother and a great aunt. Furthermore, the patient’s sister had a significant oncologic history (see Sibling 2, below).

Physical examination was notable for a small right tympanic membrane perforation and a thyroid gland with diffuse slight enlargement without discrete palpable nodules. The rest of the head and neck examination was normal.

Thyroid ultrasound showed a right thyroid lobe measuring 4.2 × 1.5 × 1 cm and a left thyroid lobe measuring 4.5 × 1.9 × 1.7 cm. Three complex cystic lesions were noted, 1 within the isthmus (approximately 1.6 × 1 × 1.9 cm) and 2 in the left lobe measuring approximately 1.2 × 1.1 and 1.6 × 1.2 cm. In addition, there was a nonspecific 5-mm echogenic right lobe lesion. In summary, the ultrasound was consistent with a multinodular goiter, without suspicious calcifications or appreciable internal vascularity. Subsequent thyroid ultrasound 9 months later showed a right thyroid lobe measuring 4.5 × 1.6 × 1.8 cm, with the largest nodule in the right thyroid measuring 1.7 × 1.2 × 1.1 cm. The left thyroid lobe measured 4.1 × 2.2 × 1.9 cm with the 2 largest nodules in the left measuring 1.6 × 1.4 × 1.2 (superior pole) and 1.5 × 1.5 × 1.2 cm (inferior pole). The solid portions of multiple nodules demonstrated internal vascularity, and many of the nodules had enlarged. Fine-needle aspiration showed benign follicular cells, colloid and histiocytes, consistent with multinodular goiter.

Transabdominal pelvic ultrasound showed a uterus measuring 3.6 × 2.8 × 6.7 cm, with an endometrial thickness of 5 mm. The right ovary was 2.75 × 1.3 × 3.03 cm, with a 1.8-cm cyst, and the left ovary was 2.13 × 1.33 × 2.29 cm, with no fluid seen in the endometrial canal or cul-de-sac and no evidence of uterine fibroids. Chest CT showed bilateral pleuropulmonary blebs and a nonspecific 3-mm right pleural-based nodule. The pleuropulmonary blebs needed further workup to rule out type I pleuropulmonary blastomas.

Laboratory test results including thyroid-stimulating hormone (TSH), free T4, thyroid-stimulating immunoglobulin, thyroid peroxidase antibodies, alpha fetoprotein (AFP) tumor marker, serum total testosterone levels, dehydroepiandrosterone sulfate (DHEA-S), and β-HCG tumor markers were all normal. Genetic testing showed a novel heterozygous premature termination mutation (c.1525C>T p.R509X) in the DICER1 gene.

Sibling 2

The 23-year-old sister of sibling 1 has also been followed at our institution for postsurgical hypothyroidism and SLCT. She initially presented with abdominal distention and abdominal pain at 8 years of age. A CT scan revealed a left ovarian mass for which she underwent left oophorectomy and omentectomy. Pathology revealed a Sertoli-Leydig cell tumor of intermediate differentiation. Testosterone level was not obtained at that time, and she did not have hirsutism. She had her menarche at 11 years of age.

At 14 years of age, sibling 2 was found to have an enlarged thyroid gland. Thyroid ultrasound and scan revealed a cold nodule of the left thyroid gland and the absence of a right thyroid lobe, consistent with unilateral agenesis. Hemithyroidectomy (functional total thyroidectomy) was eventually performed. The pathology showed multiple benign nodules indicating a multinodular goiter. Furthermore, at 14 years of age, she had hirsutism and irregular menses without excessive weight gain. The testosterone level was increased to 68 ng/dL (normal range, 20–38). A CT scan revealed a new right-sided ovarian mass. She underwent right oophorectomy and bilateral salpingectomy. The mass was also identified to be an SLCT of intermediate differentiation that was thought to be asynchronous and an independent primary tumor. She therefore did not receive chemotherapy, although 10% of intermediate differentiated tumors are clinically malignant. She was started on levothyroxine sodium (Levoxyl) and the Ortho Evra birth-control patch (MCNeil-PPC, Inc., New Brunswick, NJ) for hormone replacement. The family moved to Michigan and transferred her endocrine care to our institution when she was 15 years of age.

DISCUSSION

Current recommendations for the management of non-toxic MNG are based on the fact that it carries a risk for
thyroid cancer similar to that of a solitary thyroid nodule, approximately 1% to 5%.\textsuperscript{23,24} To date, thyroid cancer has not been reported in DICER1 syndrome. However, new guidelines for MNG management are warranted, given recent advancements in the genetic cause for this disorder. Most cases of "MNG" referred to endocrine clinics are more often due to conditions of autoimmune, such as Hashimoto’s thyroiditis and not true MNG. Careful interpretation of the sonographic findings is paramount. Hyperthyroidism associated with toxic MNG warrants treatment. Occasionally, toxic MNG may be associated with McCune-Albright syndrome. If the patient indeed has true MNG without abnormality in thyroid function and without thyroid autoimmunity, a thorough inquiry into the family oncologic history and monitoring of tumor markers are warranted. We believe measurement of testosterone, DHEA/DHEA-S, AFP, β-HCG, and CA-125 levels along with TSH, free T4, and T3 should be performed annually or sooner if signs or symptoms warrant.

Our patient has a heterozygous mutation in DICER1, which is most likely the reason for her MNG. The father and older sister were tested at an outside institution and found to carry the familial DICER1 mutation first identified in the younger sister at our institution. Consequently, the clinical phenotype of the older sister is consistent with her molecular result. To date, no comprehensive guidelines are available for tumor surveillance in this new syndrome. Due to our patient’s mutation and her family history of tumors, close monitoring is warranted.

Most DICER1 mutations noted in patients with PPB were predicted to result in truncated proteins.\textsuperscript{20,26} Rio Frio et al\textsuperscript{5} noted 3 mutations that were nontruncating with high penetrance for MNG. The nonsense DICER1 mutation in codon 509 in our patient most likely results in a truncated protein. Thus, although penetrance is low, our patient underwent a chest CT showing 2 small cystic lesions. Analysis of germline DICER1 mutations from a large series of probands with differentiated thyroid cancer with and without MNG showed no correlation between the DICER1 mutation and thyroid carcinoma.\textsuperscript{5} Because DICER1 mutations have not been associated with thyroid carcinoma to date, and our patient is asymptomatic, surgical intervention is currently not recommended. In addition, we recommend tumor surveillance for our patient for SLCT via laboratory and annual ultrasound.

Our report stresses the importance of a thorough inquiry into the family oncologic history in patients who have multinodular goiter without abnormality in thyroid function and without thyroid autoimmunity. Genetic testing is warranted for patients with a family history of cold multinodular goiter and/or ovarian Sertoli-Leydig cell tumors.

REFERENCES

HEAD & NECK—DOI 10.1002/HED DECEMBER 2013 E371