ABSTRACT. Multiple endocrine neoplasia type 2A (MEN 2A) is most frequently caused by codon 634 activating mutations. Medullary thyroid carcinoma has occurred before the age of 2, with pheochromocytomas and primary hyperparathyroidism occurring later in childhood. We report cases of 4 siblings with C634Y-positive MEN 2A (all <11 years old); 3 with medullary thyroid carcinoma (1 had nodal metastasis, and another had a parathyroid adenoma) and 1 with C-cell hyperplasia. *Pediatrics* 2005;116:e468–e471. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2005-0033; multiple endocrine neoplasia, MEN 2A, hyperparathyroidism, parathyroid adenoma, medullary thyroid carcinoma, pheochromocytoma, RET protooncogene.

ABBREVIATIONS. RET, rearranged during transfection; MEN 2A, multiple endocrine neoplasia type 2A; MTC, medullary thyroid carcinoma; PHE, pheochromocytoma; PHPT, primary hyperparathyroidism; iPTH, intact parathyroid.

The rearranged during transfection (RET) protooncogene codes for the tyrosine kinase receptor on chromosome 10q11.2 and is expressed in neural crest-derived cells of the thyroid and parathyroid glands, adrenal medulla, and enteric autonomic plexus.1,2 Normally, when a ligand binds to the receptor, a cascade of intracellular signals is triggered, which leads to eventual cellular maturation and growth. Activating mutations allow the receptor to function in the absence of ligand binding, causing unchecked cellular growth that results in tumor development.2 Point mutations of the transmembrane tyrosine kinase receptor on chromosome 10q11.2 result in the development of multiple endocrine neoplasia type 2A (MEN 2A). These mutations are found more commonly in the extracellular domain at codons 609, 611, 618, 620, 630, and 634 and less frequently involve intracellular domain codons 768, 790, 791, 804, and 891.3 An activating mutation of the extracellular 634 codon is the most prevalent RET protooncogene mutation leading to the development of MEN 2A.1,3–5 MEN 2A is characterized by medullary thyroid carcinoma (MTC), pheochromocytoma (PHE), and primary hyperparathyroidism (PHPT). MTC occurs in virtually all patients with MEN 2A, whereas adrenal PHEs and PHPT occur in only 50% and 10% to 30%, respectively.6,7 Machens et al1 found that of 207 patients studied with MEN 2, ~63% carried an abnormal RET 634 codon as opposed to 9.2%, 6.8%, and 2.9% for codons 618, 620 and 790, and 891, respectively. In that same study, Machens et al noted a positive correlation between the MEN phenotypes and the different affected RET protooncogenes. For example, all of the 4 patients with an affected 918 codon displayed phenotypic characteristics of MEN 2B. Similarly, 95% of carriers with 634 mutations demonstrated the familial phenotype of MEN 2A. They classified families with mutations of codons 918 and 634 as a higher risk category, because these mutations are associated with earlier malignant transformation and development of MTC relative to other codon mutations. Additionally, Machens et al concluded that the involvement of the parathyroid and adrenal glands occurred more often in families with the higher-risk-category RET oncogene mutations.

MTC has been reported in a 15-month-old child who had codon 634 mutation. The current recommendation is for children with known 634 codon mutations to undergo prophylactic thyroidectomies before 5 years of age.3,5,9 We report a family of 4 siblings with MEN 2A, all <11 years old: 3 with MTC (the youngest with C-cell hyperplasia), but including 1 with nodal metastasis, and 1 with a parathyroid adenoma. Informed consent was given by the children's parents, and this study was approved by the Children's Hospital of Philadelphia Institutional Review Board.

CASE REPORTS

At the time of initial presentation, 3 of 5 children, siblings A, B, and C, were known to have the C634Y mutation. The family history of affected paternal relatives included a father and grandmother with MTC and PHE and an aunt with MTC (Fig 1). Of the 5 children in this family, the oldest was found not to be affected, and the youngest (who was <2 years old) had not been tested yet. At the initial visit, all 3 were asymptomatic. On physical examination, sibling A, a 10-year-old girl, had a palpable, nontender, single nodule lateral to the right lobe of her thyroid gland without cervical adenopathy. Her initial serum calcitonin was 124 pg/mL (36.3 pmol/L [normal: <4 pg/dL]) and calcium was 10 mg/dL (2.50 mmol/L [normal: 8.5–10.4 mg/dL]). Sibling B, a 9-year-old girl, had no thyromegaly or thyroidal irregularities. Her initial serum calcitonin was 67 pg/mL (19.6 pmol/L) and calcium was 10.2 mg/dL (2.54 mmol/L). Sibling C, a 6-year-old boy, also had no thyroid abnormalities on examination. His initial serum calc-
calcitonin was 47 pg/mL (13.8 pmol/L) and calcium was 9.9 mg/dL (2.47 mmol/dL). None of the children had parathyroid hormone levels measured at the time of initial presentation. Surgical pathology from the thyroid tissue obtained during each of the total thyroidectomies was positive for MTC. Sibling A's thyroid gland weighed 5.6 g, which is an appropriate thyroid weight and was noted to have several foci of MTC in the middle of both thyroid lobes. She was also found to have metastatic MTC in a single lymph node (Fig 2). Sibling B's thyroid gland fell in the normal range for weight at ~4 g and revealed multiple foci of C-cell hyperplasia, micronodular medullary carcinoma, and a focus of medullary carcinoma with sclerotic stroma. Additionally, microscopic evaluation of a parathyroid gland revealed a compressed normal parathyroid gland with admixed fat in relation to 2 nodular regions with trabecular histology consistent with a parathyroid adenoma (Fig 3). The pathology on sibling C's thyroid gland revealed a normal-weight 3.8-g thyroid gland with MTC in both lobes as well as focal C-cell hyperplasia; there was no lymph node or parathyroid gland involvement. Ten months after total thyroidectomy, all 3 siblings were healthy, their calcitonin levels were 4.1, <1, and <1 pg/mL (1.2, <1, and <1 pmol/L) for siblings A, B, and C, respectively, and all had normal calcium, intact parathyroid (iPTH) hormone levels, and negative serum metanephrines at that time.

Subsequently, the youngest child, sibling D, at the age of 2 was found to have inherited the mutation as well. Her preoperative physical examination was normal; her initial serum calcitonin was 43.8 pg/mL (12.8 pmol/L) and calcium was 9.5 mg/dL (2.37 mmol/L). Sibling D had a total thyroidectomy. The surgical pathology was significant for a 2.17-g thyroid gland with several distinct foci characterized by clusters of C cells without formation of distinct nodules or masses, which is consistent with C-cell hyperplasia.

**DISCUSSION**

Of children from MEN 2A kindred, MTC has been found to occur as early as 1 year of age, although nodal invasion rarely occurs before adolescence. Once malignant transformation is present, the rate of progression to nodal metastases is estimated to be ~6.6 years later. PHEs and PHPT occur later in childhood; a PHE has been identified in a child as early as 12 years old and PHPT in a 10-year-old. Previous studies have demonstrated a correlation between the development of PHPT and PHEs in patients with 634-codon-mutation–positive MEN 2A. Additionally, it has been reported that of MEN 2A kindred with parathyroid gland involvement, 73% were found to have RET protooncogene codon 634 mutations. It has also been suggested that the occurrence of parathyroid abnormalities may be influenced by growth factors released by thyroid glands affected by MTC. Furthermore, when patients with MEN 2A develop PHPT, they frequently
have been found to only have normal to slightly increased calcium and parathyroid hormone levels\textsuperscript{12} rather than overt hypercalcemia as seen in other causes of PHPT. At the age of 9, sibling B is one of the youngest reported patients to develop a parathyroid adenoma in a MEN 2A kindred. Also, this patient’s PHPT was not suspected by calcium determination, suggesting the need to measure iPTH hormone levels in surveillance of MEN 2A families with the higher-risk category \textit{RET} oncogene mutations such as 634. Elevated iPTH hormone levels can be seen in normocalcemic patients such as sibling B, nevertheless resulting in abnormalities such as osteitis fibrosis. In children known to have MEN 2A codon mutations, an elevated iPTH hormone level may signify the presence of a parathyroid adenoma before hypercalcemia occurs. In such cases, these children could have an ultrasound obtained to screen for the presence of a parathyroid adenoma and more frequent surveillance for calcium abnormalities, including imaging studies such as sestamibi scans.

Surveillance methods, once genetic analysis has confirmed the presence of a \textit{RET} protooncogene mutation, include measuring calcitonin, total calcium, and metanephrine levels in the serum. Given the almost 100% risk of developing MTC in MEN 2A, it is currently recommended that known 611, 618, 620, or 634 codon mutation carriers undergo prophylactic total thyroidectomy before the age of 5.\textsuperscript{3,8,9} Szinnai et al\textsuperscript{3} found that in addition to demonstrating the earliest progression from C-cell hyperplasia to MTC, patients with 634 codon mutations have higher rates of metastatic disease when compared with patients with other mutated codons from the extracellular domain of chromosome 10. For these codon-mutation carriers, earlier thyroidectomy would be advantageous in limiting the potential for the development of metastatic MTC as well as parathyroid adenomas. However, some barriers to earlier thyroidectomy are the morbidity associated with pediatric anesthesia, especially in young infants, as well as surgical risks for recurrent laryngeal nerve palsy and hypocalcemia. Other than the airway and anesthetic risks, the technical risks of thyroidectomy are not increased in infancy. The risk of these complications, when thyroidectomy is performed under the care of pediatric-trained anesthetists and surgeons, does not outweigh the benefits of prophylactic thyroidectomy in affected carriers of the 634 codon mutation.

The presence of both a parathyroid adenoma and metastatic MTC in this family demonstrates the variability of disease expression with the C634Y gene mutation. This kindred reaffirms the need for earliest possible surgery. Of the 4 affected siblings, sibling D, at the age of 2, is the only known member of this family whose pathology was negative for MTC. Therefore, we propose that prophylactic thyroidectomy before 5 years of age, perhaps even as early as 2 years of age, may be warranted in children with known C634Y mutations to prevent the development of MTC. Furthermore, if the suggestion by Iler et al\textsuperscript{8} is correct, prevention of MTC may also be preventive of PHPT, although surveillance in this family will include measurement of iPTH hormone levels.

REFERENCES


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\textbf{Fig 3.} The parathyroid adenoma surrounded by compressed normal parathyroid cells are each individually labeled.
Multiple Endocrine Neoplasia Type 2A in a Kindred With C634Y Mutation
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