

Prophylactic Thyroidectomy in MEN-2A — A Stitch in Time?

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Multiple endocrine neoplasia (MEN) type 2A (MEN-2A) and type 2B (MEN-2B) illustrate the remarkable pace of knowledge that has been acquired about a group of heritable disorders. In 1961, Sipple made astute clinical observations associating bilateral pheochromocytomas with carcinoma of the thyroid gland.¹ Others subsequently identified the thyroid neoplasm involved as medullary thyroid carcinoma, which is derived from calcitonin-producing parafollicular, or C, cells. Serum calcitonin concentrations were found to be elevated in patients with medullary thyroid carcinoma, and these increased levels served as a useful tumor marker. Clinical syndromes associated with hereditary medullary thyroid carcinoma include MEN-2A, or Sipple's syndrome — an autosomal, dominantly inherited disease with variable expression and a high degree of penetrance. Its phenotype includes medullary thyroid carcinoma (highly penetrant, occurring in more than 90 percent of patients), as well as pheochromocytoma (50 percent) and parathyroid neoplasia (5 to 10 percent). There is a long latent period for the development of the full MEN syndrome, which often does not appear until the third or fourth decade of life. Bilateral and multicentric medullary thyroid carcinoma is the most common cause of death in patients with MEN-2A. The MEN-2B syndrome also includes medullary thyroid carcinoma and pheochromocytoma but is characterized by a distinct phenotype: the presence of mucosal neuromas, gastrointestinal ganglioneuromatosis, a marfanoid habitus, and tall stature but the absence of parathyroid disease.

On the basis of advances that have been made in understanding the molecular pathways in MEN-2A and MEN-2B, there are now age-specific recommendations for prophylactic thyroidectomy in children who carry mutations and are at risk for medullary thyroid carcinoma. Indeed, the age at which surgery is recommended may depend primarily on the individual mutation that is present as well as on other manifestations.² Germ-line mutations in MEN-2A and MEN-2B carriers have been found in the *RET* ("rearranged during transfection") proto-oncogene, which encodes a transmembrane tyrosine kinase receptor.^{3,4} (Somatic *RET* mutations were also found in some sporadic medullary thyroid car-

cinomas.) The need for genetic identification of carriers resulted in the establishment of international collaborations and consortia, such as the EUROMEN (European Multiple Endocrine Neoplasia) Study Group, which permitted genotype-phenotype correlations within the MEN-2 spectrum.

Medullary thyroid carcinoma follows an orderly pattern of development, beginning as C-cell hyperplasia, progressing to microscopic medullary thyroid carcinoma and then to a visible focus. The time to occurrence of metastasis is unknown. The finding that medullary thyroid carcinoma was an inevitable consequence of early hyperplastic transformation resulted in the recommendation that in MEN-2 carriers thyroidectomy be performed during childhood to prevent occult metastasis before resection.⁵

A recent important advance that resulted from the EUROMEN Study Group was the finding of an age-dependent progression of early medullary thyroid carcinoma specific to the *RET* codon.⁶ Codon-directed prophylactic surgery was recommended on the basis of the youngest age at first diagnosis of medullary thyroid carcinoma according to codon.² The recommended age for prophylactic thyroidectomy for most *RET* genotypes was five years (including mutations at codon 634, which accounts for approximately 80 percent of germ-line *RET* mutations). The EUROMEN data also indicated that nodal metastases are uncommon before the age of 10 years in patients with any of several common *RET* genotypes (codons 630 and 634). In the light of these recommendations, the results presented by Skinner et al. in this issue of the *Journal* provide the best long-term follow-up data to suggest that young patients with the MEN-2A genotype can be "cured" (or at least kept free of disease for a minimum of five years) after prophylactic thyroidectomy.⁷

Prophylactic surgery for children must be approached with special caution and the potential benefits carefully weighed against the consequences of delayed intervention. The risks of thyroidectomy have been known to physicians for generations. The age at which surgery should be considered and the extent of that resection are important questions facing the clinicians caring for these patients.

In the study by Skinner et al., complete extirpa-

tive resection of the thyroid gland and the surrounding fatty, lymph-node-bearing tissue of the central neck was performed. Since it is not possible to tell during surgery in these children whether or not an occult medullary thyroid carcinoma exists, the operation was designed to remove all neck tissue that could be considered to contain either primary or metastatic disease. At completion, the only structures left in the anterior neck between the carotid sheaths were the esophagus, the trachea and larynx, and the recurrent laryngeal nerves. Dissection of the lymph nodes of the central neck after a thyroidectomy typically results in increased morbidity, due to obscured delicate structures such as recurrent laryngeal nerves in the scar tissue; thus, sequential initial thyroidectomy followed by central neck dissection in the event that cancer develops is a less desirable method of prophylactic surgery than the method used in this study. In addition, the parathyroid glands were extracted from the resected specimen, minced, and reimplanted in cervical or forearm muscles. Successful parathyroid autotransplantation allows the patient to maintain normal calcium homeostasis.

Thyroidectomy may have dangers. In particular, the surgical risks include unilateral or bilateral injury to the recurrent laryngeal nerves, permanent hypoparathyroidism, postoperative cervical hematoma, and perioperative death. There is also the potential for concomitant undiagnosed pheochromocytomas in patients with MEN-2A and MEN-2B, entities for which patients should be screened preoperatively and periodically after surgery. If a pheochromocytoma is diagnosed, thyroid surgery should be deferred until the pheochromocytoma is removed, since otherwise serious, even fatal, hemodynamic disturbances can occur during the operation. Although unilateral recurrent-nerve injury is well tolerated in children, bilateral injury can result in total airway obstruction; the required tracheostomy may be semipermanent and not removable until the larynx matures enough to allow surgery of the vocal cords to succeed (at age 10 years or so).

Permanent hypoparathyroidism is relatively asymptomatic when treated appropriately but still might cause premature cataracts, calcification of the basal ganglia, and occasional extrapyramidal disorders. Cervical hematoma can be fatal because of compression of the membranous trachea, but postoperative inpatient monitoring can facilitate

early identification and management of this complication.

Perioperative deaths after thyroidectomy are highly unusual, particularly when care is provided by experienced clinicians in institutions with systematic redundancies to prevent basic errors. It is a tribute to the four surgeons involved in the care of the young subjects described by Skinner et al.⁷ that permanent postoperative hypoparathyroidism, with its attendant morbidity, was observed infrequently, and no other complications were encountered. Thus, for these 50 subjects, the “cost” of surgery was transient pain and hospitalization but little more. Elsewhere, in centers with equal expertise, however, the complication rates associated with pediatric thyroid surgery may be considerably higher, with rates of permanent hypoparathyroidism of 5 percent and of unilateral recurrent-nerve injury of 1 percent.⁸ Some groups have reported complication rates that are four to five times higher.⁹ The frequency of the more serious bilateral nerve injury or fatal hematoma is unreported.

The reported rates of complication from thyroid surgery in adults are lower than those generally reported for children, creating the sense that complication rates bear a relationship to the age of the children and the size of their cervical structures. Thus, extensive surgery on older children might carry a reduced potential for long-term morbidity. High-risk genetic mutations such as those in codons 883, 922, or 918 might justify surgery in infancy, whereas low-risk mutations such as those in codon 804 might allow postponement of surgery until the child has entered adolescence. However, reported cases of patients with mutations in codon 804 who undergo a second, somatic mutation with the development of much more aggressive disease as a toddler are of concern. Thus, the wait-and-see approach must be tempered with caution.

These considerations lead to several conclusions. First, for the time being, this complex pediatric endocrine surgery should be conducted at centers with demonstrable expert teams of surgeons, endocrinologists, anesthesiologists, geneticists, and pediatricians. To do otherwise is to put a small number of patients needlessly at risk. An integral member of such a team at most centers should be a genetic counselor who constructs family pedigrees, arranges for screening of persons at risk (information is available at www.genetests.com), and provides information and emotional support to the

patient and the family. Second, surgery should occur at the earliest age at which the team can perform it safely. In the absence of completely definitive data linking genotype to phenotype, the age at which surgery is safe is likely to be three years or younger, as more experience accumulates. The additional parathyroid-related morbidity of the central neck dissection conceivably would be avoided by thyroidectomy only at this early age. Finally, it is likely that the risks associated with surgery will never be completely eliminated. Alternative strategies deserve investigation. In particular, the development of imaging methods for tumors may help delay the surgery for some patients. Drugs to inhibit the development or growth of these tumors — which might be possible with tyrosine kinase inhibitors — hold promise for the future. Until nonoperative approaches are developed, children with this mutation appear to be best treated by early total thyroidectomy.

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