AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY DISEASE STATE CLINICAL REVIEW: TIMING OF MULTIPLE ENDOCRINE NEOPLASIA THYROIDECTOMY AND EXTENT OF CENTRAL NECK LYMPHADENECTOMY

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Abbreviations:
ATA = American Thyroid Association; **CLND** = central lymph node dissection; **Ct** = calcitonin; **HPT** = hyperparathyroidism; **MTC** = medullary thyroid carcinoma; **MEN** = multiple endocrine neoplasia

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This review article is a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with, and not a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.

INTRODUCTION

Excellent sources currently exist that offer clinical treatment guidelines for the management of medullary thyroid carcinoma (MTC) in patients with the multiple endocrine neoplasia (MEN) type 2 syndromes (1,2). These guidelines include both evidence-based recommendations and expert opinion. The current summary is a disease state clinical review addressing practical issues in the management of patients with the MEN hereditary endocrine cancer syndromes, based on available evidence as well as expert opinion and best clinical judgement. It is not intended to replace existing clinical guidelines, but is rather a concise, current review of state of the art evaluation, early diagnosis, surgical treatment, and management of the endocrinopathies arising in pediatric patients with MEN 2 syndromes.

There is a paucity of available literature regarding the management of this uncommon disorder in the pediatric population; therefore, some of the clinical management recommendations offered are necessarily based on best medical opinion. This clinical summary was prepared from a panel of expert physicians with significant experience in the management of these patients, with representation of multiple specialties. A case study model is employed to illustrate important clinical aspects within this framework. **(Endocr Pract. 2015;21:839-847)**

I. CLASSIFICATION AND RISK STRATIFICATION OF *RET* PROTO-ONCOGENE MEN 2 MUTATIONS

Hereditary MTC consists of a spectrum of disorders inherited in an autosomal-dominant fashion, including MEN 2A, MEN 2B, and familial MTC. All 3 subtypes are caused by activating missense germline mutations of the *RET* proto-oncogene (3-6). The association between genotype and MTC aggressiveness has been characterized previously by classification schemes intended to

stratify patients according to level of risk. The Seventh International Workshop on MEN in 2001 developed a genotype-based classification system and consensus guidelines for screening and timing of early thyroidectomy based on *RET* mutations (1). The American Thyroid Association (ATA) incorporated updated data and issued guidelines in 2009 that stratified mutations into 4 categories of risk (ATA risk levels A through D, see Table 1) and included the concept of safely delaying early preventative thyroidectomy with careful expectant monitoring in lower risk level A and B mutations (2). Because these previously used risk stratification schemes are currently evolving, we have chosen a simplified classification scheme including high, intermediate, and low genetic risk levels for the purposes of this clinical review.

Differences in the age of onset and clinical behavior of MTC between various *RET* mutations within the same risk level and even within the same family present a challenge for counseling patients in regards to timing of early (preventative) thyroidectomy (7-10). Mutation risk level has a lower false-negative rate than either calcitonin or ultrasound alone, but it may not predict the presence of invasive MTC on final pathology in the lower risk groups (11). A recent analysis of published cases for carriers in the lowest risk group supports a "codon-based" approach to the management of MTC but suggests that the current risk levels may need to be further optimized and that clinical data should be considered when determining the timing of early thyroidectomy (12). The highest risk group, for which thyroidectomy is recommended within the first year of life, primarily involves patients with MEN 2B. The predictive experience of MTC outcomes in MEN 2B is largely limited to *RET* codon 918 mutations, which make up >95% of cases (2,13,14). Although patients with A883F mutations share similar developmental features of ganglioneuromatosis of the gut and oral mucosa and marfanoid habitus, they may have a less aggressive MTC course than patients with a codon 918 mutation (15).

MTC is the malignant component of the spectrum of endocrinopathies that occur in patients with MEN 2. Because early detection and intervention significantly influences disease-related mortality with MTC, early thyroidectomy should be performed prior to the development of lymph node or distant metastases (1,16-18). However, additional studies are needed to better define goals for clinical management of asymptomatic carriers, optimal timing of thyroidectomy, extent of surgery, and reduction of potential complications.

Case Study 1

A 56-year-old male with newly diagnosed MTC T2N1bM0 reports no family history of thyroid cancer but does have 2 nephews in their 30s who were diagnosed with Hirschsprung disease as young children. *RET* germline testing reveals a C609Y mutation (intermediate risk group) in the index case, his nephews, and their mother (the patient's sister). The family's concerns include at what age the youngest members of this kindred should undergo genetic testing and whether positive members who are asymptomatic with no clinical findings of MTC can delay thyroidectomy.

For this family, genetic testing of potentially affected family members over the age of 5 years was recommended. The proband's adult nephews with Hirshsprung disease, along with their mother, were positive for the C609Y mutation; the young children of his nephews were negative. Based on the presence of a lower-risk mutation (intermediate group) and after individualized discussion with the patient(s), the current management includes monitoring with annual basal calcitonin and neck ultrasound and a plan to perform thyroidectomy if abnormalities develop.

II. STATEMENT OF GOALS FOR OPTIMAL CLINICAL MANAGEMENT

Inheritance of a disease-associated *RET* mutation confers a lifetime risk of developing neoplasms in a spectrum of endocrine and nonendocrine target tissues. The MTC that develops in these patients is responsible for almost all of the disease-related mortality. MTC is characterized by C-cell hyperplasia and the subsequent development of multifocal carcinoma, with a time course of progression to cancer and lymph node dissemination that varies according to the specific germline mutation present. These critical differences are the basis for the development of risk stratification categories for use in clinical management guidelines. The pheochromocytomas and hyperparathyroidism (HPT) that develop in patients with MEN 2 result in clinically important syndromes of hormone excess that require effective strategies for early diagnosis and optimal surgical management. These entities are not, however, associated with a significant malignancy risk. The HPT and pheochromocytomas are detected with standard clinical diagnostic tests, and the recommendations for the timing and appropriateness of intervention are generally based on established guidelines for patients with sporadic disease. The genetically conferred lifetime predisposition to a spectrum of endocrine neoplasms, the variable age of onset and biological behavior of the MTC, and the occurrence of these disorders in otherwise young healthy patients results in some unique considerations for management. The optimal treatment strategies would be timed to prevent thyroid cancer formation by removal of the end organ at risk (thyroid gland) prior to malignant dissemination, prevent complications or progression from disorders relating to endocrine hormone overproduction, and minimize morbidity from the therapeutic or preventative interventions.

Treatment recommendations should be based on good clinical judgment, in the context of available evidence. The C-cell neoplasia that is conferred by inheriting a *RET*

Table 1
American Thyroid Association Risk Categories for Various *RET* Proto-oncogene Mutations

				MEN 2A[b]			MEN 2B[b]		ATA risk level[c]
	Exon	Codon	FMTC[a]	MTC	PHPT	PHEO	MTC	PHEO	
Extracellular cysteine-rich domain	5	321	+	***					A
	8	515	+	***					A
		533	+	***		*			A
	10	609	+	***	**	*			B
		611	+	***	**	*			B
		618	+	***	**	**			B
		620	+	***	**	**			B
	11	630	+	***	*	*			B
		631	+						B
		634	+	***	**	***			C
		634 bp dup	–	***	**				B
		649	+	**	*				A
		666	+	***/**		**			A
Intracellular tyrosine kinase domain	13	768	+	***	*	*			A
		777	+	**					A
		790	+	***	*	**/*			A
		791	+	***	**	**			A
	14	804	+	***	**/*	*			A
		804+805	–				***	***	D
		804+806	–				***	***	D
		804+904	–		**		***		D
		819	+						A
		833	+						A
		844	+						A
	15	866	+	***					A
		883	–				***	***	D
		891	+	***	*	*			A
	16	912	+	**					A
		918	–				***	***	D

Abbreviations: ATA = American Thyroid Association; bp = base pair; dup = duplication; FMTC = familial medullary thyroid cancer; MEN = multiple endocrine neoplasia; MTC = medullary thyroid cancer; PHEO = pheochromocytoma; PHPT = primary hyperparathyroidism.

[a] Inheritance (+) of MTC without PHPT or PHEO has been described. Familial MTC (FMTC) (–) when MTC in isolation is highly unlikely.

[b] Phenotype penetrance: ***most cases, **few cases, *rare.

[c] A, may delay surgery beyond 5 years if criteria met; B, consider surgery before age 5 years and may delay if criteria met; C, surgery before age 5 years; D, as soon as possible within the first year of life.
Criteria are normal annual basal and/or stimulated serum calcitonin, normal annual neck ultrasound, family history of less aggressive MTC.

Adapted from Waguespack et al, *Nat Rev Endocrinol*. 2011;7:596-607 and Metzger and Milas, *Curr Opin Oncol*. 2014;26:51-61.

mutation in every cell represents a "field-effect" risk of the thyroid gland for subsequent development of multifocal microcarcinomas and early regional lymph node metastases. The intent of operative intervention is to extirpate the entire thyroid gland (and C-cell population) prior to the development of metastatic disease. Microscopic residual MTC is not amenable to targeted treatment with radioactive iodine ablation as are well-differentiated papillary or follicular thyroid cancers. Because MTC is not particularly sensitive to radiation or chemotherapeutic treatment strategies, complete surgical removal prior to extrathyroidal spread is paramount. This operation should be performed with the intent of meticulously removing all thyroid tissue. Furthermore, because the intervention is performed as part of a "preventative" strategy in otherwise young, healthy patients, surgery should be achieved with a very low incidence of complications. A strong argument should be offered that these patients are best managed in the context of a high-volume center and a team of physicians with prior extensive experience in and interest in these unusual hereditary syndromes. A meticulous total thyroidectomy with a low incidence of surgical complications, including permanent hypoparathyroidism and recurrent or superior laryngeal nerve dysfunction, is best performed by a surgeon with experience in this complex operation and in the decision making with respect to age of intervention and extent lymphadenectomy. Centers that manage these patients should have a systematic screening program to identify and risk-stratify patients with MEN-associated mutations to optimize therapy. The management of pediatric patients with risk of thyroid cancer is associated with both complex procedures and clinical decision making and the potential for life-long consequences from both treatment outcomes and potential complications.

The specific goals of early thyroidectomy in patients with MEN 2 are:

1. **Complete removal of the thyroid gland;**
2. **Early removal of metastatic disease and prevention of the development of lymph node metastases;**
3. **Preservation of parathyroid and laryngeal function;**
4. **Minimize morbidity of treatment and allow for satisfactory neurologic growth and development with lowest impact on psychological stress and social development;**
5. **Initiate appropriate, practical evidenced-based screening for development of associated endocrinopathies (pheochromocytoma, HPT) in patients at risk.**

III. TIMING OF PREVENTATIVE THYROIDECTOMY

MEN 2 patients that have clinically evident MTC at presentation often have extensive disease and experience a low rate of cure. In the past, newly identified MEN 2 patients underwent biochemical surveillance in attempt to detect MTC early, before the disease had spread, which did lead to some improvement in surgical cure rates. However, more recent guidelines recommend early preventative thyroidectomy for all MEN 2 patients, and in selected patients, central compartment lymphadenectomy. Early preventative thyroidectomy in infants and children is associated with the risks of recurrent laryngeal nerve injury and/or hypoparathyroidism, which may be higher in this young population owing to increased difficulty and complexity of the surgical procedure (17). This risk should not deter interventions on these patients but only serves to emphasis the need for referral to experienced centers in infants and young children requiring intervention.

A. Genotype-Based Risk Stratification

MEN 2 patients have been previously stratified into 4 risk categories based on known *RET* codon mutations (2). The *RET* mutations were grouped into categories A, B, C, and D. Category A mutations (codons 768, 790, 791, 804, and 891) carry the least risk for aggressive MTC; category B mutations (codons 609, 611, 618, 620, and 630) carry a variably increased risk; category C mutations (codon 634) carry a higher risk; and category D mutations (codons 883 and 918) have the highest risk (2). These categories can be simplified into **high** (category D), **intermediate** (categories C and B), and **low** (category A) risk groups for clinical applications, and we will utilize this simplified classification for the purposes of the discussion in this clinical review.

B. Management Recommendations According to Risk Level

The high-risk group, comprised of all MEN 2B patients, has a highly aggressive form of MTC even when early thyroidectomy is performed shortly after birth. A number of *RET* codon 918 mutation (MEN 2B) patients have been identified with clinically evident MTC before 13 months of age, including a 3 month-old infant with lymph node metastases and a 2.7-year-old with distant metastases (19-22). Due to the aggressive and early onset of MTC in these patients, we recommend that MEN 2B patients undergo early preventative thyroidectomy with central lymph node dissection (CLND). Review of the current evidence and recommendations for performing CLND is

discussed in section IV below. Judicious surgical decision making must be employed to achieve the goal of removing the regional (central) lymph nodes at risk at the initial procedure, while maintaining excellent surgical outcomes. For these reasons, this treatment should be ideally performed at an experienced endocrine surgery center. Operative intervention is recommended as soon as the diagnosis is made, even if in the first months of life, but definitely within the first year. All patients should have a cervical ultrasound performed upon diagnosis and a serum calcitonin (Ct) level if diagnosed after 6 months of age (Ct may be difficult to interpret due to limited evidence for appropriate reference values in healthy children under the age of 1 year) to assess for possible locoregional spread (22).

MEN 2A patients with a *RET* mutation in codon 634 (intermediate group) have an increased risk for early onset MTC compared to other MEN 2A patients. Previously, MTC has been reported in patients as early as 15 months (20) and 17 months (23). The earliest reports of MTC were in 3 patients with a codon 634 mutation that underwent thyroidectomy between 10 and 12 months of age and were noted to have MTC at the time of surgery (22). The focus of the cancer was small, and there was no clinical evidence of nodal metastases in these patients. However, a Chinese study reported 8 years of age as the earliest presentation of MTC their cohort of patients with codon 634 mutations (24,25). We recommend that MEN 2A patients with a codon 634 mutation undergo early thyroidectomy and CLND (see section IV below) before 5 years of age, with strong consideration to performing thyroidectomy as young as 1 year of age in an experienced tertiary center and after discussion with the family. At a minimum, annual neck ultrasound as well as basal and stimulated serum Ct levels should be performed starting at 3 to 5 years of age or earlier.

There is more variation in age at presentation for the remaining patients with MEN 2A mutations in the intermediate group. As the youngest reported patients were 7 years of age (codons 611 and 618) (20,26-28), we recommend that early preventative thyroidectomy be strongly considered before the age of 5 years in patients with ATA risk-level B mutations *with* or *without* CLND (see section IV below). However, due to the varying level of aggressiveness in these mutations, consideration can be given to strict monitoring with annual neck ultrasound as well as basal and stimulated serum Ct levels starting at 3 to 5 years of age and delaying thyroidectomy beyond 5 years of age based on family preference and the presence of a less-aggressive MTC family history.

All remaining MEN 2A mutations fall in to the lowest-risk group. These patients have lower serum Ct levels, lower tumor stage, and higher rates of biochemical cure when they undergo thyroidectomy after 4 years of age (16). Although MTC does not present as early in these patients, it is still optimal to perform a preventative thyroidectomy prior to development and/or spread of MTC, so one must weigh the risks of early thyroidectomy versus the risks of delaying surgery, possible loss to follow-up, and the development of MTC (29). The youngest patients reported with MTC based on these codon mutations have been 12 years (codon 790), 13 years (codon 891), 15 years (codon 630), and >20 years of age (codons 791 and 768) (1,20,30). Based on available evidence and best clinical judgement, we recommend that at a minimum, these patients should be monitored very closely, with annual neck ultrasound as well as basal and stimulated serum Ct levels starting at 3 to 5 years of age. Early preventative thyroidectomy may be delayed beyond 5 years of age depending upon the above assessments, family history, and family preference, with intent to perform preventative thyroidectomy prior to the expected subsequent development of thyroid cancer. The need to perform CLND may be individualized based on patient and family factors as well as expert opinion and assessment of ongoing risk.

Summary: Primary Thyroidectomy

1. **In patients with highest risk, an early preventative thyroidectomy should be performed as soon as possible shortly after birth, optimally within the first year of life.**
2. **In patients with intermediate risk, an early preventative thyroidectomy should be performed within the first 5 years of life, especially for patients with codon-634 mutations. For patients with other mutations in the intermediate-risk group, more variable behavior is possible and timing can be individualized.**
3. **In patients with the lowest risk, monitoring should be performed in years 3 to 5 and preventative thyroidectomy can be offered after 5 years of age, depending on the exact clinical parameters.**

IV. EXTENT OF CERVICAL LYMPHADENECTOMY FOR EARLY PREVENTATIVE THYROIDECTOMY

In patients with hereditary MTC, age-related progression of malignant disease occurs, with lymph node and distant metastases typically occurring years after the onset of tumorigenesis. In the current era of genetic testing, a presymptomatic identification of a *RET* mutation with identification a particular mutation can be used to estimate the clinical features, such as risk of malignancy, lymph node involvement, distant metastases, and age of presentation of MTC (17).

The magnitude of the surgical intervention should be appropriate to the age-related cancer risk based upon genotype and basal serum Ct levels and should avoid exposure to risk of long-term complications, specifically permanent

hypoparathyroidism and laryngeal nerve dysfunction (1). Important issues related to the optimal timing of surgical intervention include technical challenges of performing thyroidectomy in the smallest pediatric patients, including parathyroid gland identification and preservation of recurrent laryngeal nerve function.

CLND, which is defined as a systematic removal of all lymphatic tissue in the perithyroidal space between the jugular veins from the hyoid bone to the thoracic inlet, may accompany a preventative thyroidectomy. CLND for MTC in MEN or in sporadic cases has been quite varied in the extent of dissection and extirpation of lymphatic tissue in the bilateral neck or ipsilateral central neck. As recurrence in MTC is most likely in the central-neck compartment, we emphasize to the surgeon the need for a systematic excision of all lymphatic tissue in the central-neck compartment and the need to avoid a partial lymphadenectomy. Inadequate nodal clearance may lead to future recurrence and a need for re-operation, with associated additional risks of surgical complications. The systematic removal of lymph nodes should apply to all patients undergoing therapeutic thyroidectomy with MEN and existing MTC. Based upon evidence and expert opinion, the following general recommendations have been established for performing a CLND along with an early preventative total thyroidectomy.

Summary: Primary Central Lymph Node Dissection

1. **In patients with highest risk, an early preventative thyroidectomy *should* be accompanied by a routine CLND. These patients are the most likely to have lymph node metastases even with small tumors, and they have been documented in the first year of life (22,31).**
2. **In patients with intermediate risk, an early preventative thyroidectomy *should* optimally be accompanied with a routine CLND, based on individual patient factors and expert clinical judgement. These patients often have an occult MTC on final pathology. A few patients have lymph node involvement with recurrence and also have elevated Ct levels in long-term follow-up, particularly in patients >8 years of age. Although no lymph nodes with metastatic disease were identified in any patient series, codons 618 and 620 were associated with recurrence in one series (17).**
3. **In patients with the lowest risk, an early preventative thyroidectomy does not require a routine concomitant CLND, but this may still be considered based upon patient or surgeon preference and other factors. The risks of CLND may outweigh the benefit and may increase complications from treatment.**

Case Study 2

A 4-year-old presented with known family history of MEN 2A, with a C611F mutation (intermediate risk). Eight family members had previously undergone a therapeutic total thyroidectomy. In the kindred, 2 members had a known recurrence and they required re-operative surgery. One member had a pheochromocytoma and another had HPT. The patient's thyroid ultrasound was normal, serum calcium was 9.2 mg/dL, serum parathyroid hormone was 34 pg/mL, and basal serum Ct level was 16 pg/mL. After evaluation and discussions with a pediatric endocrinologist, surgery was recommended. During discussions with the parents of the patient, the predominant issues were safety and decreasing the lifetime risk of recurrence if MTC was found. A total thyroidectomy with bilateral CLND and autotransplantation of 1 parathyroid gland into the sternocleidomastoid muscle was performed. Pathology identified C-cell hyperplasia, and 14 benign lymph nodes were resected. Postoperatively, the patient has normal calcium, parathyroid hormone, and Ct levels.

V. MANAGEMENT OF THE PARATHYROID GLANDS DURING PREVENTATIVE THYROIDECTOMY FOR PATIENTS WITH MEN 2

Clinical Features of Hyperparathyroidism in MEN 2

In contrast to the thyroid and adrenal glands of patients with MEN 2, the parathyroid glands develop abnormalities more infrequently. The prevalence of HPT is estimated to be 20 to 30% in MEN 2A and is associated most commonly with *RET* mutations in exon 11 (codon 634, and less frequently, codons 611, 618, 620, and 630). Unlike sporadic primary HPT, parathyroid disease as part of MEN 2A is more frequently asymptomatic. The majority of patients with MEN 2 and HPT are diagnosed before age 39, nearly 2 decades sooner than sporadic disease. Finally, and seemingly inconsistent with the concept of a germline genetic disorder, parathyroid disease in MEN 2A is not always multiglandular. Single adenomas, asymmetric and asynchronous multigland disease, and unusual patterns of ectopic and supernumerary glands have been described.

These characteristics influence the surgical management of parathyroid glands during preventative thyroidectomy for patients with MEN 2A. This topic has been controversial owing to the rarity and complexity of MEN 2 and paucity of outcome studies. Variable but significant rates of both permanent hypoparathyroidism (9 to 25%) and recurrent HPT (0 to 28%) are reported in the literature (32-39), regardless of surgical approach. This precludes advocating a uniform operation for parathyroid glands at the time of preventative thyroidectomy. These unique considerations

also underscore the need for treatment at experienced centers that individualize the extent of surgery based on genotype (*RET* codon mutation) and have experience in the surgical identification and preservation of parathyroid glands in pediatric patients. It is also optimal that the surgery be performed by a team that is experienced in performing heterotopic autotransplantation and in cryopreservation of parathyroid tissue in order to salvage patients at risk for postoperative hypocalcemia. For patients who develop transient postoperative hypocalcemia, it is important to treat and correct hypomagnesemia concurrently with the hypocalcemia.

Genetic Risk Assessment for Later Development of Hyperparathyroidism, and the Role of Autotransplantation

The realization that only specific *RET* mutations result in a significant lifetime risk for HPT has resulted in recent advocacy for less extensive operations and selective parathyroidectomy when appropriate. The ideal surgical approach would be one that cures concurrent HPT, preserves parathyroid function, minimizes the risk of recurrent HPT, and limits complications from necessary subsequent interventions. Twigt and colleagues (33) summarized the literature favoring a selective and less-aggressive surgical approach, with preservation of vascularized parathyroid glands in situ for most patients.

A few practical points can be shared in hopes of achieving ideal results in the current era. First, a surgeon should be experienced with in situ parathyroid preservation. Few illustrated or video-based resources are available to demonstrate these specific aspects of surgical technique, which must frequently be individualized to the patient. The general admonition would be to maintain delicate tissue handling, patience, and meticulous effort to save the vascular pedicle to a parathyroid gland. The surgeon should optimally also have the capability of parathyroid cryopreservation (34) and familiarity with autotransplantation. Several excellent technical descriptions have recently been published and vary little from the original and effective method described by Wells et al (35,36). The key principle is that excised parathyroid glands are minced into 1- to 3-mm fragments and then implanted in sufficient aggregate quantity (30 to 50 mg) in discrete muscle pockets to optimize revascularization. Second, the identification of patients who can avoid central neck dissection with the preventative thyroidectomy would also help avoid potential hypoparathyroidism, especially with regard to preserving the vascular supply to the inferior parathyroid glands. This decision is based on the *RET* codon mutation and known risk assessment for metastatic MTC based on genotype-phenotype patterns. Finally, genetic assessment (based on *RET* codon mutation assessment) for the risk of developing of primary HPT may be used to decide which patients need parathyroidectomy at all, and if so, what extent of resection.

It should be emphasized, however, that expertise in performing autotransplantation is essential in the management of selected patients. For some technical challenges which may be encountered, this technique may represent the best surgical option. Preservation of viable, vascularized parathyroid glands in the neck may not be possible or practical in all patients, and the following points may influence the decision to perform autotransplantation: (*1*) during comprehensive total thyroidectomy and central lymphadenectomy (level VI) for MTC, it may be difficult to preserve parathyroid glands (especially the inferior glands) and achieve an adequate clearance of the central paratracheal lymphatics; (*2*) in very young pediatric patients, parathyroid gland identification can be very challenging, even for an experienced surgeon, and in some cases, the number and potential viability of the parathyroid glands identified definitely at the time of operation may be limited, requiring consideration for autotransplantation of those glands that have been found if their viability is in question; and (*3*) some *RET* mutations do confer a variable risk of subsequent development of HPT, and revision neck surgery to remove such hyperfunctioning glands is associated with incremental difficulty and increased risk of complications. These considerations impact surgical decision making for individual patients and may form the basis for selection of the most appropriate extent of parathyroid resection. As for many of the aspects of surgical management in these challenging patients, these decisions require experience and judgment by the operating surgeon.

Table 1 summarizes known genotype-phenotype associations related to parathyroid disease in MEN 2A.

Case Study 3

A 12-year-old boy undergoes genetic testing and is found to have a *RET* codon-634 mutation. He has no palpable thyroid nodules and an undetectable basal Ct level. At the time of total thyroidectomy, all 4 parathyroid glands are identified, and he is noted to have asymmetric enlargement of only the 2 upper parathyroid glands. A complete central (level VI) lymphadenectomy is performed. The parathyroid glands are managed with a total parathyroidectomy and forearm autotransplantation. Cryopreservation of a portion of the parathyroid tissue is also performed.

The decision to perform a total parathyroidectomy and autotransplantation in this patient was influenced by the presence of a codon-634 mutation (which carries a higher risk of parathyroid disease), the presence of multiglandular disease, and the potential difficulties of preserving adequate vascularized parathyroid tissue during a complete central zone cervical lymphadenectomy. Avoidance of permanent hypoparathyroidism is an important component of any surgical treatment for medullary carcinoma in MEN2,

and the management of the parathyroid glands must be appropriate to the clinical setting. Selective parathyroidectomy and preservation of vascularized parathyroid tissue in the neck is appropriate for many patients. Examples include patients with *RET* mutations conferring a very low risk of the development of parathyroid disease, patients with a single enlarged parathyroid gland, or in cases in which a lymphadenectomy is not performed.

CONCLUSION

In summary, a single operative strategy for parathyroid management at the time of preventative thyroidectomy that can be uniformly advised for all patients with MEN 2A remains elusive. Genetic risk assessment is crucial because it identifies families with a strong chance of HPT (31,37-39). Preserving parathyroid gland function (especially during central lymphadenectomy) to avoid permanent hypocalcemia is paramount.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

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