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Full Length Research Paper

Management of syndromic and familial medullary thyroid carcinoma

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Medullary thyroid carcinoma is rare but has a high mortality rate, especially when the source is genetic inheritance. Multiple endocrine neoplasia and familial cancer syndrome have a spectrum of symptoms that determine interventions depending on tumor aggressiveness. A comprehensive data review was prepared using recent articles from PubMed written in English language about hereditary medullary thyroid carcinoma, surgery and follow-up of these patients. The genetic basis of syndromes that involve medullary thyroid carcinoma was confirmed, and guidance was developedfor surgical management with a focus on early diagnosis and treatment.It is essential that we characterize the type of medullary carcinoma for each patient. Early surgery and restricted follow-up maylead to better oncologic outcomes.

Keywords: familial medullary thyroid carcinoma, multiple endocrine neoplasia, syndromic medullary thyroid carcinoma, prophylactic thyroidectomy.

INTRODUCTION

Medullary thyroid carcinoma (MTC) is a malignant neuroendocrine tumor of parafollicular C cells in the thyroid gland. It is a heterogeneous tumor that may be stable for many years or become a highly malignant tumor. MTC accounts for 3% of all thyroid cancers and 14% of deaths related to thyroid cancer in general. It can be sporadic or hereditary/syndromic. We will discuss hereditary/syndromic MTC, which accounts for 25% of all

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cases of MTC (Chen et al., 2010).

MTC is caused by a single germline mutation in rearrangement during transfection of theRET proto-oncogene. In 1991, the RET gene was found on chromosome 10q11.2, which encodes a transmembrane receptor tyrosine kinase (Donis-Keller et al., 1993). While sporadic MTC usually presents as a unifocal clone of a population of tumor cells, hereditary MTC is typically bilateral and multifocal (Pinchot et al., 2008).

More than 100 different germline RET mutations were identified in families with familial MTC (FMTC). The most affected codons were 609, 611, 618, 620 (exon 10), 634 (exon 11),the rich domain extracellular cysteine and codon 768 (exon 13) and codon 804 (exon 14) of the intracellular domain tyrosine kinase (Carlomagno, 1997; Cosci, et al., 2011).

The germline mutations were found in 98% of MEN2A, 95% of MEN2B and 88% of families with FMTC. In MEN2A, the mutation at codon 634 accounts for 85% of all mutations found, and a replacement of cysteine by arginine (C634R) is the most common amino acid substitution (50%). Mutations of codons 609, 611, 618 and 620 (exon 10) account for 10 to 15% of the remaining mutations. In MEN2B, 95% of patients have a substitution of methionine for threonine at codon 918 (M918T) in exon 16, and RET mutation A833F (exon 15) affects 2 to 3% of patients (Clayton, 1996; Miyauchi, 1999).

Both MEN2B syndrome and FMTC are inherited in an autosomal dominant pattern. More than 1000 families with these endocrinopathies have been identified worldwide.

In MEN2A, MEM2B and FMTC, the changes are activated unlike other hereditary syndromes. They are associated with DNA damage repair or inactivation of suppressor genes. The recent discovery of somatic mutations in HRAS, KRAS and MRAS, which occur in 10-45% of sporadic MTC cases, suggested an alternative molecular pathway for the development of this malignancy (Moura, 2011; Ciampi, 2013).

Through proper literature analysis, this article shows the genetic aspects for defininghereditary syndromes related to MTC and discusses the information necessary to make a decision about surgery and follow-up of this rare illness.

MATERIALS AND METHODS

An extensive data review was conducted on PubMed with descriptors for hereditary medullary thyroid carcinoma, early surgery and follow-up of these patients.Some articles discussedthe history and definition of MTC. Additionally, other papers exposed new nomenclatures and classifications according to the aggressiveness of the manifested symptoms. Therefore, adoption of new directions for surgical management was suggested.

RESULTS

Clinical manifestations of MEN2A, MEN2B and FMTC

MEN2A is responsible for 80% of MTC hereditary syndromes. Of all patients who have MTC, 50% develop pheochromocytoma and 25-30% present with hyperparathyroidism, depending on the RET codon mutation. Patients with MEN2A can also develop cutaneous lichen, amyloidosis, and Hirschsprung's disease. Pheochromocytoma will develop in approximately 50% of patients with MEN2A and MEN2B. The average age at first appearance of pheochromocytomas was 36. Pheocrhomocytomas are usually benign and confined to one adrenal gland. In 65% of cases, pheochromocytomas can turn of multicentric and bilateral. Patients with pheochromocytomas develop one-sided contralateral pheochromocytoma within an estimated period of 10 years (Schuchardt et al., 2006; Jain et al., 2009).

Pheochromocytoma has significant morbidity and mortality. Therefore, in MEN2A and MEN2B patients, it is important to remove pheochromocytomas before thyroid surgery. Metanephrines should be measured in the plasma and urine, and tests such as computed tomography and magnetic resonance imaging should be requested to diagnose adrenal masses (Lenders et al., 2006).

Unilateral adrenalectomy is indicated in the presence of a unilateral pheochromocytoma. For a bilateral pheochromocytoma, both adrenals are resected with the patient receiving corticoid treatment throughout the operation. The standard treatment is laparoscopic, and subtotal adrenalectomy is also widely used to preserve the function of the adrenal gland (Lairmore et al., 1993; Scholten et al., 2011).

Hyperparathyroidism develops in 25-30% of patients with MEN2A. Hypercalcemia is mild, and 85% of patients are asymptomatic. The parathyroid size varies greatlyand can affect 1 to 4 glands, and the most affected histological pattern ispseudonodular hyperplasia. In MEN2A, surgical treatment of hyperparathyroidism rangesfrom simple resection of the single enlarged gland (with measurement of intraoperative PTH) to subtotal resection of the four glands, leaving a remainder of a single gland or performing a heterotopic autotransplantation (Yoshida et al., 2009; Scholten et al., 2011).

Cutaneous lichen with amyloidosis occurs in 10% of families with MEN2A, which affects scapular region primarily, with intense itching due to amyloid deposits (Nunziata et al., 1989; Gagel et al., 1989).

Hirschsprung's disease can occur in patients with MEN2A and FMTC characterized by failed neural crest cell migration, proliferation and differentiation in the intestinal submucosa (Meissner), myenteric (Auerbach) and deep submucosa (Henle) in the intestinal plexuses.

Table 1. Clinical Rating MEN2 and FMTC, and the occurrence of MTC associated with tumors and other diseases.

Subtype	Percentual	Start (age)	FMTC%	PHEO%	HPT%	Diseasesassociated
MEN2A	56	10	100	50	25	Linquen cut., amyloid, Hirschsprung´s disease
MEN2B	9	2	100	50	-	Neuromas, marfanoid habitus
CMT	35	30	95	-	-	Rare

MTC = medullary thyroid carcinoma; FEO = pheochromocytoma; HPT = hypoparathyroidism.

The main RET mutation is inendothelium receiver 3 (Amiel et al., 2008).

MEN2B accounts for 5% of hereditary MTC,and 50% will develop pheochromocytoma, presenting with marfanoid habits, eye abnormalities, musculoskeletal abnormalities, and general neuromas. Over 90% of patients will develop symptoms such as abdominal pain, constipation, diarrhea and megacolon (Smith et al., 1999; Cohen et al., 2002).

It is important that the physician who first attends to a child with MEN2B is very careful because this syndrome is highly aggressive and thyroidectomy performed at the right time can be curative (Sanso et al., 2002; Camacho et al., 2008).

Family thyroid medullary carcinoma accounts for 15% of MTC cases. In 1968,Stener described a family with MTC, pheochromocytoma and Cushing's syndrome. They suggested the name MEN2.

Fardon described FMTC. Originally, it was necessary that 10 family members be affected with MTC or have a mutation for more than 50 years as well as an appropriate medical history, and it was necessary to exclude pheochromocytoma and hyperparathyroidism (Farndon et al., 1986).

A less rigid definition is the presence of at least 4 family members with MTC and no other MEN2A manifestation. Defining and distinguishing these two entities has been a challenge with much controversy because the early characterization of a FMTC may have been a failure to identify a pheochromocytoma. This is well illustrated in families with the RET mutation G533C in exon 8. In 2003, a large family in Brazilhad six generations with this mutation, including 76 members who were only carriers of the gene (29 with MTC and none with pheochromocytoma or hyperparathyroidism), and this family wasdescribed as having FMTC (Da Silva et al., 2007).

Currently, the majority of clinical investigators agree that FMTC cannot be framed as a single syndrome. They believe it should be a spectrum of diseases correlated with MEN2A syndrome. The ATA (American Thyroid Association) notes that FMTC cannot be defined as a distinct hereditary syndrome from MEN2A or MEN2B.

Therefore, FMTC must be rearranged as a variant of MEN2A to include families that have only MTC.With unique FMTC criteria, small families with at least two generations, but less than 10 generations, with germline mutations in RET and one single generation with at least two members with a RET germline mutation should be included in the spectrum.

Thus, there should be two MEN2 syndromes: MEN2A and MEN2B. Within MEN2A, which accounts for 95% of MEN2 cases, patientscan be divided into four variants:

1. MEN2A - MTC, less frequent pheochromocytoma and hyperparathyroidism or both;
2. MEN2A - sameasnumber 1but associated with cutaneous lichen and amyloidosis;
3. MEN2A - with Hirschsprung's disease;
4. MEN2A - with FMTC (families with germline mutations of MTC, but no evidence of pheochromocytoma or hyperparathyroidism yet) (Wells Jr et al., 2015).

Classification and risk criteria for MTC and syndromic patients

The North American Neuroendocrine Tumor Society, The National Comprehensive Cancer Network and the American Thyroid Association (ATA) have published guidelines for disease behavior in patients with FMTC. The terms used were levels I, II, and III or high, very high and higher to designate progressive increases in the aggressiveness of MTC (Tuttle et al., 2010; Chen et al, 2010).

Aggressiveness is based on the development of MTC at younger ages and the appearance of metastases. The ATA used the letters A, B, C, and D according to the increasing degree of aggressiveness. This categorization has created some confusion.Therefore, in 2015, the ATA created a task force to reformulate these criteria:

ATA-HST (category D): includes patients with MEN2B and RET M918T mutated codon;

ATA-H (category C): includes patients with mutations in the RET codon C634 and RET codon A883F;

ATA-MOD (category A and B): all other different mutations of the aforementioned conditions. (Example: G533C, C609F, C611F, C620F, C630, D631, K666E, E768D, L790F, V804L, 5891A) (Wells SA Jr et al, 2015).

MTC Diagnostics

In general, the measurement of serum levels of calcitonin, especially after secretagogues stimuli such as calcium or pentagastrin or a combination of the two, serves as a primary evaluation or screening for family members at risk for FMTC. Since the introduction of detection analysis for the RET mutations, the two methods above are rarely used (Wells Jr, 1978). The reference values for basal serum calcitonin are <10 pg / ml for men and <5pg/ml for females.

In new families with hereditary MTC where the state of RET is unknown, the strategy used to diagnose at-risk members is to sequence the most commonly affected exons. If negative,the remaining exons are sequenced. If no mutation is found, all of the genes need to be tagged (Elisei et al., 2007). Most laboratories do sequencing exons 10, 11 (C609, C611, C618, C620, C630, C634), 13, 14, 15 and 16. Some laboratories sequence exon 8. Prenatal diagnosis is offered in some laboratories using COLD-PCR combined with HRM (high resolution melting), which is an analysis that can reach 100% accuracy (Macher et al., 2012).

Patients with the MEN2B phenotype should be tested for RET mutation M918T (mutation of exon 16), and if the test is negative, clinicians should investigate RET mutation A883F (exon 15). If no mutations are found, all RET codons must be examined (Raue et al., 2012).

Genetic counseling

Genetic counseling and genetic testing for germline mutations should be offered to:

a) 1st degree relatives of patients with proven FMTC;

b) Parents whose children have FMTC;

c) Patients with cutaneous lichen and amyloidosis;

d) Children and young people with Hirschsprung's disease and germline mutation in exon 10 RET and adults with MEN2A and mutation in exon 10 who have symptoms suggestive of Hirschsprung's disease (Wells Jr et al., 2015).

Patients with thyroid noduleswhose fine-needle aspiration (FNA) ispositive for MTC, will require a differential diagnosis for papillary thyroid carcinoma, follicular thyroid carcinoma, paraganglioma and eventually sarcomas and lymphomas. MTC expressed cytokeratin A, but the most important markers are calcitonin (CTN) and CEA. The immunocytochemistry or immunohistochemistry when the tumor is very undifferentiated can be reduced to CTN and positive for CEA (Mendelsohn et al., 1984).

Therefore, patients with MTC who had no family history should have direct analysis of their DNA from blood cells to detect germline mutations in RET. If hereditary MTC does occur, one must search for pheochromocytoma and hyperparathyroidism as well as determining the expression of CTN and CEA.

With calcitonin levels lower than500 pg/ml, the patient is less likely to have distant metastases. Ultrasonography is the best test for neck, thyroid and cervical lymph nodes. A CT scan should be used to diagnose lung metastases and mediastinal. For diagnosis of liver metastasis, computed tomography in 3 phases or contrast resonance are the most sensitive tests. Bone scintigraphy and axial magnetic resonance are the most sensitive tests for bone metastasis. The compounds 2-18F-fluoro-deoxy-D glucose (FDG) and F-dihydroxyphenylalanine (F-dopa-PET / CT) are less sensitive for detecting metastasis (Giraudet et al., 2007).

Importantly, CTN levels may be predictive of cervical metastases. Normal levels are under than 10pg/ml. If the patient has a CTN level<20pg/ml, the chance of metastasis is very low. Levels above 20, 50, 200 and 500pg/ml reflect central lymph node metastasis, central and ipsilateral side (II, III, and IV); central and contralateral side; and superior mediastinum (Elisei R et al., 2012). Even in the absence of lymph nodes with CTN>20 pg/ml, the neck should be examined closely for metastasis.

Prophylactic thyroidectomy in children with hereditary MTC

The main criteria to indicate a prophylactic surgery in a patient with a hereditary cancer syndrome are:

1. The genetic mutation is caused by complete or nearly complete penetrance;

2. There is an extremely reliable test to detect the mutation;

3. The organ at risk is dispensable or otherwise unneeded and there is a replacement therapy organ function;

4. The organ can be removed with minimal morbidity and no mortality;

5. There is a test to determine whether the surgery was curative.

We will use the term prophylactic for thyroid removal before the development of MTC or removal when MTCis "silent" and restricted to the gland. Currently, the biggest question is not whether prophylactic thyroidectomy should be performed, but when it should be executed.

Table 2. Management patients RET mutations

Characteristic	Codons: 321, 515, 533, 600, 603, 606, 635, 649, 666, 768, 776, 790, 791, 804, 819, 833, 844, 861, 891, 912	Codons: 609, 611, 618, 620, 630, 631	Codons: 634, 883	Codon: 918
Category ATA	MOD	-	H	HST
MEN2 subtype	FMTC	FMTC/MEN2A	MEN2A	MEN2B
MTC: aggression	Moderate	High	High	Highest
MTC: age of onset	Youth/adult	5years	< 5 years	First months
Profilactic thyroidectomy	CTN lifting , 5-10 years or familiar desire	5years	< 5 years	First months
Search pheochromocytoma	≥16 years	≥16 years	≥11 years	≥11 years
Search hyperparathyroidism	≥16 years	≥16 years	≥11 years	≥11 years

MOD = moderate risk of aggressiveness of medullary thyroid carcinoma; H = high risk; HST = very high risk; CTN = calcitonin.

DISCUSSION

Regarding aggressivenessand the starting age of tumor manifestations, large differences can be noticed not onlyfordistinct families with the same RET mutation (except for mutations at codon 634 and 918) but also within families with the same genotypic expression.

The decision of which age prophylactic thyroidectomy must be performed will not be based only on the direct analysis of the patient's DNA but also the stimulatedCTN serum levels.The thyroidectomy should be performed on MTC when CTN starts to increase above 5 years of age orthere is an abnormal ultrasound, and a rigorous assessment should be conducted every 6 months. If the parents are very concerned, this procedure should be performed at 5 years of age. However, it should be taken care when dealing with very young children, especially children under 2 years old, due to the risk of causing hypoparathyroidism (Elisei et al., 2012).

Children with MEN2A and the RET mutation in codon 634 (category ATA-H) usually develop MTC in the early years of their life. Therefore, physical examination, ultrasound and measurement of CTN should begin when children are 3 years old. ATA-MOD, however, is less aggressive than ATA-H,and individuals with this mutationtypically develop MTC at a later age.If CTN is below 40 pg/ml, total thyroidectomy without neck dissection is an appropriate therapy. This surgery, especially in the ATA-H, should be carried out at 5 years of age or earlier. Children with ATA-MOD who are closely monitored and have low CTN may postpone thyroidectomy (Skinner et al., 2005).

In patients with MEN2B and mutation M918T in the RET codon (ATA-HST), MTC is highly aggressive, and thyroidectomy should be considered as soon as possible. These children should have their thyroidectomies in the first year of life and, if possible, in the first month. CTN levels are very high in the first month of life, and the parathyroid glands are difficult to identify. In the absence of suspicious lymph nodes, the surgeon must performcentral emptying if the parathyroid glands can be found.

It is important to note that only 25% of patients with MEN2B know at birth that they are carriers of this mutation, and 75% have a mutation in RET with phenotypically normal parents.As such, the diagnosis is often made later (Leboulleux et al., 2002).

A patient who is not diagnosed with pheochromocytoma and is going to undergo a thyroidectomy is at serious risk for potential mortality. Therefore, for MTC, it is crucial to exclude pheochromocytoma through the measurement of urinary or plasmametanephrines, abdominal CT or MRI are important as well. In the presence of a single pheochromocytoma during MTC surgery, unilateral adrenalectomy is sufficient. Contralateral pheochromocytoma will develop over a period of 10 years. If bilateral, the risk of Addison's syndrome must be taken into account, and some surgeons have preferred adrenalectomy that maintains 10 to 15% of adrenal function.However, corticosteroids should be provided before, during and after surgery. The recurrence is 20% within 10 years following this procedure. Screening for pheochromocytoma should be started at age 11 with children who have ATA-H and ATA-HST and at 16 with children who have ATA-MOD (Thosani et al., 2013).

The investigation of hyperparathyroidism (HPT) should start at age 11 in ATA-H patients and age 16 in-ATA MOD patients.The investigation should include measuresof calcium corrected by albumin, ionized calcium, total calcium and PTH.

HPT will occur in patients with a mutation in the exon 11 codon and will occur more often in codon 634 and less frequently in exon 10. HPT is lighter and asymptomatic in MEN2A (Carling et al., 2005).

Treatment options are: A) subtotal parathyroidectomy, leaving 1 gland; B) Total parathyroidectomy with an autograft of small portions of the less-affected gland in the forearm or sternal region; C) resection only of the increased gland with intraoperative monitoring of PTH

(most adopted procedure) (Scholten et al., 2011). Patients who develop HPT after thyroidectomy for treatment of MTC should have the same conduct described above.

Patients should be evaluated for the first 6 months with physical examination and tests for CTN and CEA levels. If the levels of these two markers are undetectable within a period of five years, there is no need for further studies, and patients could be followed annually. The time at which the values of these markers doubled was very important. If the level of CTN doubled between 6 months and2 years, survival at 5 and 10 years was 92 and 37%, respectively, whereas if CTN doubled in less than 6 months, the survival rate at 5 and 10 years was 25 and 8% (Miyauchi, 1984). CTN and CEA are strongly correlated, but CEA can rise without CTN change. If CTN was 150 - 200 pg/ml, for example, and TC showed nodes in a neck dissection, but there was no evidence of lymph nodes, compartmental emptying is only curative for 30% of patients (Tisell et al., 1986).

The development of distant metastases will cause a drastic drop in patient survival. Survival at 1 year was 51%, 26% at 5 years, and 10% at 10 years. Response to treatment with chemotherapy waspoor, ranging from 10 to 20%. Doxorubicin is the most used and approved drug (Scherübl et al., 1990).

Radioimmunotherapy directed with biospecific monoclonal antibodies (for example I^{131}-conjugated antibodies against CEA) has shown promising results in clinical trials, but there has been no phase III prospective randomized study (Chatal et al., 2006).

Molecular targetedtherapies, particularly of tyrosine kinase inhibitors, have been studied. Several studies have shown responses ranging from 2 to 50%. Two examples include vandetanib and cabozantinib, which were evaluated in randomized phase III prospective double-blind studies. They showed significant improvement in disease-free survival compared to placebo and wereapproved by the FDA (Federal Drug Administration) for advanced MTC treatment (Wells et al., 2012; Schoffski et al., 2012).

CONCLUSION

According to the literature,it is fundamental knowing and applying the association between genotype and phenotype in clinical practicefor patients with medullary thyroid carcinoma. All evidence suggests that surgery is the only potentially curative treatment for these patients, and surgery should be performed as early as possible.In the hands of experienced surgeons, the progression of the disease can be changed. Potentially fatal cancer turnsinto a curable disease.

We hope that the continued advances in biotechnology and the amount of existing genomic information will allow for tracking of new drugs, new treatments, development of new classes of molecular targeted therapies, and better control of this disease and other hereditary diseases in an era of personalized medicine.

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