REVIEW

IMPACT OF RET PROTO-ONCOGENE ANALYSIS ON THE CLINICAL MANAGEMENT OF MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

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Multiple endocrine neoplasia type 2 (MEN2) is an autosomal dominant disease characterized by the presence of medullary thyroid carcinoma, primary hyperparathyroidism, and pheochromocytoma. Multiple endocrine neoplasia type 2 is still an underdiagnosed, or late-diagnosed condition in many areas of the world. Since 1993, when the first missense RET proto-oncogene (RET) mutations were reported in MEN2, up to 46 different RET-causing disease mutations have been described. Since a strong genotype-phenotype correlation exists for MEN2, the detection of RET mutations has produced a major impact in early recognition and treatment of MTC and MEN2. Presently, RET mutation analysis should be performed for all MEN2 cases and their at-risk familial relatives. Further, prophylactic total thyroidectomy is indicated in all cases harboring activating gametic RET mutations.

In most RET mutation carriers, prophylactic total thyroidectomy is indicated at ages as early as a few months to 4 years of age, promoting longer survival and improvement of quality of life or even definitive cure. We discuss the large impact of RET proto-oncogene analysis on the clinical management of MEN2 and the role of early RET molecular DNA diagnosis in providing clinicians and surgeons with valuable information that enables them to indicate early total thyroidectomy.

KEYWORDS: Endocrine Neoplasia. MEN2. RET proto-oncogene. Pheochromocytoma. Hyperparathyroidism. HSCR. MTC. FMTC.

INTRODUCTION

Multiple endocrine neoplasia type 2 (MEN2) is associated with the occurrence of 3 inherited endocrine tumors: medullary thyroid carcinoma (MTC), primary hyperparathyroidism (HPT), and pheochromocytoma (PHEO). Multiple endocrine neoplasia type 2 is transmitted by an autosomal dominant gene, which imposes the need of genetic screening of all family members at risk having inherited a predisposition to this condition. The 3 neoplasias involved are derived from neural crest cells, such as C thyroid cells, parathyroid oxyphilic and chief cells, and chromaffin cells of the adrenal medulla. Sympathetic, parasympathetic, and enteric ganglia and the urogenital tract have been also reported as expressing high levels of several hormonal and nonhormonal substances produced by the affected glands.1-13,16-20

Despite all efforts performed towards the management of MEN2, this condition is still an underdiagnosed, or late-diagnosed disease in many areas of the world. Presently, molecular DNA diagnosis to identify RET mutations is mandatory for all MEN2 cases and for their relatives at risk for a predisposition to MEN2. This diagnostic procedure is turning out to be a fundamental tool in early MEN2 diagnosis, enabling correct therapeutic surgical management.12

MOLECULAR MEDICINE

In 1986, with the identification of DNA polymorphisms
in chromosome 10 in large MEN2 genealogies, the study of the RET proto-oncogene gained further interest. Transfection DNA studies of several MTC tumors revealed important foci of proliferation in NIH-3T3 cells, represented by the presence of different genetic DNA sequences. Among these sequences, one – RET (rearranged during transfection) – was present in all tumor specimens. Soon afterwards, the RET sequence was localized in the chromosome band 10q11.2. The RET gene has 60 kb of the human genome spread through 21 exons, with 60 to 287 base pairs (bp), having a 24 kb intron between the first and second exons and encoding a protein of approximately 1,100 amino acids. In 1993, Mulligan et al and Donnis-Keller et al (1993) identified the first missense mutations in the RET extracellular RET domain in patients with MTC and MEN2.

**RET** is the only gene that has been associated with MEN2, and gametic mutation in this proto-oncogene has been extensively studied. Management of MEN2 using DNA sequencing information represents an excellent example of how molecular DNA diagnosis may improve clinical management.

### CLASSIFICATION

Table 1 summarizes the accepted classification of MEN2, as suggested by the international consensus on MEN. This classification is based on clinical pictures of affected MEN2 patients.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td><strong>Multiple endocrine neoplasia2A (1):</strong></td>
<td>Families with medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism phenotype</td>
</tr>
<tr>
<td><strong>Multiple endocrine neoplasia2A (2):</strong></td>
<td>Families with medullary thyroid carcinoma and pheochromocytoma phenotype in at least one at risk relative</td>
</tr>
<tr>
<td><strong>Multiple endocrine neoplasia2A (3):</strong></td>
<td>Families with medullary thyroid carcinoma and hyperparathyroidism phenotype in at least one at risk relative</td>
</tr>
<tr>
<td><strong>Multiple endocrine neoplasia2B:</strong></td>
<td>Families with medullary thyroid carcinoma, associated or not with pheochromocytoma and muscular/skeletal abnormalities and mucosal neuromas</td>
</tr>
<tr>
<td><strong>Familial medullary thyroid carcinoma:</strong></td>
<td>Families only with medullary thyroid carcinoma phenotype in at least four at risk relatives</td>
</tr>
<tr>
<td><strong>Others:</strong></td>
<td>Families with less than four relatives with medullary thyroid carcinoma phenotype</td>
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Thyroid cancer is a relatively rare event comprising 0.6% and 1.6% of all carcinomas affecting men and women, respectively. Medullary thyroid carcinoma comprises 10% of all thyroid cancers, presenting as sporadic (75%) or inherited (25%) forms. Multiple endocrine neoplasia type 2 has an estimated prevalence of 1 in 30,000 individuals, and more than 90% of RET carriers will develop MTC. The international consensus on MEN estimates that 95% of MEN2 patients have a detectable RET mutation. Mutations in exons 10, 11, and 16 are present in 90% to 95% of cases.

Multiple endocrine neoplasia type 2A comprises 75% of all MEN2 cases. In MEN2A, MTC is prevalent in almost 100% of patients, whereas PHEO (50%) and HPT (20%–30%) are less frequently expressed. The mean age of clinical diagnosis of MEN2A is 20 to 40 years, but this should soon decrease, as new young RET mutation carriers are recognized and treated earlier in life.

The familial form of MTC (FMTC) comprises 20% of all MEN2 cases, and it is characterized by the presence of MTC in the absence of both PHEO and HPT, both in index cases and affected family members. Usually in FMTC, MTC tends to present less aggressive behavior and better prognosis than in MEN2A or MEN2B.

Five percent (5%) of MEN2 cases have the phenotype of MEN2B, the most aggressive form of MTC. This form is characterized by the association of MTC, PHEO, marfanoid habitus, and mucosal neuromas (lips, tongue, eyebrows, and intestinal tract), whereas the presence of HPT is very rare. Medullary thyroid carcinoma in MEN2B usually appears very early, usually before 12 months of age.

### MEDULLARY THYROID CARCINOMA (MTC)

Affected families usually have several members with MTC. Even since molecular diagnosis has been performed, increasing incidences and prevalences of inherited forms of MTC have been reported. Familial forms of MTC are constitutive events that lead to bilateral, multicentric thyroid cancer. Among several bioactive substances secreted by thyroid C cells, calcitonin is the most representative and the best tumor marker for MTC.

Thyroid C-cell hyperplasia is usually the earlier histologic abnormality in MTC and represents a premalignant stage. It initially occurs as small foci, progressing to nodular diffuse hyperplasias that may evolve to focal and finally to metastatic MTC. The usual clinical presentation of MTC is a solitary thyroid nodule. At the stage of palpable thyroid nodules, MTC measures at least 1 cm, and 50% of patients already have local neck lymph node metastases and more rarely lung, liver, and bone metastases. It has been suggested that routine calcitonin measurements should be performed in all patients with solid thyroid nodules, since this procedure would permit presurgical diagnosis of the sporadic form of MTC as well.
as in familial MTC index cases, permitting the establishment of an adequate surgical plan.\textsuperscript{35,36} Fine-needle biopsy followed by immunocytochemistry for calcitonin is also helpful for the presurgical diagnosis of MTC.\textsuperscript{1,11,12,37–40} Total thyroidectomy associated with extensive resection of neck lymph nodes is the only effective treatment for MTC, as the tumor is usually resistant to iodo-, chemo-, and radiotherapy.\textsuperscript{1,11,12} In early diagnosed cases, C-cell hyperplasia is predominant, and neck lymph node resection may be less massive.\textsuperscript{1,11,12}

Genetic sequencing of MTC has resulted in dramatically lower mortality rates. Before Genetic sequencing was available, mortality rates for MEN2 were up to 20%, whereas after \textit{RET} mutation analysis, mortality has been as low as 5% in some samples.\textsuperscript{1}

**PHEOCHROMOCYTOMA (PHEO)**

Five to fifteen percent of all PHEOs are associated with MEN2, and most of them (90%) are benign. Pheochromocytomas associated with MEN2 are usually located on the adrenals (90%), but extra-adrenal cases have been reported.\textsuperscript{1} Most tumors (50%–80%) are bilateral. Patients with PHEO/MEN2 present a preneural stage characterized by nodular or diffuse hyperplasia of chromaffin adrenal cells.\textsuperscript{1,41–48} The diagnosis of PHEO is usually accomplished after the recognition of MTC (40%–50%); however, it may occur before or synchronously with MTC diagnosis.\textsuperscript{1,41} Thus, \textit{RET} analysis should be considered in all PHEO cases.\textsuperscript{1}

Notably, the possibility of an undiagnosed PHEO must be ruled out in all MTC patients before surgery to avoid the intrasurgical risk of an adrenal hypertensive crisis. Since a contralateral tumor may appear many years after the first diagnosis, PHEO/MEN2 patients need long-term follow-up. Image studies with MIBG (metaiodobenzylguanidine) and serum/urinary measurements of catecholamines are useful in this task.\textsuperscript{1,41}

**HYPERPARATHYROIDISM (HPT)**

Hyperparathyroidism associated with MEN2 (HPT/MEN2) results from a hyperplastic process of parathyroid chief cells involving the 4 parathyroid glands. In most HPT/MEN2 cases (68%), associated adenomas have been also reported.\textsuperscript{1,49} Primary HPT associated with MEN2 is a mild disease presenting slightly elevated concentrations of PTH and calcium. Several measurements may be needed to enable the biochemical diagnosis of HPT.\textsuperscript{1} In early-diagnosed MEN2 cases, HPT tends to be asymptomatic. Late-diagnosed cases are usually symptomatic, and renal stones are usually reported as the first clinical symptom. Osteoporosis may occur in such cases. During neck surgery for MTC in MEN2 cases, enlarged parathyroid glands are frequently found.\textsuperscript{1}

Two surgical approaches have been used for HPT in MEN2. In the first approach, the 4 parathyroid glands are removed and half of a gland is implanted in the nondominant forearm. In the other approach, 3 1/2 glands are removed. Postsurgical parathyroidism is less often achieved in HPT/MEN2 than in sporadic primary HPT, and its recurrence rate may be high.\textsuperscript{1,49} When HPT is present, parathyroidectomy and total thyroidectomy are usually performed during the same surgical stage.\textsuperscript{50}

Prior to 1993, i.e., before the advent of genetic analysis for \textit{RET}, all individuals at risk for MTC, PHEO, and HPT underwent annual screening (from 6 years of age). This procedure usually included measurements of basal and stimulated calcitonin, serum and urinary catecholamines, calcium, and PTH. \textit{RET} genetic analysis is indicated for all patients with MTC or PHEO.\textsuperscript{1} In apparently sporadic HPT, in the absence of other clinical suspicion for hereditary MEN2, analysis for \textit{RET} is not usually performed.\textsuperscript{1}

**HIRSCHSPRUNG DISEASE (HSCR)**

A nonendocrine entity such as congenital megacolon or Hirschsprung disease (HSCR) has been described in association with gametic inactivating \textit{RET} mutations and MEN2 cases. This disorder is due to an embryonic defect in the enteric nervous system. In HSCR associated with MEN2, myenteric and submucosal plexi are affected in extensive areas of the distal enteric tube. Most patients present with intestinal obstruction and constipation. Colectomy is frequently performed at early ages in order to correct intestinal transit.\textsuperscript{31,51}

**MOLECULAR ASPECTS**

The \textit{RET} proto-oncogene encodes for a tyrosine kinase cell membrane receptor. The extracellular domain of this protein is rich in cysteine residues, and it is encoded by the first 10 exons of \textit{RET}. Exon 11 encodes for the transmembrane domain, and the 2 intracellular domains of the protein are encoded by 10 other exons.\textsuperscript{8,36,52,53} The \textit{RET} extracellular domain includes coding for a cadherin-binding site that is important in intercellular signaling. Extracellular cysteines play an important role in receptor dimerization. At least 10 \textit{RET} isoforms have been reported as result of 5’ and 3’ splicing of exon 21; however, their physiological function still partially unknown.\textsuperscript{8,36,53}

The protein encoded by \textit{RET} plays an important role...
in embryologic migration and development of neural crest-derived cells, such as thyroid C cells, chromaffin adrenal cells, sympathetic, parasympathetic, and enteric ganglia cells, as well as in urogenital tract. The RET proto-oncogene is also expressed in parathyroid cells derived from branchial arches. Binding proteins such as GDNF (glial cell line-derived neurotrophic factor) and its receptor, GFRα1 (GDNF family receptor alpha one) interact with the RET-encoded extracellular protein, promoting cell survival of central and peripheral neurons. The RET proto-oncogene also plays an essential role in renal and enteric neural development.

The same dimerization process occurs independently of ligand binding when activating RET germline mutations (constitutive mutation) are present in the RET extracellular domain, favoring the development of the neoplastic phenotypes. RET mutations encode for the intracellular protein that leads to disturbances in the substrate catalytic core affinity, favoring the appearance of the neoplastic process.

Biochemical and transfection studies of tyrosine kinase have revealed differential RET expressions at the cell membrane level. Thus, cysteine residues next to the 5′ region (such as mutant codons 609 and 611) present lower protein expression compared to codon 634 mutations, located next to the transmembrane domain. The potency of cell neoplastic transformation of codon 634 RET mutations is clearly higher than that occurring in codons 609 and 611. This finding may be due to modulation of expression of mature RET-encoded protein receptors at the cell membrane, where most of the RET-encoded protein expression occurs. Thus, most patients with MEN2 who harbor RET 634 mutations will have thyroid, adrenal, and parathyroid tumors, whereas patients with 609 or 611 mutations will present only thyroid cancer. Further, tissue-specific sensitivity may also be modulated by codon-specific RET mutations. Tissue sensitivity is therefore high in thyroid tissue, intermediate in the adrenals, and low in parathyroid glands. These observations may also explain why activating RET mutations are usually associated with MEN2, whereas inactivating RET mutations are associated with HSCR. Mutations in codons 618 and 620 usually result in RET-encoded receptor amounts sufficient to transform thyroid and possibly adrenal cells, but insufficient to produce disturbances in normal intestinal gangliogenesis. Hirschsprung disease may be considered a polygenic disease, because RET, GDNF, endothelin receptor-2 genes, and genes located at 9q31 and 22q11 bands are involved.

GENOTYPE-PHENOTYPE CORRELATIONS

Multiple endocrine neoplasia type 2A (MEN2A)

The genotype-phenotype correlations in MEN2 are summarized in Table 2. The vast majority of MEN2A cases (98%) harbors a missense RET mutation, primarily in exon 10 and 11 and in codons 609, 611, 618, 620, 630, and 634, which comprise a small 25-amino-acid domain. Rarely, small insertions in codons 635 and 637 have been reported. Codon 634 is involved in 85% of MEN2A mutations; 52% of them have a Cys634Arg mutation, and 26% present the Cys634Tyr mutation. Further, MTC tumor aggressiveness induced by these 2 mutations differ: metastases tend to be more frequent and early in Cys634Arg cases, as compared to Cys634Tyr cases.

In relatives of patients presenting an increased incidence of HPT and the absence of PHEO, a 12 bp duplication was found between codons 634 and 635, corresponding to 4 amino acids and co-segregated with a Cys634Arg mutation. Recently, Nunes et al, of our laboratory, described a case with double RET mutations (Val648Ile/Cys634Arg). In this family, 2 siblings were Val648Ile carriers and so far have presented neither clinical nor biochemical abnormalities compatible with MEN2A. The other 2 affected siblings presented the usual Cys634Arg RET mutation and early classical MTC presentation. The father presented a rare phenotype of MEN2A associated with an ectopic ACTH-producing PHEO. He was an obligatory carrier of the double RET mutation. The MEN2A in this specific case had a relatively mild presentation.

Mutations in the RET intracellular protein receptor domain RET in codons 790 and 804 are rarely associated with MEN2A. Mutations associated with codon 804 are frequent in FMTC. In most of these cases, thyroid tumor tends to present a late onset, slow course, and low aggressiveness, when compared to phenotypes presenting RET extracellular-domain mutations. These patients may exhibit incomplete neoplastic transformation induced by the 804 mutation; however, aggressive MTC tumors and even death due to MTC have been reported in cases harboring codon 804 mutations.

Hirschsprung disease has been described in association with MEN2A or FMTC cases that are associated with mutations primarily in codons 609, 611, 618, and 620.
Most FMTC cases (85%) present RET mutations in exons 10 and 11. The Cys618Ser genotype is found in 33% of cases; the Cys634Tyr genotype is found in 30% cases; whereas, the Cys634Arg genotype is rarely associated with this phenotype. 

Mutations in codons 609, 611, and 620 and those of Glu768Asp, Val804Leu, and Val804Met occurring in tyrosine kinase domains are accepted to be related to FMTC, even though they may also occur in MEN2A. Other mutations in RET tyrosine kinase domains, such as in codons 790, 791, and 891, have been reported. 

Less frequently, hot spots and mutations, such as those in codons 630, 790, 791, 891, and a 12 bp duplication be-
between codons 634 and 635, have been reported in FMTC families, associated with an indolent form of MTC.6,64

Additionally, a 9 bp duplication in RET exon 8 creating a new cysteine residue in the extracellular portion of the RET protein receptor was reported in a FMTC family, possibly associated with HSCR. The affected case did not present germline mutations in exons 10, 11, 13, 14, or 15 or somatic mutations in exons 11, 13, 15, and 16, suggesting the neoplastic activity of this mutation.26

Recently, a new exon 8, Gly533Cys RET mutation was reported in 76 FMTC carriers belonging to a family of Spanish extraction in which 229 individuals were at risk.65

### Multiple endocrine neoplasia type 2B (MEN2B)

A RET intracellular tyrosine kinase domain mutation, Met918Thr, has been reported in 95% of MEN2B cases.56 In 4 families with MEN2B from Germany, United Kingdom, and Australia, an Ala883Phe substitution in exon 15 was described, comprising 4% of all MEN2B phenotypes reported to date.8,13,56 Some rare mutations have been described, such as Ser922Tyr and a double mutation in codon 804 and Tyr806Cys occurring in the same allele, which was detected in a patient with MEN2B.13

Genotype-phenotype correlations in MEN2 have a major and immediate impact in clinical medicine, since genetic testing may differentiate RET carriers from noncarriers. RET carriers should undergo total thyroidectomy at ages that depend on the mutated codon,1,67 following the MEN consensus (Table 3). Conversely, noncarriers of the RET mutation should be excluded from annual clinical follow-up, an expensive and stressing procedure for patients. In skillful surgical hands, the risks of neck surgery are minimal even in children. False positives in genetic testing are exceedingly low.1,10 All these data have generated an international consensus on MEN regarding which MTC patients should undergo surgery at ages preferably less than 5 years, depending on the mutated codon.1,67 (Table 3). At the time of writing, molecular DNA diagnosis in MEN2 has become an important tool to a) confirm clinical and laboratory diagnosis of MTC; b) identify as early as possible mutant RET carriers in premalignant stages of the disease; and c) identify noncarrier family members and rule them out for clinical follow-up.33

### MODIFIER GENES IN RET EXPRESSION

Transgenic animal models expressing RET mutation are used to better address the question of MEN2 MTC tumor aggressiveness. Medullary thyroid carcinoma occurs in transgenic lines with analogous pathology to that seen in patients with MEN2. When the transgene codon 634 mutation was introduced into 4 different genetic backgrounds (BALB/c, C57BL/6J, FVB/N and CBA/ca), 65% of all animals developed MTC, showing incomplete penetrance. None of the FVB/N transgenic progeny developed MTC, 14% of transgenic progeny BALB/c, 64% of C57BL/6J, and 98% CBA/ca mice developed thyroid tumors by 10 months of age, indicating that incomplete tumor penetrance could be modulated by genetic background. Furthermore, tumors in the CBA/ca and C57BL/6J mice were significantly larger than those in BALB/c transgenic mice. These results are relevant to human MEN2 disease, because this model system may be used to study genes modifying thyroid tumor penetration in this dominantly inherited human cancer syndrome.68

### ROUTINE PROCEDURES IN MOLECULAR RET DIAGNOSIS

Investigators working on studies dealing with humans should follow the Helsinki decisions; thus, before collecting blood samples for DNA analysis, projects should be approved by local ethic committees, and patients involved in research projects should sign a written informed consent.

For genomic DNA extraction, a salting-out method is indicated since it is a simple, low-cost procedure.69 For ampli-
Figure 1 - Electropherograms showing five different types of RET mutations in MEN2, using a DNA sequencer (ABI 310 DNA Sequencer - Applied Biosystems, USA)
ification of genomic DNA, fragments of interest are usually amplified using the polymerase chain reaction (PCR) strategy. Primers should contain flanking sequences of intron-exon boundaries for adequate RET proto-oncogene analysis, and if a laboratory chooses the DGGE (denaturing gradient gel electrophoresis) strategy for screening mutation analysis, primers may also contain a 50bp GC-clamp coupled in one of the sequences. The presence of adequate amplified sequences are confirmed using runs in 1% agarose gel electrophoresis stained with ethidium bromide. After obtaining PCR products, direct sequencing analysis (the gold-standard method for RET mutation diagnosis) should be performed in all MEN2 index cases. Once the genotype of the RET mutation in the index case is known, it may be used as intrafamilial positive control. For at-risk family members, screening methods may be used. In this latter alternative, it is possible to use DGGE, single-strand conformation polymorphism (SSCP) or restriction enzyme approaches. The DGGE and SSCP techniques are based on differential migration mobilities in polyacrylamide gel. Thus, applying these techniques, it is possible to discriminate between mutant carriers and noncarriers. Different electrophoretic migration patterns are influenced by denaturant substances, such as urea and formamide (in DGGE) or heteroduplex formation (in SSCP). Particularly when screening large MEN2 families, these methods are very useful; for instance, using DGGE, one might analyze 16 exons in 24 hours. Restriction enzymes may possibly be useful in genetic screening for RET mutations, as mutations create or destroy restriction sites recognizable by endonucleases. However, this method should only be applied to confirm DGGE or SSCP findings, considering that interferences may occur as follows: a) inadequate recognition of restriction site and consequently no defined band in agarose gel electrophoresis or b) incomplete discrimination of amplified sequences with similar base pair sizes.

Using direct genetic sequencing analysis (the gold-standard method), DNA fragments of interest are sequenced by enzymatic or chain termination, as described by Sanger in 1977. In this technique, each primer must be added separately to sense and missense reaction tubes, with a commercial buffer (Big Dye Terminator Cycle Sequencing, Applied Biosystems, Foster City, USA) and processed in a thermocycler. After the sequencing reaction, samples are purified with isopropanol and ethanol and diluted in blue dextran buffer with deionized formamide. The sequencing products are then denatured at 90 °C for 2 minutes, imme-
diately cooled, and applied into a specific electrophoresis polymer for the DNA sequencer. Using these procedures, good reproducibility is usually obtained, avoiding the need of a confirmation reaction. Figure 1 illustrates examples of electropherograms showing MEN-2 RET mutations.

CONCLUSIONS

Before RET molecular diagnosis was possible, first-degree relatives of MEN2 patients (who have a 50% chance of being carriers) were clinically and biochemically followed up every 12 months for MTC, PHEO, and HPT. Individuals had to be annually evaluated from 6 years of age on. Thus, basal and stimulated calcitonin serum levels were measured in these individuals, as well as serum PTH, calcium, and serum/urinary cathecolamines. The sensitivity of these tests was variable, and as a consequence, MTC was usually diagnosed late. This prolonged follow-up was expensive; individuals at risk were maintained in a stressing condition; survival rates were diminished, and cure was almost never achieved due to late MEN2 diagnosis and high prevalence of lymph node metastases.

At the time of writing, because almost 95% of affected MEN2 patients harbor a mutation, genetic diagnosis of MEN2 has become a great success story in the management of patients that are RET mutation carriers. Direct DNA sequencing is of course the gold-standard method for RET mutation analysis and should be performed routinely in all index cases and possibly in all suspected cases. Alternatively, once the presence of a RET mutation is ascertained, screening methods may be used in analyzing family members at risk. Whatever DNA method is used, early RET mutation analysis provides information to clinicians and surgeons allowing them to make adequate surgical decisions. As a consequence of these procedures, mortality rates in MEN2 have dropped from up to 20% in 1993 to 5% currently. Finally, early RET mutation analysis should be performed in all MTC and PHEO cases, as suggested by the MEN consensus.

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RESUMO


A neoplasia endócrina múltipla tipo 2 (NEM2) é caracterizada pela ocorrência do carcinoma medular de tireóide (CMT), hiperparatiroidismo primário (HPT) e feocromocitoma (FEO).1-12 Desde 1993, quando as primeiras mutações do tipo missense no proto-oncogene RET (RET), associadas a NEM2 foram identificadas, 46 diferentes mutações causadoras de doenças foram descritas.13-17 Como há uma forte correlação genótipo-fenótipo na NEM2, a detecção de mutações no RET adquiriu grande impacto no tratamento precoce do CMT e NEM2. A NEM2 persiste como uma doença subdiagnosticada e/ou tardiamente diagnosticada em várias áreas geográficas do globo. A análise de mutações do RET deve ser realizada em todas as casas de NEM2 e atualmente, a tireoidectomia total profilática é indicada para todos os indivíduos portadores de mutações no RET.1 Para a grande maioria dos portadores de mutações gaméticas ativadoras no RET este procedimento cirúrgico é indicado nos primeiros anos de vida, promovendo melhora na qualidade de vida, aumento da sobrevida ou mesmo levando à cura definitiva.1 Discutimos nesta revisão, o impacto da análise do proto-oncogene RET na conduta clínica da neoplasia endócrina múltipla tipo 2. Além disso, o diagnóstico molecular do RET fornece à clínicos e cirurgiões a mais valiosa das informações, permitindo indicação de tireoidectomia total profilática.


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