

# Revisão dos Casos de MEN2A numa População Pediátrica

## Review of MEN2A Cases in a Paediatric Population

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### Resumo

**Introdução:** As neoplasias endócrinas múltiplas do tipo 2A consistem na tríade carcinoma medular da tiroide, feocromocitoma e hiperplasia das paratiroides. Os testes genéticos constituem uma ferramenta importante na deteção e seguimento destes doentes. Este estudo tem por objetivo descrever a experiência dos autores no seguimento de crianças diagnosticadas com neoplasias endócrinas múltiplas do tipo 2A.

**Métodos:** Estudo observacional e descritivo de crianças com neoplasias endócrinas múltiplas do tipo 2A, acompanhadas num centro terciário de endocrinologia pediátrica. Foram utilizados os critérios da American Thyroid Association para a definição de risco das mutações encontradas.

**Resultados:** Foram estudadas cinco crianças com neoplasias endócrinas múltiplas do tipo 2A, com idades entre 3-14 anos. Três apresentavam mutações de alto risco e duas de risco moderado. Quatro foram submetidas a tiroidectomia profilática. Uma criança desenvolveu hipoparatiroidismo pós-cirúrgico. Relativamente à análise histológica, uma peça operatória apresentou alterações. Em dois doentes verificou-se ausência de correlação genotípica-fenotípica.

**Discussão:** De acordo com a experiência dos autores, a referência tardia para a consulta resultou no atraso da tiroidectomia profilática em dois casos. Após realização de tiroidectomia profilática é mandatório manter a monitorização destes doentes, que vão necessitar de terapêutica de reposição hormonal e de forma a detetar outras potenciais manifestações da doença.

**Palavras-chave:** Códon; Criança; Neoplasia Endócrina Múltipla Tipo 2a; Proteínas Proto-Oncogénicas c-ret

### Abstract

**Objectives:** Multiple endocrine neoplasia syndrome type 2A (MEN2A) consists of medullary thyroid carcinoma, pheochromocytoma, and parathyroid hyperplasia. Genetic tests are an important tool for screening and disease management. This study aims to describe the authors' experience in the follow-up of children diagnosed with MEN2A.

**Methods:** The authors assessed children with MEN2A followed in a paediatric endocrinology unit, using the American Thyroid Association criteria to define mutation risk.

**Results:** Five children with MEN2A were studied, aged between 3 and 14 years. Three, two of them siblings, had high-risk mutations, and two had moderate-risk mutations. Four patients underwent prophylactic thyroidectomy. One child developed post-surgical hypoparathyroidism and one showed altered histology in thyroid tissue. Absence of genotype-phenotype correlation was found in two patients.

**Discussion:** In the authors' experience, late referral for consultation resulted in delayed prophylactic thyroidectomy in two cases. Patients with MEN2A will require hormone replacement therapy and must continue to be

monitored after prophylactic thyroidectomy, in order to screen for other manifestations of the disease.

**Keywords:** Child; Codon; Multiple Endocrine Neoplasia Type 2a; Proto-Oncogene Proteins c-ret

### Introduction

The multiple endocrine neoplasia (MEN) syndromes form a heterogeneous set of familial disorders, which are caused by mutations inherited in an autosomal dominant pattern with very high penetrance.<sup>1</sup> These mutations occur in the Ret proto-oncogene, which comprises 21 exons located on chromosome 10q11.2 and encodes a tyrosine kinase transmembrane receptor. The Ret tyrosine kinase receptor is expressed in a variety of neuronal cell lineages, including thyroid C-cells and adrenal medulla.<sup>2</sup> The disease phenotype strongly correlates with mutations in specific Ret codons. Genetic testing has become an important tool in the assessment of these patients and in the decision whether to perform prophylactic thyroidectomy.<sup>1</sup>

Multiple endocrine neoplasia syndrome type 2A (MEN2A) is the most common of the MEN syndromes,

with an estimated prevalence of 1 per 30 000 in the general population.<sup>3</sup> There are four variants of MEN2A:

- Classical MEN2A;
- MEN2A with cutaneous lichen amyloidosis;
- MEN2A with Hirschsprung disease;
- Familial medullary thyroid carcinoma (MTC).

In this paper, the authors discuss classical MEN2A, and refer to it simply as MEN2A.

MEN2A consists of MTC, pheochromocytoma, and parathyroid hyperplasia. In 95% of these patients, mutations occur in codons 609, 611, 618 or 620 of exon 10; or codon 634 of exon 11. Virtually all patients develop MTC and a much smaller number develop pheochromocytoma or parathyroid hyperplasia, the frequency of each depending on the specific Ret mutation.<sup>4</sup>

MTC arises from the parafollicular or C-cells of the thyroid gland that produce calcitonin,<sup>5</sup> and occurs as a bilateral, multifocal proliferative process. MTC is the most common cause of death in MEN2A syndromes. Recently, the American Thyroid Association (ATA) reviewed the guidelines published in 2009 for diagnosis and management of patients with MTC and changed the risk categories for hereditary MTC.<sup>4</sup>

Early diagnosis, by screening of at-risk family members in MEN2A kindreds, is essential, because MTC is a life-threatening disease that can be cured or prevented by early thyroidectomy. If a family member has the Ret mutation, prophylactic thyroidectomy is indicated. The timing of thyroidectomy is based upon the specific Ret mutation, and in some cases, serum calcitonin levels.<sup>3</sup>

The possibility of developing pheochromocytoma should also be taken into consideration in Ret gene mutation carriers. Penetrance and age at diagnosis of pheochromocytoma depends on specific Ret germline mutations, with 50% occurrence in codon 634, 22% in codon 618, 9% in codon 620, and 4% in codon 609.<sup>2</sup>

Parathyroid hyperplasia in patients with MEN2A is usually mild and associated with few if any symptoms. A Ret codon 634 mutation is associated with a penetrance of parathyroid hyperplasia of up to 30%, and Ret mutations in codons 609, 611, 618 and 620 are associated with a penetrance between 2% and 12%.<sup>4</sup>

There is no universal agreement on the management of MEN2 syndromes in children. This study aims to characterise children diagnosed with MEN2A in a tertiary paediatric endocrinology centre in terms of approach and follow-up.

## Methods

An observational, descriptive study was performed, assessing five patients diagnosed with MEN2A, followed

in a tertiary paediatric endocrinology centre in 2015. The patients' medical records were consulted. The variables assessed were demographics, genetic study, type of mutation, mutation classification according to ATA score, criteria for prophylactic thyroidectomy, age at which surgery was performed, postoperative complications and follow-up.

The authors used the ATA classification of the risk level of hereditary MTC:

- ATA-HST: highest-risk category – patients with MEN2B and the Ret codon M918T mutation;
- ATA-H: high-risk category – patients with Ret codon C634 mutations;
- ATA-MOD: moderate-risk category – patients with Ret codon mutations other than M918T and C634.

## Results

Five children with MEN2A were studied. Their ages ranged from 3 to 14 years, and three were male. Three, two of them siblings, had high-risk mutations (Ret codon 634), and two had moderate-risk mutations (codon 611).

Four underwent prophylactic thyroidectomy between the ages of 5 and 8. The 3-year-old child had not undergone surgery at the time of the study. Thyroidectomy of patients with high-risk mutations was conducted at the age of 5, except for one female patient who was referred at the age of 5 and underwent prophylactic thyroidectomy at the age of 6. The patient who had the procedure done at 8 years of age was diagnosed at the same age, and has a moderate-risk mutation. In all four cases, pre-surgical serum calcitonin values were normal. One patient developed post-surgical hypoparathyroidism, and is being treated with calcitriol. Another patient had transient postoperative hypoparathyroidism. Regarding pathology, one patient with a high-risk mutation, who underwent thyroidectomy at 5 years of age, showed focal C-cell hyperplasia in both thyroid lobes. All other patients had normal histological findings.

The results are summarised in Table 1.

## Discussion

Children with certain Ret mutations can develop clinically apparent MTC at an early age. The goal in patients with known Ret mutations (but without clinically apparent disease) is to perform prophylactic thyroidectomy before MTC develops, or while it is confined to the thyroid gland.<sup>4</sup> For those with Ret mutations, prophylactic thyroidectomy in family members is timed based on

Table 1. Summary of multiple endocrine neoplasia syndrome type 2A cases in our hospital

Age / Gender	14 Y / Male	13 Y / Female*	10 Y / Male*	9 Y / Female	3 Y / Male
Age at first visit (Y)	8	4	2	5	3
Mutation (codon)	611	634	634	634	611
ATA risk	Moderate	High	High	High	Moderate
CTN (pg/mL) (ng/m <sup>3</sup> )	< 2	2.2	4.2	114	-
Age at prophylactic thyroidectomy (Y)	8	6	5	5	To schedule
Post-surgical complications	Hypoparathyroidism	None	Transitory hypoparathyroidism	None	-
Histology	Normal	Normal	C-cells focal hyperplasia	Normal	-
Plan	- Thyroxin and calcitriol - Screen PHEO $\geq$ 16 Y	- Thyroxin - Screen PHEO and HPTH	- Thyroxin - Screen PHEO and HPTH $\geq$ 11 Y	- Thyroxin - Screen PHEO and HPTH $\geq$ 11 Y - Brother 2 Y: schedule genetic study	- Ultrasound thyroid and CTN - Schedule thyroidectomy 5 Y - Sister 14 M: schedule genetic study

ATA - American Thyroid Association; CTN - calcitonin; HPTH - parathyroid hyperplasia; M - months; PHEO - pheochromocytoma; Y - years old.

\* siblings.

the specific DNA mutation in the Ret proto-oncogene occurring in the family (Table 2). The risk-benefit ratio is strengthened by the ease of thyroid hormone replacement after thyroidectomy and the relatively low morbidity of the surgery, even in children, when performed by high-volume surgeons.<sup>6</sup> Ret mutations can be categorised as highest, high, and moderate risk, referring to the potential risk for local and distant MTC metastases at an early age. Although some Ret mutations (e.g. Ret codons 634 and 918) are uniformly associated with more aggressive and earlier-onset MTC, there is heterogeneity in presentation with other Ret mutations, even among different families with the same mutation or within an individual family having the same Ret mutation. Therefore, measurement of serum calcitonin (baseline or stimulated) may be helpful for establishing the timing of thyroidectomy.<sup>3,4</sup>

Our patients with high-risk mutations underwent prophylactic thyroidectomy at 5 years of age, except one female patient who was referred at the age of 5 and underwent the procedure at the age of 6. The patient

who had the procedure at 8 years of age was diagnosed at the same age, and has a moderate-risk mutation. Although calcitonin levels in this patient were within the reference range, it was decided to perform thyroidectomy at that age. Despite the genotype-phenotype correlation described above, in our sample the siblings with the same mutation (high-risk) showed different results regarding the histological findings after thyroidectomy. The brother's prophylactic thyroidectomy was at 6 years of age, with a normal histologic examination, and that of the sister with the same mutation, at 5 years of age, already showed focal C-cell hyperplasia.

Immediately after surgery, the patient should be closely monitored for the development of hypoparathyroidism or injury to the recurrent or superior laryngeal nerves.<sup>3</sup> In our cases, only one patient developed persistent post-surgical hypoparathyroidism. One child had transient post-surgical hypoparathyroidism. In this case, calcium carbonate was discontinued after three months. According to the ATA recommendations,<sup>4</sup> children in the ATA-H category should undergo thyroidectomy at age 5

Table 2. Clinical monitoring for medullary thyroid carcinoma and timing of thyroidectomy in carriers of a mutation in the Ret gene

Risk	Ret codon mutation	Begin annual screening for MTC	Prophylactic thyroidectomy
Highest	918		$\leq$ 1 Y
High	634, 883	3 Y	$\leq$ 5 Y
Moderate	533,609,611,618, 620,630,666,768, 790,804,891,912	5 Y	Childhood or young adulthood

MTC - medullary thyroid carcinoma; Y - years-old.

years, or earlier if elevated serum calcitonin levels are detected. Children in the ATA-MOD category should have a physical examination, ultrasound of the neck, and measurement of serum calcitonin levels beginning around 5 years of age. The timing of thyroidectomy should be based on the detection of an elevated serum calcitonin level. Parents who are concerned about a long-term assessment programme may opt to have their child's thyroid gland removed around 5 years of age.

Pheochromocytoma may develop as early as 8 years of age in children in ATA-H and as early as 19 years of age in children in the ATA-MOD category.<sup>7,8</sup> Screening for pheochromocytoma in children in the ATA-H and ATA-MOD categories should begin at 11 and 16 years of age, respectively.<sup>4</sup> Screening consists of measuring free plasma metanephrines and normetanephrines, or 24-hour urinary metanephrines and normetanephrines. Adrenal imaging by computed tomography or magnetic resonance is indicated in patients with positive biochemical results.

Parathyroid hyperplasia occurs primarily in patients with exon 11 Ret codon mutations, almost always in those with Ret codon 634 mutations, and less frequently in patients with exon 10 Ret codon mutations. As more families with MEN2A have been studied, it has become apparent that their parathyroid hyperplasia, in contrast to that occurring in families with MEN1, is mild and often asymptomatic.<sup>9,10</sup> The ATA recommends that patients in the ATA-H and ATA-MOD categories should be screened for parathyroid hyperplasia at the time of screening for pheochromocytoma (by age 11 in patients in the ATA-H category and by age 16 in patients in the ATA-MOD category).<sup>4</sup> Surveillance for parathyroid hyperplasia should include albumin-corrected calcium or ionised serum calcium measurements (with or without serum intact parathyroid hormone levels) beginning at age 11 years in patients in the ATA-H category and at age 16 years in patients in the ATA-MOD category.

#### WHAT THIS STUDY ADDS

- As described in the literature, most of the Ret gene mutations occur at codon 634, which was also observed in our study.
- Patients with MEN2A will require hormone replacement therapy and must continue to be monitored after prophylactic thyroidectomy, in order to screen for other manifestations of the disease, particularly pheochromocytoma and parathyroid hyperplasia.

#### Conflitos de Interesse

Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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#### Proteção de Pessoas e Animais

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#### Confidencialidade dos Dados

Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.

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