Clinical Presentations and Genetic Analyses of Patients with Multiple Endocrine Neoplasia Type 2A: A Single Thai Tertiary Center Experience

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Background

Multiple endocrine neoplasia type 2A (MEN 2A) is an autosomal dominant disorder characterized by the presence of medullary thyroid carcinoma(MTC), pheochromocytoma and/or primary hyperparathyroidism (PHP). The associated Hirschsprung's disease and cutaneous lichen amyloidosis can be present or absent. The prevalence of MEN 2A is approximately 1:25,000.[1]

MEN2A diagnosis is based on the presence of one of these tumors and genetic testing to identify a germline mutation, which has good genotypic-phenotypic correlation with regard to aggressiveness of MTC, time of onset of MTC and the presence and absence of other endocrine tumor.[2-4] The recognition that certain RET mutation may guide the management of patients and their relatives.[5]

Objectives

To analyze clinical and genetic data of patients with MEN2A at King Chulalongkorn Memorial Hospital, Chulalongkorn University

Materials and Methods

A retrospective study of 5 probands and 5 family members diagnosed as MEN2A at our center during 2000-2015 was performed. Direct sequencing of the RET gene successfully identified all mutant alleles of the affected individuals. Demographic data, clinical profiles, mutation types and genotype-phenotype correlation were analyzed.

Results

- 10 RET-carried subjects (5 probands + 5 family members)
- Probands: 3 males and 2 females, age 31-46 year
- Family members: 2 males and 3 females, age 2-50 years
- RET gene: direct sequencing
- Analysis: Clinical profiles, Mutation type, genotype-Phenotype correlation

- At the diagnosis, four probands had pheochromocytoma and MTC whereas the other one developed all three.

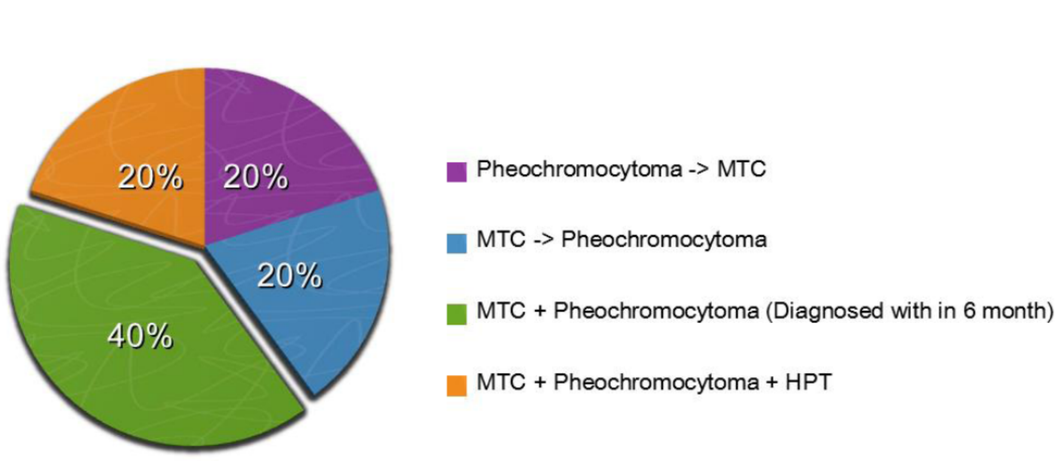

Figure 1. Clinical presentations of the probands

Results

MTC

- Mean age at diagnosis 36.86 years [13 - 54 years] (100%)
- 60% Multifocal
- Two of the probands initially presented with MTC with multiple foci at the diagnosis.
- Serum calcitonin 101 [17.4-1168 pg/ml]
- Lymph node metastasis in 66.67% (2/3) of patients
- No distance metastasis at diagnosis

Pheochromocytoma

- Mean age at diagnosis 41.71 years [range 31 – 51 years]
- Average tumor size 5.4 cm [range 2 - 8 cm]
- Bilateral pheochromocytoma 50% (3/6)
- Benign: 100%

Hyperparathyroidism

- Parathyroid hyperplasia was identified in one case.

None of the probands have cutaneous lichen amyloidosis nor Hirschsprung's disease.

Patient	Gender	Age at Dx	First presentation	MEN2A manifestations			Mutation Exon 11	Follow up (month)	Outcome
				MTC	Pheo	HPT			
1	M	46	Pheo	+	Bilateral	-	C634S	72	Remission
2	M	32	MTC	+	Unilateral	-	C634S	24	Remission
3	M	38	Pheo	+	Unilateral	-	C634S	8	Remission
4	F	42	Pheo	+	Bilateral	+ (hyperplasia)	C634R	Loss F/U	N/A
5	F	31	MTC	+	Bilateral	-	C634R	-	Death

Table 1. Clinical profile and genetic analysis of the probands

Two distinct mutations which all located in codon 634 of exon 11 in RET proto-oncogene, C634S (60%) and C634R (40%), were detected. A prophylactic thyroidectomy based on a classification of RET mutations in an asymptomatic MTC 10-year-old girl was performed successfully.

Conclusions from our study

- RET mutation "hot spot" to codon 634
- High prevalence of MTC and pheochromocytoma
- Low prevalence of hyperparathyroidism
- Screening and early detection of MEN2A mutation carrier are very effective clinical intervention.
- As described in the literature, MTC is usually the first manifestation in patients with MEN2A; however, pheochromocytoma may be the presenting tumor due to its alarming symptoms.
- In this study the identified frequent loci of the RET gene will facilitate the molecular diagnosis of MEN 2A in Thai population.

References

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