

Multiple endocrine neoplasia, the old and the new: a mini review

D. PASQUALI¹, F.M. DI MATTEO², A. RENZULLO¹, G. ACCARDO¹, D. ESPOSITO¹,
F. BARBATO¹, V. COLANTUONI⁴, L. CIRCELLI⁵, G. CONZO²

SUMMARY: Multiple endocrine neoplasia, the old and the new: a mini review.

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Multiple endocrine neoplasia syndromes have since been classified as types 1 and 2, each with specific phenotypic patterns. MEN1 is usually associated with pituitary, parathyroid and paraneoplastic neuroendocrine tumours. The hallmark of MEN2 is a very high lifetime risk of developing medullary thyroid carcinoma (MTC) more than 95% in untreated patients. Three clinical subtypes MEN2A, MEN2B, and familial MTC (FMTC) have been defined based on the risk of pheochromocytoma, hyperparathyroidism, and the presence or absence of characteristic physical features. MEN2 occurs as a result of germline activating missense mutations of the RET (REarranged during Transfection) proto-oncogene. MEN2-associated mutations are almost always located

in exons 10, 11, or 13 through 16. Strong genotype-phenotype correlations exist with respect to clinical subtype, age at onset, and aggressiveness of MTC in MEN2. These are used to determine the age at which prophylactic thyroidectomy should occur and whether screening for pheochromocytoma or hyperparathyroidism is necessary. Specific RET mutations can also impact management in patients presenting with apparently sporadic MTC. Therefore, genetic testing should be performed before surgical intervention in all patients diagnosed with MTC. Recently, Pellegata et al. have reported that germline mutations in CDKN1B can predispose to the development of multiple endocrine tumours in both rats and humans and this new MEN syndrome is named MENX and MEN4, respectively. CDKN1B. A recent report showed that in sporadic MTC, CDKN1B V109G polymorphism correlates with a more favorable disease progression than the wild-type allele and might be considered a new promising prognostic marker. New insights on MEN syndrome pathogenesis and related inherited endocrine disorders are of particular interest for an adequate surgical and therapeutic approach.

KEY WORDS: MEN1 - MEN2 - MENX - MEN4.

The term multiple endocrine neoplasia (MEN) arose from postmortem reports of diffuse gastrointestinal ganglioneuromatosis in association with medullary thyroid cancer (MTC) and pheochromocytoma (1-3). MEN syndromes are inherited diseases characterized by endocrine tumours occurring as autosomal dominant genetic diseases with high penetrance. MEN syndromes have since been classified as types 1 (MEN1) and 2 (MEN2), each with specific phenotypic patterns. The

MEN1 and 2 have long been known and are well characterized. These syndromes are caused by germ line mutations in the MEN1 and RET genes, respectively, and have a different tumor spectrum. MEN1 is usually associated with pituitary, parathyroid and paraneoplastic neuroendocrine tumours. The hallmark of MEN2 is a very high lifetime risk of developing MTC more than 95% in untreated patients. Three clinical subtypes MEN2A, MEN2B, and familial MTC (FMTC) have been defined based on the risk of pheochromocytoma, hyperparathyroidism, and the presence or absence of characteristic physical features. The prevalence of MEN2 has been estimated at 1 in 35,000 individuals. MEN2 occurs as a result of germ line activating missense mutations of the RET (REarranged during Transfection) proto-oncogene. RET, a 21-exon proto-oncogene located on chromosome 10q11.2, encodes a receptor tyrosine kinase that functions as a signal transducer upon interaction with the glial-derived neurotrophic factor family of ligands. Binding of these ligands induces dimerization

¹ Second University of Napoli, Napoli, Italy
Department of Cardiothoracic and Respiratory Sciences

² "Sapienza" University of Roma, Italy
Dipartimento di Scienze Chirurgiche

³ Second University of Napoli, Napoli, Italy
Department of Anesthesiological, Surgical and Emergency Sciences

⁴ University of Sannio, Benevento, Italy
Department of Biological, Geological and Environmental Sciences

⁵ CEINGE SCARL, Advanced Biotechnologies, Napoli, Italy
University of Napoli "Federico II", Napoli, Italy

Department of Biochemical and Medical Biotechnology

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of RET receptors, autophosphorylation of intracellular tyrosine residues, and ultimately cell growth and survival mediated by the mitogen-activated protein kinase intracellular signaling cascade. Mutations in RET associated with MEN2 cause ligand-independent activation of the downstream pathways and result in unregulated cell growth and survival. MEN2-associated mutations are almost always located in exons 10, 11, or 13 through 16, although mutations in exons 5 and 8 have been reported on rare occasions. A definitive diagnosis of MEN2 in cases of apparently sporadic MTC and in patients with an equivocal family history usually depends on the identification of a germ line RET mutation. Strong genotype-phenotype correlations exist with respect to clinical subtype, age at onset, and aggressiveness of MTC in MEN2. These are used to determine the age at which prophylactic thyroidectomy should occur and whether screening for pheochromocytoma or hyperparathyroidism is necessary. The presence or absence of specific RET mutations can also impact management in patients presenting with apparently sporadic MTC. The genotype-phenotype correlations of classical cysteine RET mutations have been the subject of several comprehensive reviews (4). MEN2A accounts for 90-95% of childhood MTC cases and is most commonly due to mutations in codon 634 of RET. MEN2B is associated with the most aggressive clinical presentation of MTC and is almost always due to the Met918Thr mutation of RET. Accordingly, MEN 2A patients can be stratified into three risk groups depending on the RET mutation (Table 1) (5). Management uncertainties remain regarding patients bearing uncommon RET mutations or genetic variations for which mutation-specific risk profiles and treatment recommendations are unavailable. We reported the thirteen year clinical and surgical follow-up of a patient with MEN 2A bearing three *de novo* RET mutations at codons 634, 640 and 700 (p.C634R, p.A640G and p.M700L) in exon 11: a combination of mutations which has not previously been described (6-8). Therefore,

we suggest to retest MEN 2A patients in whom the original genetic studies were some time ago, if the clinical course is atypical. Our patient bears two additional gene variants whose influence on RET function and hence on clinical prognosis and the patient's outcome is still unknown. This case underlines the need to share information to achieve the best genetic, clinical, surgical and psychological support in the management of patients carrying rare RET mutations of similar patients. Surgery is the primary treatment and only chance of cure, although the advent of targeted therapies seems to be improving progression-free survival in advanced cases. Since the discovery of the role of RET in MEN2A, considerable advances in the management of this syndrome have occurred, and most of the children with MEN2A who have undergone early thyroidectomy will now lead full, productive lives. Strong genotype-phenotype correlations have facilitated the development of guidelines for interventions. Contemporary approaches for deciding the appropriate age at which surgery should take place incorporate data from ultrasonography and calcitonin measurements in addition to the results of genotyping. The recommended surgical approaches are usually based on the age of the affected carrier/patient, tumor staging and the specific rearranged during transfection codon mutation. Therefore, genetic testing should be performed before surgical intervention in all patients diagnosed with MTC (Table 1). Successful management of medullary thyroid carcinoma in these cases depends on early diagnosis and treatment. Total thyroidectomy should be performed before 6 months of age in infants carrying the rearranged during transfection 918 codon mutation, by the age of 3 years in rearranged during transfection 634 mutation carriers, at 5 years of age in carriers with level 3 risk rearranged during transfection mutations, and by the age of 10 years in level 4 risk rearranged during transfection mutations (9).

Recently, Pellegata et al. have reported a variant of the MEN syndromes arose spontaneously in a rat colony and

TABLE 1 - MEN2A PATIENTS STRATIFIED INTO THREE RISK GROUPS DEPENDING ON RET MUTATION: INTERVENTION STRATEGIES.

Level 1:	Level 2:	Level 3:
Codon 918	Codon 609, 611, 618, 620, 634	Codon 768, 790, 791, 804 and 891
Intracellular catalytic core: total thyroidectomy in the first year of life.	Extracellular domain: total thyroidectomy after five years of age and in selected cases (carriers of mutation of 630 e 634 codons with elevated basal CT) before five years of age.	Intracellular domain: there is still no consensus. Before five years up to ten years of age.

was named MENX (10). Affected animals consistently develop multiple endocrine tumors, with a spectrum that shares features with both MEN1 and MEN2 human syndromes. Genetic studies identified a germ line mutation in the *Cdkn1b* gene, encoding the p27 cell cycle inhibitor, as the causative mutation for MENX. Phenotypically, in the rat an overlap of both MEN1 and MEN2 is observed. Affected animals develop bilateral pheochromocytomas and parathyroid adenomas, multifocal thyroid C-cell hyperplasia, paragangliomas and pancreatic hyperplasia. The development of bilateral cataracts is also observed in affected animals. Two patients with clinical features of the MEN1 syndrome, with no detectable mutation in the MEN1 gene, have been described as showing a mutation in the CDKN1B (11,12). These findings support an association between germ line mutations of CDKN1B and a MEN1 syndrome condition. However, another study did not find any change in the CDKN1B gene in sporadic or familial cases of parathyroid and pituitary adenoma combinations, leaving unresolved the role of CDKN1B mutation in MEN-like syndrome (13). The recognition of both the MENX (rat) and the MEN4 (human) syndromes has demonstrated that *Cdkn1b*/CDKN1B is a new tumor susceptibility

gene for multiple neuroendocrine tumors in both species (14). Several observations, together with studies of engineered mouse models with defective or mutant p27, confirm a critical role for p27 in regulating cell proliferation in neuroendocrine cells. As novel CDKN1B mutations are discovered, our understanding of the relationship between p27 and neuroendocrine tumor predisposition will increase. The characterization of the molecular properties of mutant p27 proteins associated with MEN4 may facilitate the development of more effective targeted therapeutic strategies for the patients carrying those mutations.

We recently reported that in sporadic MTC, CDKN1B V109G polymorphism correlates with a more favorable disease progression than the wild-type allele and might be considered a new promising prognostic marker (15).

Recent insights on MEN syndrome pathogenesis and related inherited endocrine disorders have a major clinical impact and fundamental studies are now in progress in order to identify all genetic events leading from a normal endocrine tissue towards a fully malignant phenotype. This data are of particular interest for an adequate surgical and therapeutic approach.

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