Multiple endocrine neoplasia type 2 (MEN 2)

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Introduction

Multiple endocrine neoplasia type 2 (MEN 2) is an autosomal dominant tumour syndrome caused by germ-line-activating mutations of the *RET* proto-oncogene. It is characterised clinically by the presence of medullary thyroid carcinoma (MTC), bilateral pheochromocytoma, and primary hyperparathyroidism (MEN 2A) within a single patient or family. Three distinct clinical forms have been described: (i) classical MEN 2A, (ii) MEN 2B, an association of MTC, pheochromocytoma, and mucosal neuroma, and (iii) familial MTC (FMTC), which is associated with a very low incidence of other endocrinopathies. Each variant of MEN 2 results from a different *RET* gene mutation, with strong genotype–phenotype correlation. Genetic testing detects nearly 100% of mutation carriers and is considered the standard of care for all first-degree relatives of patients with newly diagnosed MTC. Recommendations on the timing of prophylactic thyroidectomy and extent of surgery are based on classification of RET mutations into three risk levels according to genotype–phenotype correlations. MEN 2 provides a unique model for early prevention and cure of cancer and for the stratified roles of mutation-based diagnosis of carriers.

Clinical syndromes of MEN 2

MEN 2 (OMIM 171400) is an autosomal dominant tumour syndrome with an estimated prevalence of 2.5 per 100,000 in the general population.

MEN 2 syndrome occurs in three clinically distinct varieties with MTC as a common manifestation. These three subtypes of MEN 2 differ with respect to incidence, genetics, age of onset, association with other diseases, aggressiveness of MTC, and prognosis [1] (Table 1).

MEN 2A syndrome

MEN 2A syndrome is characterised by MTC in combination with pheochromocytoma and/or multiple tumours of the parathyroid glands in a single patient, or the presence of two or more tumour types in multiple members of a single family. It is the most common form of all MEN 2 syndromes, representing 55% of cases [2]. The frequency of MTC is over 90% among patients with MEN 2A, while the frequency of pheochromocytoma and multiple parathyroid gland hyperplasia are 40–50% and 10–20%, respectively. MTC is generally the first manifestation of MEN 2A and develops between the ages of 5 and 25 years. Rare variants of MEN 2A exist, including MEN 2A with cutaneous lichen amyloidosis and FMTC (or MEN 2A) with Hirschsprung's disease.

MEN 2B syndrome

MEN 2B syndrome is the most aggressive form of MEN 2 and accounts for 5–10% of MEN 2 cases. It consists of MTC, pheochromocytoma, an absence of hyperparathyroidism, visible physical stigmata such as raised bumps on the lips and tongue (due to cutaneous neuromas), ganglioneuromas, and a Marfanoid habitus

Table 1
Clinical classification of MEN 2 and occurrence of MTC, associated tumours and other diseases

Subtype	Percent (%) of total cases	MTC %	Pheo %	HPT %	Associated diseases
MEN 2A	56	100	50	25	Cutaneous lichen amyloidosis, Hirschsprung's disease
MEN 2B	9	100	50		Ganglioneuromatosis, Marfanoid habitus
FMTC	35	95			very rare

MTC, medullary thyroid carcinoma; Pheo, pheochromocytoma; HPT, hyperparathyroidism.

with skeletal deformations and joint laxity. Patients with MEN 2B typically have disease onset in the first year of life and have a more aggressive form of MTC with higher morbidity and mortality rates compared to MEN 2A patients. Patients with MEN 2B often do not have a family history of the disease, in which case the syndrome is due to a *de novo* mutation.

FMTC syndrome

Familial MTC (FMTC) is the mildest variant of MEN 2. It has been diagnosed more frequently in recent years and is reported to account for 35–40% of all MEN 2 cases [3–5]. With FMTC, there is a strong predisposition to develop MTC with a very low incidence of the other clinical manifestations associated with MEN 2A. The diagnosis of FMTC can only be considered when four or more family members across a wide range of ages have isolated MTC. In general, the clinical course of MTC in FMTC is more benign than that seen in individuals with MEN 2A and MEN 2B, and FMTC typically has a late onset or no clinically manifest disease. FMTC carries a good prognosis; however, aggressive MTC tumours and even death due to MTC have been reported in cases harbouring codon 804 mutations. A family history is often inadequate in establishing the diagnosis of familial disease, and a more thorough evaluation by genetic and biochemical screening often reveals a family history of MTC in patients originally thought to have the sporadic form of the disease.

RET proto-oncogene: structure, function, and genetic abnormalities

The MEN 2 gene was localised to centromeric chromosome 10 (10q11.2) by genetic linkage analysis in 1987. Subsequently, point mutations of the *RET* proto-oncogene were identified in MEN 2A, MEN 2B, and FMTC in 7 exons located near this region (exons 8, 10, 11, 13–16) [6,7] (Fig. 1). Analysis of *RET* in families with MEN 2A and FMTC revealed that nearly 100% of these families have germ-line mutations, and that only those family members with the germ-line missense mutations have the disease. This discovery prompted major advances in our understanding of the molecular genetic basis of MTC and has significantly changed the clinical management of families with hereditary tumours. At present, mutation analysis has identified over 50 different missense mutations associated with the development of MEN 2 [5].

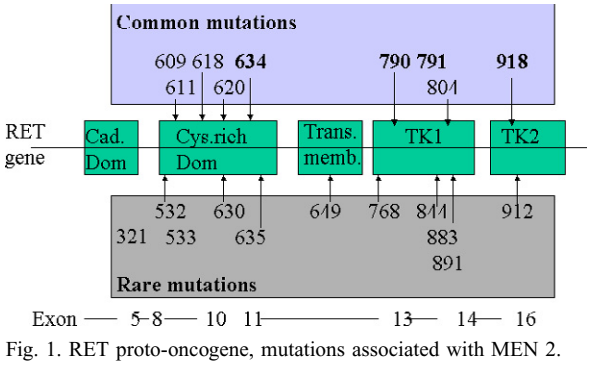

Fig. 1. RET proto-oncogene, mutations associated with MEN 2.

The *RET* gene has 21 exons and encodes a receptor tyrosine kinase that appears to transduce growth and differentiation signals in several developing tissues, including those derived from the neural crest. The protein consists of an extracellular segment with a ligand-binding domain, a cadherin (Ca^{2+}-dependent cell adhesion)-like domain, and a cysteine-rich domain close to the cell membrane. It has a single transmembrane domain and an intracellular segment with two tyrosine kinase subdomains, TK1 and TK2. The RET protein is activated upon ligand-induced dimerisation [8].

RET is expressed in neuroendocrine cells including C-cells of the thyroid, the precursors of MTC, and in pheochromocytomas. Hereditary MTC is caused by autosomal dominant gain-of-function mutations in the *RET* proto-oncogene. Mutation of the extracellular cysteine at exon 11 codon 634 causes ligand-independent dimerisation of receptor molecules, enhanced phosphorylation of intracellular substrates, and cell transformation. Mutation of the intracellular tyrosine kinase (codon 918) has no effect on receptor dimerisation but causes constitutive activation of intracellular signalling pathways and also results in cellular transformation. There is a significant age-related progression from C-cell hyperplasia (CCH) to MTC, which correlates with the transforming capacity of the respective *RET* mutations [9]. MTC is generally the first neoplastic manifestation in patients with MEN 2A because of its earlier age and higher rate of penetrance compared with pheochromocytoma or parathyroid hyperplasia. This indicates that C cells are more susceptible to oncogenic *RET* activation than adrenal medullary or parathyroid cells.

Genotype–phenotype correlation in MEN 2

Clear associations are documented between specific *RET* mutations (genotype) and the age of onset and aggressiveness of MTC and the presence or absence of other endocrine neoplasms (phenotype), such as pheochromocytoma or hyperparathyroidism [10,11].

Table 2
Codon-based genotype–phenotype correlation

Risk of MTC development	Mutated codon	MEN 2 subtype
high (level 1)	609, 649, 768, 791, 790, 804, 891	FMTC, MEN 2A
higher (level 2)	634, 611, 618, 620, 630, 631	MEN 2A
highest (level 3)	918, 883	MEN 2B

MTC, medullary thyroid carcinoma; MEN, multiple endocrine neoplasia; FMTC, familial medullary thyroid carcinoma.

Although some overlap exists between *RET* mutations and the resulting clinical subtype of MEN 2, 85% of patients with MEN 2A have a mutation of codon 634 (exon 11, cystein-rich domain); mutations of codons 609, 611, 618, and 620 account for an additional 10% to 15% of cases. Hyperparathyroidism in MEN 2A is most commonly associated with codon 634 mutations, and in particular with the C634R mutation [12].

Pheochromocytoma are associated with 634 and 918 mutations in approximately 50% of patients, and are not infrequently associated with mutations in exon 10 (codon 609, 611, 618, 620) but rarely with exon 15 (codon 791, 804) [13,14].

The association between disease phenotype and *RET* mutation genotype may have important implications for the clinical management of MEN 2 patients and their families. If the genotype can be fully correlated with certain phenotypic features, then a clinician could use a patient's genotype to decide if intense screening for pheochromocytoma or hyperparathyroidism is necessary in those patients with mutations associated with a higher risk of disease.

All cases of MEN 2A with Hirschsprung's disease have mutations in exon 10 (codon 609, 611, 618, 620), and MEN 2A with cutaneous lichen amyloides is associated with mutations in codon 634.

More than 95% of MEN 2B patients have mutations in codon 918 (exon 16, tyrosine kinase domain), but mutations are rarely identified at codon 883 exon 15. The 918 mutation resulted in an ATG (methionine) to ACG (threonine) alteration, which is significant because Met 918 is a critical component of the substrate recognition pocket in the tyrosine kinase catalytic core of the RET protein.

In FMTC, germ-line mutations are distributed throughout the *RET* gene with an accumulation in exon 13 (codon 768, 790, 791), and exon 14 (codon 804, 844); some of these mutations have also been identified in families with MEN 2A. Because FMTC shares a common genetic defect with MEN 2A, it can be difficult to distinguish a family that initially appears to be FMTC from one with MEN 2A, as the manifestation of pheochromocytoma and/or hyperparathyroidism occurs later in the course of the disease.

Extensive reports in the literature show a correlation between the specific germ-line *RET* mutation and the age of onset and aggressiveness of MTC development and the presence of nodal metastases [9]. Patients with codon 918 mutation and MEN 2B have a high risk of aggressive MTC occurring at a young age. In contrast, patients with codon 791 mutations have a relative low risk of aggressive disease, and develop slow-growing tumours as a late manifestation [15]. This genotype–phenotype correlation between mutation and age of onset and tumour aggressiveness is the basis for decision making in the clinical management of MEN-2 patients. This is particularly true in pre-symptomatic *RET* mutation carriers, as prophylactic thyroidectomy has to be performed prior to the development of cancer. This strategy for prevention of familial MTC should be tailored according to the specific mutation carried by each patient.

Recommendations for the timing of prophylactic thyroidectomy and the extent of surgical resection are based upon a model that utilises these genotype–phenotype correlations to stratify mutations into three risk levels [16,17] (Table 2). Patients with level 1 mutations (codons 609, 768, 790, 791, 804, and 891) have a high risk for MTC development and growth, patients with level 2 mutations (codons 611, 618, 620, and 634) are at a higher risk, and patients with level 3 mutations (codons 883 and 918) are at the highest risk for early development and growth of MTC (Table 2).

Codon-specific prognosis would facilitate individual risk stratification for each patient (Table 3). Furthermore, good evidence exists for a significant age-related progression from C-cell hyperplasia (CCH) to MTC that correlates with the transforming potential of level 2 (codon 634) and level 3 mutations (codon 918) [9]. In the cases of these higher risk mutations, a thyroidectomy is recommended at the age of 5 years

Table 3
Management of patients with different RET mutations

Mutated RET Codon	609, 791, 790, 804, 649, 891, 768	634, 611, 618, 620, 630, 631	918, 883
Risk level	1	2	3
MEN 2 subtype	FMTC (rarely MEN 2A)	MEN 2A	MEN 2B
MTC aggressiveness	high	higher	highest
Age of onset	usually adults	5 years	first year of live
Recommended age at prophylactic thyroidectomy	when calcitonin raises/5 to 10 years of age	age 5 years	first months of life
Other endocrine tumours	rarely	Pheo, HPT	Pheo

MTC, medullary thyroid carcinoma; Pheo, pheochromocytoma; HPT, hyperparathyroidism; FMTC, familial medullary thyroid carcinoma; MEN, multiple endocrine neoplasia.

Table 4
Codon-based genotype–phenotype correlation, strength of data

Phenotype: Risk of MTC development	Genotype – Codon of *RET* mutation		
	Very good evidence, large number of families	Sufficient evidence	Single cases, less clinical experience
high (level 1)		609, 791, 790, 804	649, 891, 768
higher (level 2)	634	611, 618, 620	630, 631
highest (level 3)	918		883

MTC, medullary thyroid carcinoma.

with level 2 mutations, and as early as possible, preferably in the first year after birth, for patients with level 3 mutations [16]. For patients with level 1 mutations there are three alternatives concerning recommended age at prophylactic surgery: some authors suggest thyroidectomy at age 5, others at age 10, while others, including the current authors [15], suggest that surgery may be postponed until an abnormal C cell stimulation test result is observed (i.e. an abnormal Calcitonin response to pentagastrin or calcium stimulation). Further studies, particularly regarding rare mutations [18], are necessary before common recommendations can be made (Table 4).

Pheochromocytoma

Pheochromocytoma occur in approximately 20% to 50% of MEN 2A patients depending on the mutation. Pheochromocytomas are associated with 634 and 918 mutations in approximately 50% of patients, and are not infrequently associated with mutations in exon 10 (codon 609, 611, 618, and 620) but rarely with exon 15 (codon 791, 804) [16]. As with MTC, the pheochromocytomas of MEN 2 are also multi-centric with diffuse adrenomedullary hyperplasia developing bilateral pheochromocytoma in half of the cases, but often after an interval of several years [14]. Almost all pheochromocytomas are located in an adrenal gland, malignant pheochromocytoma are rare. In index cases, the clinical manifestation of pheochromocytoma associated with MEN 2 is similar to that in sporadic cases with signs and symptoms such as headache, palpitations, nervousness, tachycardia and hypertension. However, pheochromocytomas are usually identified early as a result of regular biochemical screening in gene carriers and clinical manifestations are thus subtle or absent. It is unusual for pheochromocytoma to precede the development of MTC and be the initial manifestation of MEN 2. Annual biochemical screening by measuring plasma and/or 24 h urinary excretion of catecholamines and metanephrines should be performed. Once the biochemical diagnosis is made, imaging studies like magnetic resonance imaging (MRI) or metaiodobenzylguanidine (MIBG) scanning are appropriate. The presence of pheochromocytoma must be ruled out prior to any surgical procedure. Patients with MTC should be evaluated for possible pheochromocytoma. A coexisting pheochromocytoma should be removed before thyroidectomy.

Table 5
Diagnostic procedures in the follow-up of MEN 2 patients

Biochemistry, every 3–6 months
Thyroid stimulating hormone (TSH), free-T4 (FT4), free-T3 (FT3)
Calcitonin, carcinoembryonic antigen (CEA)
Serum-Calcium, Parathyroid hormone
Catecholamines, Metanephrines (Plasma/Urine)
Imaging: once or twice a year
ultrasound of neck and abdomen
computed tomography/magnetic resonance imaging (MRI) of the neck and mediastinum/abdomen
metaiodobenzylguanidine (MIBG)-scintigraphy/MRI if pheochromocytoma is suspected

Primary hyperparathyroidism

Primary hyperparathyroidism with hypercalcaemia and an elevated serum parathyroid hormone level occurs in 10% to 25% of MEN 2 gene carriers (especially codon 634). Hyperparathyroidism develops slowly, is usually mild and clinical features do not differ from those seen in mild sporadic hyperparathyroidism. The diagnosis is established by finding high parathyroid hormone concentrations in the presence of hypercalcaemia. Pathological findings show chief cell hyperplasia involving multiple glands. Annual measurement of serum calcium concentration in gene carriers is probably adequate for screening purposes.

Treatment

Surgery

The appropriate surgery for sporadic MTC and index patients in MEN 2 is total thyroidectomy and careful lymph node dissection of the central and, if necessary, lateral compartment of the neck. The latter is necessary for tumour staging and prevention of later midline complications related to local metastatic disease. If there is no evidence of local lymph node metastases during the primary surgical procedure, a surgical cure is likely and further neck dissection is probably unnecessary. Total thyroidectomy is absolutely necessary in hereditary cases because of the bilateral and multifocal nature of MTC. If the initial surgical procedure was inadequate then reoperation with an appropriate surgical procedure is indicated [19,20]. All patients should receive adequate L-Thyroxine replacement therapy after total thyroidectomy.

Perhaps the most difficult problem associated with the management of MTC is what to do with the patient who has persistently elevated plasma calcitonin levels after an adequate surgical procedure. In almost all cases, persistent elevation of plasma calcitonin implies the presence of tumour. A thorough evaluation should be undertaken to define the extent of local and distant metastatic disease (Table 5). Localisation of metastases or recurrence can be done by different imaging methods like ultrasonography of neck and abdomen, computed tomography (CT) of neck, mediastinum, lung and liver or MRI. Selective venous catheterisation with blood sampling for CT determination is helpful in detecting liver metastases at a very early stage and identifying a particular region of the neck or mediastinum that the surgeon should focus upon. Octreoide or 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning may also be helpful, especially in identifying lung metastases at a very early stage of MTC. At the conclusion of these diagnostic procedures, a decision regarding reoperation must be made.

If the primary operation was inadequate, if there is no evidence of distant metastases and if local disease is found in the neck or/and mediastinum, reoperation is advocated. A successful cure, even long after the primary operation, is possible in a small number of patients by meticulous lymph node dissection of all compartments of the neck and mediastinum, with the complete removal of the lymphatic and fatty tissue between important anatomical structures. This surgical technique has produced a cure rate of 25% in such patients.

If distant metastases are found, there is no indication for surgical intervention unless the patient develops diarrhoea or local complications, for which tumour debulking may be beneficial.

Recommendations for the timing of prophylactic thyroidectomy in MEN 2 patients are based upon a model that utilises genotype–phenotype correlations to stratify mutations into *three risk levels* (see chapter on genotype–phenotype correlation).

Surgery for pheochromocytoma in MEN 2 should precede surgery for MTC. Before adrenalectomy all

patients should receive appropriate pharmacotherapy (alpha- with/or without beta-adrenergic antagonist). Approximately one-third of patients who undergo a unilateral adrenalectomy will eventually require a second operation for contralateral pheochromocytoma, but this may not occur for many years, during which time the patient will not be steroid dependent. Adrenal cortical-sparing adrenalectomy is a promising technique for preventing adrenal insufficiency.

The parathyroid glands in MEN 2 patients are frequently found to be enlarged at thyroidectomy for MTC and should therefore be carefully evaluated. The goal in MEN 2 patients with primary hyperparathyroidism is to excise the enlarged glands and to leave at least one normal parathyroid gland intact. If they are all enlarged, a subtotal parathyroidectomy or total parathyroidectomy with autotranplantation should be performed.

Postsurgical follow-up and management

All patients with MTC should undergo calcitonin and carcinoembryonic antigen (CEA) determination at regular intervals after total thyroidectomy. Normal basal and pentagastrin-stimulated calcitonin levels suggest a tumour-free state and thus patients require no further treatment. They can be followed-up at half yearly intervals with physical examination and calcitonin determination as well as thyroxine substitution therapy (Table 5).

Patients with persistent elevation of plasma calcitonin after total thyroidectomy should be thoroughly evaluated to define the extent of local and distant disease (see above). If there is no evidence of distant metastases and if local disease is found in the neck, reoperation is advocated using meticulous dissection and microsurgical techniques.

In patients remaining calcitonin-positive with evidence of non-curable and non-operable disease (diffuse distant metastases) or occult disease (no local recurrence is found and adequate operation has been done), close observation of changes in serum calcitonin and CEA concentration is required. Many patients may exhibit a remarkable stable course and no further treatment is recommended; a "wait and see" approach is advocated, as experience with non-surgical therapy in the management of slow growing metastatic MTC has been disappointing [21,22]. In those patients whose disease shows rapid and steady progress, e.g. doubling of tumour marker in less than 1 year, intervention with chemotherapy, radiotherapy, or somatostatin can be considered as a palliative therapeutic modality.

The role of regional external radiotherapy in the treatment of MTC continues to be controversial. In patients with an inoperable tumour, radiotherapy can offer prolonged palliation and achieve local tumour control. Radiotherapy may be helpful for patients with expanding final stage lesions or painful osseous metastases, but the response is poor. As MTC is relative insensitive to chemotherapy and the results are correspondingly poor, such treatment might be indicated when the tumour mass seems to have escaped local control and entered a more aggressive growth phase. Monotherapy with doxorubicin ($60\,mg/m^2$ every 3 weeks) or a combination of doxorubicin and cisplatin has been used in some trials but with a response rate below 30%. Quality of life, toxic side-effects and survival have to be taken into account when chemotherapy is recommended. Therefore, chemotherapy in advanced MTC must be individualised based on clinical grounds.

The stable analogue of somatostatin, octreotide, has been used in a limited number of patients with advanced metastatic MTC. A transient reduction of calcitonin and CEA levels and a transient improvement of symptomatic diarrhoea and flushing has been reported but not confirmed in some patients, but no real effect on tumour mass has been observed.

RET seems to be a promising target for molecular therapy of patients with MTC. Different strategies that might obstruct the kinase function of RET are on the way [21]. Some competitive inhibitors of adenosine triphosphate (ATP)-binding are being tested in clinical trials. Vandetanib (ZD6474, AstraZeneca), a multikinase inhibitor that targets RET, vascular endothelial growth factor receptor (VEGFR), and epidermal growth factor receptor (EGFR), inhibits the wild-type enzyme and most of the activated forms of RET. Promising preliminary results from studies using these targeted agents have been reported in recent trials for hereditary MTC. Results of a single-arm phase 2 study using vandetanib showed partial response and stable disease rates of 20% and 30%, respectively, among 30 patients with metastatic hereditary MTC [23].

Conflict of interest statement

None declared.

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