Lessons from genes mutated in multiple endocrine neoplasia (MEN) syndromes

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INTRODUCTION

The rapid discovery of cancer-related genes in the last decade has strengthened the possibility of cancer genetic risk assessment. Since patients have been becoming increasingly aware of available genetic testing options, it is mandatory that physicians become knowledgeable in identifying and advising patients at increased risk for a hereditary cancer syndrome. In particular, recent progress in the genetic basis of endocrine tumorigenesis, provides new opportunities to apply the new acquisitions to diagnosis and management of hereditary tumour syndromes. The Rare Disease Act of 2002 defines a rare disease or condition as one that affects less than 200,000 persons in the United States whereas the European Commission on Public Health defines rare diseases as “life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them” (http://www.rare-cancer.org/rare-diseases.html). According to that, Multiple Endocrine Neoplasia syndromes (MENs) can be reasonably included in the list of the rare diseases. Although uncommon, they are important to be recognized because the gene-related mutations confer a high risk of multiple primary cancers, occurring at younger ages, affecting multiple members of a family who inherit the cancer-predisposing genetic mutation.

Lessons from genes mutated in multiple endocrine neoplasia (MEN) syndromes

Multiple endocrine neoplasia (MEN) types 1 and 2 syndromes are rare hereditary cancer syndromes expressing a variety of endocrine and non-endocrine neoplasias and lesions. The improving of both molecular and clinical genetics knowledge helps health care providers in the whole spectrum of the clinical managements of MEN patients. The MEN1 gene, a tumour suppressor gene, is responsible of MEN1 syndrome, and is probably involved in the regulation of several cell functions, including DNA replication and repair and transcriptional machinery. RET proto-oncogene encodes for a receptor tyrosine kinase protein whose expression is fundamental for appropriate migration, development and differentiation of neuroendocrine cells originating from neural crest. Currently, DNA testing makes possible the early identification of germline mutation in asymptomatic mutant gene carriers in both MEN syndromes. Consequently, the combination of new genetic and diagnostic tools could permit a precocious detection of MEN-associated neoplasias, and in particular the identification of a strong genotype–phenotype correlations in MEN2 syndrome demonstrates an improving outcome and quality of life for affected subjects.

Key words: Multiple endocrine neoplasia syndromes, MEN1, MEN2, MENIN, RET proto-oncogene, endocrine tumorigenesis.
More importantly, patients and physicians are recognizing the potential therapeutic advantages of identifying hereditary cancer risk. With a growing number of preventive care options available to patients and families with hereditary cancer syndromes, the process of systematically assessing risk is becoming increasingly important. In this review emerging information on both basic and clinical aspects, including treatment, of these hereditary syndromes, with multiple tumours/abnormalities in endocrine and non-endocrine tissues, will be described.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1) SYNDROME

MEN1 or Wermer syndrome (OMIM#131100) is an autosomal dominant inherited syndrome with high penetrance (nearly 100% by age of 50) and elevated inter-, intra-familial clinical variability, making difficult to foresee the clinical behaviour and the tumour localizations in an asymptomatic MEN1 carrier. MEN1 occurs with a random combination of more than 20 endocrine and non-endocrine tumours, in sporadic or, more frequently, in familial cases and it should be considered in a patient exhibiting at least two of the following three endocrine tumours: parathyroid, anterior pituitary and gastro-entero-pancreatic (GEP) tumours. Then, familial cases may be defined by an MEN1 case, as above stated, plus one first-degree relative exhibiting at least one of these tumours. According to the autosomal dominant heritability an affected parent has a 50% chance to transmit the condition to each offspring, independently by sex [14]. Other endocrine and non-endocrine tumours have been correlated with this syndrome (table IA and IB). MEN1 syndrome is most commonly diagnosed in the proband during the fourth or fifth decade of life with a considerable delay from the age of biochemically detectable onset, because symptoms are typically delayed for another 5-8 years [14, 75, 82]. Early recognition of affected and at risk individuals within kindred is today facilitated by DNA-testing [14]. Particularly, after the cloning of MEN1 gene [20] the early detection of asymptomatic carriers dramatically decreases the morbidity and mortality of MEN1, providing the opportunity to initiate appropriate treatment at early stages. Paradoxically, the consequently longer life span may result in a rising cumulative morbidity and mortality from MEN1-associated malignancies [14]. Unfortunately, the lack of genotype/phenotype correlation makes difficult the use of genetic information to predict clinical behaviour, localization, early detection and prognosis of related tumours.

Table IA
MEN1-related endocrine tumours and their prevalence.

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid adenomas</td>
<td>(90%)</td>
</tr>
<tr>
<td>GEP</td>
<td></td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>(40%)</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>(10%)</td>
</tr>
<tr>
<td>Others (VIPoma, PPoma, SSoma, glucagonoma)</td>
<td>(2%)</td>
</tr>
<tr>
<td>Non-functioning</td>
<td>(20%)</td>
</tr>
<tr>
<td>Anterior Pituitary Functioning</td>
<td></td>
</tr>
<tr>
<td>PRLoma</td>
<td>(20%)</td>
</tr>
<tr>
<td>GH-, GH/PRL-, TSH-, ACTH-secreting, or non-functioning</td>
<td>(17%)</td>
</tr>
<tr>
<td>Foregut Carcinoids</td>
<td></td>
</tr>
<tr>
<td>Thymic</td>
<td>(2%)</td>
</tr>
<tr>
<td>Bronchial</td>
<td>(2%)</td>
</tr>
<tr>
<td>Gastric (ECLoma)</td>
<td>(10%)</td>
</tr>
<tr>
<td>Adrenal gland</td>
<td>non functioning (20%)</td>
</tr>
</tbody>
</table>

Table IB
MEN1-related non-endocrine tumours and their prevalence.

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td></td>
</tr>
<tr>
<td>Tumors</td>
<td></td>
</tr>
<tr>
<td>Lipomas (they could be also visceral)</td>
<td>(30%)</td>
</tr>
<tr>
<td>Facial angiofibromas</td>
<td>(85%)</td>
</tr>
<tr>
<td>Collagenomas</td>
<td>(70%)</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td></td>
</tr>
<tr>
<td>Meningiomas</td>
<td>(5%)</td>
</tr>
<tr>
<td>Ependymomas</td>
<td>(1%)</td>
</tr>
<tr>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Leyeriomomas</td>
<td>(10%)</td>
</tr>
</tbody>
</table>

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2) SYNDROME

MEN2 or Sipple syndrome (OMIM#171400) is an autosomal dominant disease described in hundreds of families throughout the World. Three distinct clinical variants of MEN2 have been reported: MEN2A, accounting for 80% of MEN2 [35], MEN2B, and Familial Medullary Thyroid Carcinoma (FMTC). All variants of MEN2 show a high penetrance for Medullary Thyroid Carcinoma (MTC); in fact, 90% of MEN2 adult gene carriers will eventually show evidence of MTC, unilateral or bilateral pheochromocytoma (PHEO) in 50% in MEN2A and 2B, and multigland parathyroid adenomas, in 20 to 30% of MEN2A patients [14, 29, 67]. Moreover, two rare “subvariants” of MEN2A have also been evidenced: MEN2A with Cutaneous Lichen Amyloidosis (CLA) and MEN2A or FMTC with Hirschsprung’s (HSCR) disease [68]. MTC constitutes the first clinical evidence in most of the MEN2 affected individuals and it generally exhibits an earlier age onset when compared to the sporadic counterpart. FMTC syndrome is not easy to be defined and
its clinical diagnosis is essentially based by the lack of PHEO and PHPT in the familial history of proband [44]. Oppositely, MEN2B variant, exhibiting a more aggressive behaviour of MTC than MEN2A and FMTC, represents the most distinctive form of MEN2 syndrome. It also includes mucosal neuromas, throughout the gastrointestinal tract and eyelids, a Marfan-like phenotype, without ophthalmologic and vascular involvement of “classic” Marfan syndrome, other than MTC and PHEO [88]. Differently from the MEN1 syndrome, genetic studies of MEN2 syndrome clearly demonstrated the existence of a strong genotype-phenotype correlation [14].

**MEN1 GENE**

Linkage analysis in affected families localised the putative MEN1 locus at chromosome 11q13 and all the affected members within a family shared a common haplotype [49]. Studies of loss of heterozygosity in MEN1 tumour tissues revealed the loss of the allele derived from the unaffected parent at somatic level in most neoplasms [8, 32, 49], suggesting the inactivation of a tumour suppressor gene. The cloning of MEN1 gene in 1997 [20, 51] has provided the opportunity to perform germline DNA mutational analysis.

Recent advances on pathophysiological roles of menin, the protein product of MEN1 gene, disclose the existence of an intricate network composed by several molecular partners interacting with menin: JUND [2], Smad1, Smad3, Smad5, Runx2 [76], Sin3a, HDAC [47], Pem [52], COMPASS-like complex, RPA2 [78], FANCD2 [45], Hsp70, CHIP [90], Hox [92], TGFβ [73], GFAP, vimentin [54], NF-kB [40], NM23H1 [63], ERK, JUNK, Elk-1 and c-Fos [36]. However, it is still completely unknown how mutations in menin cause tumorigenesis, nor is the function of menin. Menin, mainly located in the nucleus [3], is widely expressed and may play different roles in different tissues and probably involved in the regulation of several cell functions, including DNA replication and repair and transcriptional machinery and so forth.

**MEN2 GENE: RET PROTO-ONCOGENE**

In 1993 RET proto-oncogene, on chromosome 10, was recognized as the gene responsible for MEN2 syndrome [27, 60]. RET protein expression is fundamental for appropriate migration, development and differentiation of neuroendocrine cells originating from neural crest. An in situ hybridisation study reported on the pattern of RET expression during early development of human embryos. RET gene is expressed in the developing kidney, the presumptive enteric neuroblasts of the developing enteric nervous system, cranial ganglia, and in the presumptive motor neurons of the spinal cord [6]. RET protein is a membrane tyrosine kinase receptor representing a subunit of a multimolecular complex binding several growth factors from the family of the glial derived neurotrophic factor [72]. Specifically, extracellular domains consist of four cadherin-like repeats, a calcium-binding site, and a cysteine-rich domain. RET cysteine mutants, through formation of intermolecular bonds between free cysteines, enable a covalently ligand-independent receptor dimerization resulting in a constitutive kinase activation.

At the intracellular level the protein contains a typical tyrosine kinase domain and its activating mutations (mostly methionine to threonine and rarely alanine to phenylalanine substitutions) are found in MEN2B patients [14]. The RET tyrosine kinase catalytic core is located in the intracellular domain and interacts with the docking protein FRS2 causing the downstream activation of the mitogen-activated protein (MAP) kinase signalling cascade [56]. Thus, mutations at this level, probably impairing the rate of phosphorylation and the selection of substrate, determine a constitutive ligand- and dimerization-independent activation of receptor [72]. A recent expression study by microarray technique on PHEO and MTC tissues from MEN2A and 2B patients unravelled the existence of a different gene expression profile that could account for the difference in the aggressive behaviour between these MEN2 variants [42].

**CLINICAL FEATURES AND MANAGEMENT OF MEN1**

Manifestations of MEN1 generally occur as a consequence of overproduction of polypeptide hormones by tumour cells, or as a result of tumour growth itself. The increase of clinical knowledge provided the opportunity to describe many other endocrine and non-endocrine neoplasms associated with MEN1 syndrome: for gut carcinoids, adrenal tumours, cutaneous and visceral lipomas, skin lesions such as facial angiofibromas and collagenomas [14] and central nervous system tumours such as meningiomas and ependymomas [17] (table I).

**Primary hyperparathyroidism (PHPT)**

PHPT, accounting for hypercalcaemia, represents the main MEN1-associated endocrinopathy, reaching 100% penetrance by 50 years of age, and the first clinical expression of MEN1 in 90% of patients. Its age of onset is three decades earlier than sporadic parathyroid adenoma [57]. Generally, all the parathyroid glands are asymmetrically and asynchronously involved with a
hyperplastic and/or adenomatous outgrowth. PHPT is frequently asymptomatic for a long period, but bone mass in MEN1 hyperparathyroid women could be already low at 35 years of age [16]. Moreover, the hypercalcaemia may increase the secretion of gastrin from normal and tumour gastrin-secreting cells, enhancing the gastric basal acid output and the occurrence of multiple peptic ulcers [14]. Surgery still represents the elective therapeutic approach to MEN1-PHPT and must satisfy three main requirements: a) obtaining of long-standing eucalcaemia; b) avoiding permanent hypocalcaemia; and c) facilitating a future surgery for recurrent disease. Surgical approaches are consisting of either total or subtotal parathyroidectomy [14]. Total parathyroidectomy is followed by heterotopic transplantation of resected parathyroid tissue [18].

GEP tumours

Their prevalence in MEN1-expressing adults varies in different clinical series from 30 to 75% [80], with a prevalence near to 80% at a middle age, as similarly seen in necropsy series [9, 75]. MEN1-GEP tumours develop from a polyclonal proliferation in pancreatic islet or in endocrine cells of stomach, of duodenum, or rarely of first jejunal loop or biliary tract [81]. They are represented by multiple nodular lesions of different endocrine cells ranging from microadenomas to macroadenomas to invasive and metastatic carcinomas and are exceptionally detected at an early age [11, 19]. No available biochemical markers may help the identification of highest risk cases and the prediction of the development or progression of these tumours, even if the biochemical screening may reveal high levels of markers such as chromogranin A (CgA) or pancreatic polypeptide (PP), [14, 61, 75]. Malignancies are more likely occurring with spread to the regional nodes or the liver when sized more than one cm [81]. Gastrinomas and insulinomas represent the most frequent MEN1-GEP functioning tumours, 60-80% and 20% respectively [61, 81], but also tumours secreting vasointestinal peptide (VIP), pancreatic polypeptide (PP), somatostatin (SS) and glucagon have been reported [14]. Functioning tumours, producing excess hormone, can be clinically detected by the age of 40 years, but biochemical and imaging tests may detect some tumours in asymptomatic carriers by the third decade, one decade earlier than in sporadic tumours. Generally, non-functioning PETs are the most frequent lesions in MEN1 syndrome [43] and immunostaining analysis revealed these to contain, in differing frequency and combinations, CgA and B, pancreatic polypeptide (PP), glucagon, insulin, proinsulin, somatostatin (SS), gastrin, vasoactive intestinal peptide (VIP), serotonin, calcitonin, growth hormone-releasing factor (GRF), and neurotensin [50].

**MEN1 gastrinomas**

Gastrinomas in MEN1, with multiple foci and small size (diameter <1cm), are mostly located in duodenal submucosa [61] with multiple nodular or polypoid lesions arising deep in the mucosa and expanding into the submucosa. Multiple tumoural or hyperplastic duodenal foco of gastrin cells may surround the gastrinomas [66, 81]. Approximately 40% of MEN1 patients exhibit gastrinomas, usually including a malignant component. In fact, in 50% of patients, the gastrinomas have already metastasised before the diagnosis and 30% die [61]. Diagnosis of MEN1-gastrinoma can be made on the basis of Zollinger-Ellison syndrome (ZES) clinical evidences due to elevated basal/stimulated (calcium or secretin) gastrin and basal acid output levels [14, 81]. Medications such as proton pump inhibitors, H₂ blockers and somatostatin analogues (used also to control gastroenteric hormones secretion other than gastrin) are effective in preventing severe and sometimes life-threatening morbidity in MEN1 [81]. However, cure rate for ZES in MEN1 is low when surgery is limited to tumour enucleation or full thickness duodenal wall resection. Conversely, pancreatoduodenectomy is followed by higher chance of cure [81].

**MEN1 insulinomas**

MEN1 is present in 10% of all sporadic and hereditary cases expressing hypoglycaemia. MEN1-hypoglycaemia is generally caused by one tumour in the setting of multiple islet macroadenomas [14]. Insulin hypersecreting tumours, almost always benign [58], are usually macroscopic lesions, more than 0.5cm (generally 1-4cm) in diameter [38].

Surgery is the main treatment in MEN1 patients with hypoglycaemia due to insulinoma. Even in the absence of positive preoperative imaging, the insulinoma is usually identified readily through intraoperative ultrasonography.

**Natural history of GEP tumours**

The possibility of pharmacologically treating the gastrin hypersecretion in MEN1 patients result to be effective in preventing severe and sometimes life-threatening morbidity in MEN1. However, a large retrospective analysis in 34 MEN1 kindreds revealed that 46% of MEN1 carriers died for causes related to MEN1 at a median age of 47 years, with the most frequent cause of death being malignant pancreatic endocrine tumours, followed by malignant carcinoids [26], supporting a previous evaluation in a single large kindred from Tasmania [86], and as also confirmed by the Mayo Clinic study [25]. On the opposite, a recent retrospective study in a Finnish genealogical survey revealed that obligatory MEN1 gene carrier status did not show a harmful effect on survival [28], may be due to younger
age at death of the whole population in the more remote generations because of external factors (famine, infectious disease, and wars).

**Anterior pituitary tumours**

Anterior pituitary tumours represent the first clinical manifestation of MEN1 syndrome in one fourth of sporadic MEN1 cases, and 10% of familial MEN1. Their prevalence in MEN1 largely varies, from 10 to 60%, depending on the differences among patients and methods used. However, Verges et al. [84] reported that pituitary involvement was the initial manifestation of MEN1 in 17% of individuals and that pituitary adenomas were significantly more frequent in women than men (50% vs 31%, P<0.001). Generally, symptoms depend on the pituitary hormone produced, similarly to those of sporadic tumours, other than to compressive effects.

Approximately 65% of pituitary tumours are microadenomas (diameter <1cm) and, except than “true gonadotropinoma”, all the other tropin-secreting adenomas, GH, PRL, GH/PRL, ACTH, TSH adenomas, have been described as also non functioning tumours. An aggressive pituitary macroadenoma was firstly reported in one five year old child with MEN1 [77] and later at the French-Belgium MEN1 Register approximately 85% of pituitary tumours in MEN1 were recorded as pituitary macroadenomas exhibiting a less effective response to drugs commonly used to pharmacologically treat these tumours [84].

Prolactinoma is the most common pituitary functioning tumour [14], but in some families it has been reported to be unusually common, including four families from Newfoundland reported by Farid et al. [1] as the so-called MEN1_Burin variant and those reported by Burgess et al. [15] as the MEN1_Tasman variant.

**Adrenal tumours**

Adrenal cortex tumours are present in 20-40% of MEN1 cases and are generally bilateral and non functioning, even if hyperaldosteronism has been reported [10].

**Foregut carcinoid tumours**

Foregut carcinoid tumours reach a penetrance of 10% in MEN1 patients. Thymic carcinoids are prevalent in males while bronchial carcinoids in females [79]. Generally, carcinoid tumours are asymptomatic until a later stage, but the course of MEN1-thymic carcinoid is more aggressive than the sporadic tumour and total or partial thymectomy is highly recommended during neck surgery for PHPT in MEN1 patients [14]. Multiple type II gastric enterochromaffin-like (ECL) cell carcinoids, associated with hypertrophic hypersecretory gastropathy, are quite common in MEN1 [13], usually incidentally diagnosed at gastric endoscopy for ZES. The mean age at diagnosis is 50 years. A follow-up study revealed that the 90% of MEN1 patients affected by ZES develop a fundic argyrophil cell hyperplasia and about 35% of the same patients show gastric carcinoids [71]. Malignancies are rarely present before 30 years of age.

**Non endocrine tumours**

Approximately 40-80% of MEN1 patients exhibit multiple facial angiofibromas and collagenomas, while multiple lipomas, visceral and cutaneous, are present in 30% of MEN1 patients. Evaluation of 32 consecutively ascertained individuals with MEN1 by Darling et al. [24] revealed multiple facial angiofibromas in 88%, collagenomas in 72%, cafe au lait macules in 38%, lipomas in 34%, confetti-like hypopigmented macules in 6%, and multiple gingival papules in 6%. Central nervous system tumours has recently been reported with an 8% prevalence of meningiomas, typically presenting later in life [5]. Thus, a careful investigation to detect such abnormalities must be performed in each MEN1 patient.

A consensus statement on program of tests and test schedules for tumour expression screening in highly likely carrier of MEN1 mutation has been recently reached. Biochemical tests should be performed annually while imaging tests should be taken every 3 years [14].

**Morbidity and mortality**

A deeper knowledge of MEN1-associated clinical manifestations and the improved diagnostic procedures have allowed an early identification and management of those at risk for MEN1 tumours, virtually eliminating ZES and/or complicated PHPT as a cause of death. Although the Finnish study indicate that the presence of a MEN1 mutation do not exhibit harmful effect to survival when individuals were traced back as far as 300 years [28], the data from Geerdink et al. indicate much earlier than average mortality in the Dutch population [37]. Conversely, longer life expectancy in MEN1 is likely to result in a rising cumulative morbidity and mortality from MEN1-associated malignancies, accounting for approximately 30% of deaths in MEN1.
In table II are summarized the main clinical features of MEN2 syndrome.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Subvariant</th>
<th>Tumours/lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN2A</td>
<td></td>
<td>MTC (100%) PHEO (50%) PHPT (10-20%)</td>
</tr>
<tr>
<td>MEN2A/CLA</td>
<td></td>
<td>MTC, PHEO, PHPT + cutaneous lichen amyloidosis</td>
</tr>
<tr>
<td>MEN2A/HSCR</td>
<td></td>
<td>MTC, PHEO, PHPT + enteric aganglionosis</td>
</tr>
<tr>
<td>MEN2B</td>
<td></td>
<td>MTC (100%) PHEO (50%) Marfan-like habitus (&gt;90%) Multiple ganglioneuromas (&gt;90%) (tongue, eyelids, gastrointestinal tract)</td>
</tr>
<tr>
<td>FMTC</td>
<td></td>
<td>MTC</td>
</tr>
</tbody>
</table>

Pheochromocytoma (PHEO)

PHEO is a catecholamine-producing tumour of the adrenal gland. The chromaffin cells of the adrenal medulla produce epinephrine, norepinephrine and dopamine. When present, unilateral or bilateral PHEO [21] may account for hypertensive crises. Excess of epinephrine causes palpitations, nervousness, jitteriness but not hypertension. Hypertension can develop as the norepinephrine production increases [35]. PHEO can arise many years after MEN2A or MEN2B diagnosis. Sudden death from anaesthesia-induced hypertensive crisis has been described in individuals with MEN2A and unsuspected pheochromocytoma in the past [70].

Adrenal medulla function can be easily assessed by 24 hours measurements of urinary excretion of catecholamines and their metabolites and screening is recommended on an annual basis. When signs and symptoms are consistent with a suspect of PHEO, imaging tests should be performed [CAT, NMR, meta-iodobenzyl guanidine (MIBG) scanning]. Routine screening is recommended to assess for the presence of a PHEO in MEN2 patients prior any surgery in order to avoid intraoperative hypertensive crises.

Primary hyperparathyroidism (PHPT)

It is mainly associated to MEN2A variant and it is generally less precocious and aggressive than MEN1-PHPT [14].

MEN2A

MEN2A accounts for approximately 80% of MEN2 cases [35]. MTC is present in 90% of adult gene carriers, bilateral or unilateral pheochromocytoma (PHEO) in 50% and PHPT in 20-30% [14, 29, 67].

MEN2A-MTC is generally less aggressive than the one associated to MEN2B variant [14].

MEN2A/Cutaneous Lichen Amyloidosis (CLA) subvariant

In approximately 20-30 families an association between MEN2A and CLA has been reported. Affected subjects exhibit an intense pruritus, generally occurring at 30-40 yr and causing scratching lesions, with amyloid localized over the upper back [34, 35, 62].

MEN2A/Hirschsprung (HSCR) subvariant

This HSCR disease presents at childhood with an abnormal colon relaxation, and consequent severe constipation,
due to absence of specific nerve bundles, namely ganglion cells, in the colon of affected individuals [35]. This HSCR's form does not differ from other forms of childhood HSCR disease and it is usually surgically correctable. Interestingly, RET mutations, scattered along the length of the gene, have been found in some patients with sporadic or familial form of “HSCR disease only” [7]. While MEN2A-HSCR associates with RET activating mutations (gain of function), RET mutations reported in “HSCR only” cases were inactivating (loss of function), explaining the aganglionosis as an impair RET expression on presumptive enteric neuroblasts. How to explain such discrepancies? A recent in vitro study by Arighi E et al. suggest the hypothesis of a RET dual phenotype (Janus) where activating mutations impair the GDNF-dependent RET effects on cell migration, differentiation and survival but promote cell proliferation [4].

MEN2B

The phenotypical appearance of affected individuals makes this variant the more distinctive form of MEN2 syndrome. As above reported, they exhibit multiple mucosal neuromatous lesions including the distal tongue, eyelids, identifiable by scrupulous dentists or ophthalmologists, and the gastrointestinal tract. The latter localization usually accounts for colic obstructive disorder, diarrhoea, constipation during the childhood of MEN2B patients. An abnormal upper/lower body ratio, similarly to the one observed in Marfan affected patients, is the other peculiar clinical feature of MEN2B affected individual. Finally, paediatricians may commonly observed a delayed puberty in these patients [83]. MEN2B-MTC has an aggressive course and its metastases may frequently occur during the first year of life [44]. However, local lymph nodes and distant metastases have been regularly reported during the first and the second decade of life of these patients, respectively [74, 83].

Familial Medullary Thyroid Carcinoma (FMTC)

In this clinical variant MTC constitutes the unique clinical expression of MEN2 syndrome [31] generally exhibiting a moderate aggressiveness in these kindreds. In order to avoid to diagnose as FMTC small sized MEN2A kindreds, and consequently underestimate the risk of PHEO, the correct definition of a FMTC kindred must follow extremely rigorous criteria such as the presence of more than 10 carriers in the kindred, multiple carriers or affected members over 50 years of age. Thus, an adequate medical history, especially in older members, must be collected. [14].
The impact of genetic information in the clinical management of both affected and asymptomatic carriers. Candidates for testing should include any sporadic case with two or more MEN1-related tumours and first-degree relatives of mutant proband. Periodic screening for endocrine tumour manifestations in definite or probable MEN1 mutation carriers seems likely to help improve management, but, unlike in MEN2, this has not been proven (Table IIIA). Biochemical screening is recommended yearly starting in childhood, with tumour imaging recommended less frequently (every 3-5 years) [14].

**MEN2**

DNA-based testing of the RET gene identifies disease-causing mutations in 95% of individuals with MEN 2A and MEN 2B and in about 88% of families with FMTC [14]. The aggressiveness of MTC correlates with the type of MEN2 syndrome variant and with the codon specificity of RET mutation, indicating a genotype-phenotype correlation [14, 55, 59, 91].

Mutation of codon 634 accounts for 80% of all mutations identified in MEN2 and a single cysteine to arginine substitution is found in more than one-half of kindreds with MEN2A [30].

Ten to 15% of MEN2A kindreds (also including kindreds with one of its variant or FMTC) exhibit mutations of codons 609, 611, 618, or 620, while MEN2B affected individuals have mutations at codons 883, 918, or 922, accounting for 3–5% of all RET mutations [44] (Table IIIB).

Thus, the strong correlation between genotype and clinical expression of MEN2-associated MTC provided the opportunity to create three RET codon mutation stratification categories of mutant carrier children [14].

Children with MEN2B and/or RET codon 883, 918, or 922 mutation are classified as having the highest risk from aggressive MTC and should be operated on within the first 6 months. Children with any RET codon 611, 618, 620, or 634 mutation are classified as intermediate level and should have thyroidectomy performed before the age of 5 years. Children with RET codon 609, 768, 790, 791, 804, and 891 mutations are classified as lower risk level and may be operated on at a later stage. For all groups, a more aggressive neck dissection should be performed if there is evidence of involved lymph nodes in the lateral neck [14] (Table IIIC).

However, as reported by Jimenez C and Gagel RF “the experience with codons of ‘intermediate risk’ is considerably smaller than that with other groups and is certainly insufficient to be definitive.” [44].

Genetic information can also be used to assess risk for PHEO. Individuals with RET mutations on codon 609, 611, 618, 620, 630, 634, 790, 804, 883, 918, or 922 should be routinely screened for PHEO. Currently, it is reasonably acceptable that development of a PHEO is unlikely in kindreds with codon 768
and V804M mutations [30] (table IIIc). The experience concerning PHEO in kindreds with mutations on other distinct RET codons is too limited and it has to be to considered to perform periodic measurement of urine or plasma catecholamine levels in members of these kindreds [12, 23, 41, 46, 65].

CONCLUSIONS

MEN1 and 2 are rare hereditary cancer syndromes expressing a variety of endocrine and non-endocrine tumours. The increasing knowledge on the molecular and clinical pathophysiology of MEN syndromes together with the availability of genetic screening, greatly increase the likelihood that individuals with these syndromes will live full and normal lives, providing in early future the opportunity to develop individualized treatments. Further studies on the intricate molecular pathway networks of both genes and related proteins will be helpful to design novel therapeutic modalities [22].

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Tests from genes mutated in multiple endocrine neoplasia (MEN) syndromes


