Update on multiple endocrine neoplasia Type 1 and 2

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Key points

Multiple endocrine neoplasia type 1 is a rare genetic syndrome, characterized by the co-occurrence, in the same individual or in related individuals of the same family, of hyperparathyroidism, duodenopancreatic neuroendocrine tumors, pituitary adenomas, adrenocortical tumors, and neuroendocrine tumors (carcinoids) in the thymus, the bronchi, or the stomach.

Multiple endocrine neoplastic type 2 is a rare genetic syndrome, characterized by the familial occurrence of medullary thyroid carcinoma either isolated or associated with pheochromocytoma, primary hyperparathyroidism, or typical features (Marfanoid habitus, mucosal neuromas).

Subjects with clinical MEN1 and those who carry a mutation in the MEN1 gene should be offered biochemical and imaging screening in order to detect tumors and evaluate their progression over time.

Children with mutation in the RET gene should have prophylactic total thyroidectomy according to the category of aggressiveness of the detected mutation whereas those with clinical MEN2 should be operated on upon diagnosis.

In MEN1 patients, special attention should be paid to evaluate the progression duodenopancreatic neuroendocrine tumors because of their malignant potential. Also, thymic neuroendocrine tumors should be detected as soon as possible because they represent the most lethal tumor.

In MEN2, calcitonin and carcinoembryonic antigen (CEA) serve as excellent tumor markers for medullary thyroid carcinoma. Their preoperative levels are correlated with tumor size and predict postoperative cure. Moreover, calcitonin or CEA doubling time has important prognostic value.

In both MEN syndromes, multidisciplinary approaches are very important in the care of affected patients. Moreover, those patients should be comprehensively informed and enabled to participate in the decision-making procedure. In addition to multidisciplinary approaches, every effort
should be made to follow the recommendations and guidelines issued by national (the French Group of Endocrine Tumors) and international groups.

### Points essentiels

**Les néoplasies endocriniennes multiples de types 1 et 2**

La néoplasie endocrinienne multiple de type 1 est une maladie héréditaire rare à transmission autosomique dominante, définie par l’association, chez un même patient ou chez des sujets apparentés d’une même famille, d’une hyperparathyroïdie, d’une tumeur endocrine pancréatique ou duodénale, d’un adénome hypophysaire, de tumeurs de la corticosurrénale et de tumeurs neuroendocrines bronchiques, thymiques ou gastriques (ECLomes).

La néoplasie endocrinienne multiple de type 2 est une maladie héréditaire rare à transmission autosomique dominante, caractérisée par la survenue du cancer médullaire de la thyroïde soit isolé soit associé à un phéochromocytome, une hyperparathyroïdie primaire, ou à des caractéristiques morphologiques typiques (morphologie marfanoïde, neurones de la langue et des lèvres).

Les patients NEM1 et les sujets à risque (mutation MEN1 identifiée) sont soumis à un bilan extensif pour détecter les tumeurs, évaluer leur progression, et déterminer la meilleure prise en charge. Les enfants avec mutation RET doivent être opérés de la thyroïde de manière préventive, l’âge de la chirurgie est déterminé par l’agressivité de la mutation. Les patients avec NEM2 clinique doit être opérés au moment du diagnostic après avoir éliminé (ou traité) le phéochromocytome.

Chez les patients NEM1, une attention particulière doit être portée à la détection des tumeurs endocrines pancréatiques et duodénales en raison de leur risque de malignité. Également, les tumeurs neuroendocrines thymiques doivent être évaluées soigneusement en raison de leur agressivité.

Chez les patients NEM2, la calcitonine et l’antigène carcino-embryonnaire représentent d’excellents marqueurs tumoraux. La calcitonine préopératoire est associée à la masse tumorale et à la guérison en postopératoire. Aussi, les temps de doubllement des taux de calcitonine et/ou de l’ACE ont une valeur pronostique prouvée.

Une concertation multidisciplinaire est indispensable afin de pouvoir recommander les meilleurs choix pour les traitements et le suivi de patients atteints de NEM surtout dans le contexte de l’absence de la médecine basée sur les preuves. Les patients doivent être informés de la balance bénéfice-risque et doivent participer au choix des modalités du traitement et du suivi car ces cancers évoluent de manière indolente et lente même à un stade métastatique. La prise en charge des patients atteints de NEM doit appuyer sur les recommandations du groupe d’étude des tumeurs endocrines (GTE), ainsi que les réseaux nationaux de référence des tumeurs et cancers endocriniens (RENATEN, TENPATH, TUTHYREF, COMETE, TENGEN).

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**Introduction**

Multiple Endocrine Neoplasia (MEN) are rare hereditary syndromes characterized by the co-occurrence, in the same individual or in related individuals of the same family, of multiple endocrine tumors; these tumors usually secrete detectable hormones that give rise to distinct clinical syndromes. Because of the rarity of the MEN syndromes and the complexity of their clinical picture, it is not easy to deal with MEN patients. You can either send them to an expert center or you should have your guide in your hand. It is very important that this guide (guide-line) be reliable and up to date. Two clinical practice guidelines were issued recently for MEN1 [1] and MEN2 [2]. However, it is worth mentioning that the majority of recommendations in these guidelines are weak and not based on strong level of evidence. Actually, only 11 out of 47 recommendations for MEN1 and 4 out of 67 recommendations for MEN2 are considered of high level of evidence as stated by the authors (Supplementary Table 1). All other recommendations need more evidence. To cite this article: Al-Salameh A, et al. Update on multiple endocrine neoplasia Type 1 and 2. Presse Med. (2018), https://doi.org/10.1016/j.lpm.2018.03.005
studies to establish their right place in the patients' management. The flexibility of some recommendations could lead to heterogeneous practice between centers. In this brief review, we will summarize both guidelines in order to present an update about MEN1 and MEN2 syndromes.

**Clinical picture of MEN syndromes**

MEN syndromes had two essential features: the concomitant occurrence of endocrine tumors and the secretion of detectable hormones that could play an important role in the clinical picture or be of value in the diagnosis and follow-up (table 1). So, the clinical picture is determined by the involved gland and the secreted hormone.

**Clinical picture of MEN1**

MEN1 (OMIM#131100) is typically characterized by the presence of endocrine tumors in the parathyroid gland, the duodenum and pancreas, and the pituitary gland. Thymic, bronchial, and type II gastric Enterochromaffin-Like (ECL) neuroendocrine tumors (NETs), and adrenocortical tumors are also among the main manifestations of MEN1. Moreover, many other endocrine and non-endocrine tumors have been reported in the context of MEN1 such as cutaneous tumors and central nervous system tumors. MEN1 affects all age groups, from 5 to 82 years [3,4]. Clinical or biochemical manifestations develop in more than 94% of patients by the fifth decade [5]. Although MEN1 affects both genders equally, a recent series showed overall female predominance [6]. However, these results should be taken with caution because they were not reproduced by other studies and because diagnostic means differ between centers and countries. MEN1 may be inherited as autosomal dominant trait in the majority of cases (> 80%) or may occur sporadically (sporadic form). Diagnosis of MEN1 is established in a subject if he has at least two of the main manifestations of MEN1, or if he has only one MEN1-related tumors and a first-degree relative with confirmed MEN1, or if he has a confirmed pathologic mutation in the MEN1 gene (asymptomatic form).

### Table 1

Clinical manifestations of MEN syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>MEN 1</th>
<th>MEN 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MEN 2A</td>
<td>MEN 2B</td>
</tr>
<tr>
<td>Eponym</td>
<td>Wermer syndrome</td>
<td>Sipple syndrome</td>
</tr>
<tr>
<td>Gene</td>
<td>MEN1≈85%</td>
<td>RET≈100%</td>
</tr>
<tr>
<td>Prevalence</td>
<td>1/30 000</td>
<td>1/40 000</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>&gt; 90%</td>
<td>20-30%</td>
</tr>
<tr>
<td>Duodenopancreatic NETs: non-functioning 55%, gastrinoma 40%, insulinoma 10%, glucagonoma &lt; 1%, VIPoma &lt; 1%, somatostatinoma</td>
<td>30-80%</td>
<td>–</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>30-40%</td>
<td>–</td>
</tr>
<tr>
<td>Adrenal cortical tumor</td>
<td>20-40%</td>
<td>–</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>&lt; 1%</td>
<td>50%</td>
</tr>
<tr>
<td>Medullary Thyroid Carcinoma (MTC)</td>
<td>–</td>
<td>100%</td>
</tr>
<tr>
<td>Thymic NET//Bronchopulmonary NET//Gastric NET</td>
<td>2%//5%//30%</td>
<td>–</td>
</tr>
<tr>
<td>Angiofibroma//Collagenoma//Lipoma</td>
<td>85%//70%//30%</td>
<td>–</td>
</tr>
<tr>
<td>Other tumors: meningioma 8%, ependymoma, melanoma, thyroid 25%</td>
<td>0-25%</td>
<td>–</td>
</tr>
<tr>
<td>Marfanoid habitus</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mucosal neurona</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cutaneous lichen amyloidosis</td>
<td>–</td>
<td>Up to 36%</td>
</tr>
</tbody>
</table>

MEN: multiple endocrine neoplasia; NETs: neuroendocrine tumors.
Primary hyperparathyroidism (HPT) is the most common feature of MEN1 and the first clinical manifestation of MEN1 in the majority of cases. It is typically caused by multi-glandular involvement. MEN1-related HPT is usually diagnosed during the second decade of life. The clinical picture is that of hypercalcemia and its complications. However, bone disease is reported to be more severe in MEN1-related HPT when compared with sporadic HPT [7]. Recent studies showed that menin, the protein encoded by the MEN1 gene, is important in regulating osteoblast activity [8].

Duodenopancreatic NETs are in majority non-functioning ones (either non-secreting or secreting but not associated with a clinical syndrome) but some could secrete hormones leading to distinct clinical syndromes (gastrinoma, insulinoma…). Duodenopancreatic NETs in the MEN1 settings are almost always multiple (microadenomatosis) and have uncertain behavior with a risk of malignancy [9]. Of note, assessment of tumor markers such as chromogranin A (CgA), pancreatic polypeptide (PP), and glucagon has low accuracy for diagnosing ‘non-functioning’ pancreatic NETs [10]. So, imaging studies represent the only mean for the diagnosis and follow-up of non-functioning duodenopancreatic NETs although the best modality remains to be determined.

Gastrinomas, responsible to Zollinger-Ellison syndrome, represent the most common functional duodenopancreatic tumor in the context of MEN1; they usually arise from the duodenal mucosa and can metastasize very early (even before diagnosis) to local lymph nodes (no negative impact on prognosis) and to the liver (poor prognosis). Zollinger-Ellison syndrome could represent the first manifestation of the MEN1 syndrome.

Insulinomas are the second most common functional pancreatic tumor in the context of MEN1. They lead to hypoglycemia which is the first clinical manifestation of MEN1 in about 10% of patients. Insulinomas in the MEN1 settings are usually benign. Glucagonomas, VIPomas, and somatostatinomas are rare in the MEN1 setting but they are usually malignant.

Pituitary tumors could be the first manifestation of the MEN1 syndrome and occur more frequently in female patients. MEN1-related pituitary adenomas have a higher proportion of macroadenomas when compared with sporadic ones [11]. Also they may produce more than one hormone. Prolactinoma is the most common pituitary adenoma in the context of MEN1 (≈65%) followed by somatotropinoma, ACTH-secreting tumors, and non-functioning tumors whose prevalence might be underestimated. The clinical picture of MEN1-related pituitary adenomas is similar to that of sporadic ones.

Adrenocortical involvement in the MEN1 settings is most often asymptomatic because non-functional tumors are the most common tumors. Adrenal tumors may occasionally cause Cushing syndrome or primary hyperaldosteronism whereas adrenocortical carcinoma is rare.

Thymic NETs are aggressive malignant tumors that occur more frequently in men (male/female ratio of 20 except in Japanese patients). They do not secrete hormone and their detection is therefore dependent on imaging studies. In contrast, bronchial NETs occur in both genders and have an indolent course. Recently, the largest series of patients with bronchial NETs was published. Authors reported 51 bronchial NETs in 1023 patients with MEN1 (≈5%), half of these tumors were classified as typical carcinoid. Although overall survival of patients with bronchial NETs was not different form the rest of the cohort, death was attributed to bronchial NETs in 7 patients [12].

Gastric NETs (type 2 gastric carcinoids) occur in MEN1 patients with Zollinger-Ellison syndrome and are thought to result from the chronic gastrin stimulation of the gastric EnteroChromaffin-Like cells.

Clinical picture of MEN2

The cardinal manifestation in MEN2 is medullary thyroid carcinoma (MTC), either isolated or associated with other endocrine tumors and/or typical features. Thus MEN2 is classified into three subtypes: MEN2A (70–80%), MEN2B (≈5%), and familial MTC (10–20%). MEN2 is inherited as autosomal dominant trait although some cases are caused by de novo mutations in the RET proto-oncogene.

MEN2A (OMIM#171400) is characterized by MTC associated with pheochromocytoma (PHEO) and HPT. Disease onset is usually before the age of 30 years although it is influenced by mutation location. MTC is usually the initial manifestation of MEN2A. Patients usually present with a neck mass whereas symptoms of excess hormone production (diabetes) are less frequent. Many patients already have cervical lymph node metastases at the time of diagnosis [13]. PHEO is the first manifestation of MEN2A in 10% of cases. The clinical picture is similar to that of sporadic PHEO (hypertension, headache, increased sweating and tachycardia). However, MEN2A-related PHEO are more likely to be bilateral when compared with sporadic one. HPT is typically mild and manifests concurrently or after MTC. Hirschsprung’s disease occur in 7% of MEN2A patients [14].

MEN2B (OMIM#162300) is characterized by the early development of an aggressive MTC associated with PHEO and typical features (mucosal neuromas, distinctive facial appearance, marfanoid habitus, ocular abnormalities, and musculoskeletal manifestations). Typically parathyroid disease is absent in patients with MEN2B. Some patients have diffuse ganglieneuromatosis of the gastrointestinal tract, which leads to gastrointestinal symptoms (diarrhea, constipation). MTC is most aggressive in MEN2B leading to metastatic disease at an early age. The clinical picture and behavior of MEN2B-related PHEO is similar to that of MEN2A-related PHEO.

Familial MTC (OMIM#155240) is the occurrence of many cases of MTC within the same family without any evidence of PHEO or
HPT. It is generally admitted that familial MTC is a variant of MEN2A with low penetrance of PHEO and HPT. MTC is less aggressive in familial MTC when compared to other subtypes of MEN2 syndrome. In some cases, older individuals with RET mutation but without any biological or clinical disease expression were reported [15].

**Genetics of MEN1 syndromes**

Germline inactivating mutations in the *MEN1* gene (a tumor suppressor gene) and activating mutations in the *RET* (Rearranged during Transfection proto-oncogene) gene predispose to MEN2 and MEN1 respectively.

**Genetics of MEN1**

The *MEN1* gene is located on chromosome 11q13.1 and consists of 10 exons that encode a 610 amino acid protein called menin. Germline *MEN1* mutations are not sufficient per se to develop MEN1 and loss of the unaffected *MEN1* allele is necessary for tumorigenesis (Knudson's two-hit hypothesis). Menin is predominantly a nuclear protein and is involved in several essential cell functions such as transcription regulation, proliferation, genomic stability and DNA repair, cell division, and cell cycle control. There is no genotype-phenotype correlation and this could be explained by menin' multiple interactions with intracellular mediators that could modulate its action. More than 700 different germline and somatic mutations in the *MEN1* gene locus have been reported since its cloning in 1997 [16,17]. The majority of *MEN1* mutations lead to a truncated protein lacking the nuclear localization signals whereas some mutations (missense mutations) affect the function of critical amino acid residues in menin, reduce its stability, or enhance its degradation. About 10% of MEN1 patients have *de novo* mutations. Some 10-20% of MEN1 patients do not harbor a *MEN1* mutation. In these patients, analysis of partial or complete gene deletion and searching for mutations in the promoter region or in the intronic sequences are necessary [18].

The current guidelines recommend that *MEN1* mutation analysis should be undertaken in:

* index case with two or more MEN1-associated endocrine tumors;
* first degree relatives (symptomatic or not) of a known MEN1 mutation carrier;
* in patients presenting with a single, apparently sporadic MEN1-associated tumor, the decision to perform genetic testing should be discussed on a case-by-case basis. Patients who present at an early age with a MEN1-associated tumor (HPT) and those who present with multiple lesions in the same gland (multi-gland parathyroid disease, multiple duodenopancreatic NETs) should be offered *MEN1* mutation analysis. Also, all patients with gastrinoma should have *MEN1* mutation analysis regardless of age because 25-33% of patients with gastrinomas will have MEN1.

**Genetics of MEN2**

The *RET* gene is located on chromosome 10 (10q11.2) and contains 21 exons that encode a transmembrane receptor of the tyrosine kinase family. Due to alternative splicing 3 isoforms are generated: RET-51 (1114 amino acids) and RET-9 (1072 amino acids) are the main isoforms in vivo whereas RET-43 (1106 amino acids) is less abundant. The RET protein is composed of 3 domains: an extracellular domain which contains 4 cadherin-like repeats and a highly conserved cysteine-rich region, a transmembrane domain, and an intracellular tyrosine kinase domain. RET receptor is activated when one of the glial cell line-derived neurotrophic factor (GDNF) family of ligands binds one of the glycosylphosphatidylinositol-linked GDNF-family α receptors; the ensuing complex induces RET dimerization and phosphorylation with downstream activation of several signal transduction pathways.

The distinctive MEN2 subtypes are dictated by the specific *RET* mutations that have been classified into three levels of aggressiveness (risk) according to the American Thyroid Association (ATA) classification. The highest-risk category includes patients with the *RET* codon M918T mutation (MEN2B), the high-risk category includes patients with *RET* codon C634 mutations (MEN2A) and the *RET* codon A883F mutation (MEN2B), and the moderate-risk category include patients with other *RET* mutations. Virtually all patients with MEN2 have *RET* germline mutation. *De novo* mutations account for 5% of MEN2A cases and about 50% of MEN2B cases [19]. *RET* mutations not only dictate the aggressiveness of MTC but also its associated features (PHEO, HPT, Hirschsprung’s disease). In contrast to *MEN1* gene, only ~100 variants have been reported so far (table II). However, many variants had been reported in families with very few MTC cases and more investigations are therefore needed in order to determine their pathogenic role (pathogenic vs. variant of unknown significance) [20]. Moreover, double *RET* variants had been reported in certain patients and that combined occurrence could modify the clinical phenotype of the corresponding single *RET* mutations. On the other hand, some variants, that once were considered to be associated with mild form of MTC (pathogenic), were subsequently found to be non-pathogenic [21,22]. So, it is clear that the current classification of genotype/phenotype correlation will be refined in the future as more data will be gathered about different mutations and families.

The current guidelines recommend that *RET* mutational analysis should be undertaken in:

* index case in presence of MTC or PHEO;
* asymptomatic first-degree relatives of a known MEN2 mutation carrier.

**Diagnosis and monitoring of MEN1 and MEN2**

Measurement of specific hormones and imaging of affected organs are the pillars of patient workup in MEN1 and MEN2.
However, the diagnostic workup (for initial diagnosis as well as follow-up) is different between MEN1 and MEN2. In MEN1 it is expensive, wide-ranging, and complex due to the multiplicity of affected glands. In MEN2, it is less difficult and less varied. Actually, the C-cells secrete calcitonin (Ct) and carciinoembryonic antigen (CEA), which serve as excellent tumor markers for MTC. Preoperative Ct levels are correlated with tumor size and predict postoperative Ct normalization [23]. Moreover, Ct and CEA doubling time have prognostic value as they are correlated with MTC progression.

Tests to be performed in order to detect the presence or the progression of endocrine tumors in MEN1 and MEN2 as well as therapeutic options are presented in tables III and IV, respectively. Overall, the diagnosis of MEN1 depends on imaging studies (especially for non-functional tumors in the pancreas, adrenals, and thymus) as well as hormone measurements (especially for HPT and pituitary tumors). One the other hand, the diagnosis of MEN2 mainly depends on hormone measurements (Ct, CEA) whereas imaging studies are subsequently used to evaluate the disease location (PHEO) and extension (MTC).

**Therapeutic options**

Surgical treatment to remove endocrine tumors and medical therapy to control hormonal hypersecretion are the cornerstone of MEN1 and MEN2 syndromes’ treatment.

**Treatment of MEN1-related tumors**

In MEN1 treatment options depend on the affected gland and the hormonal syndrome:

- parathyroidectomy is the treatment of choice for hyperparathyroidism but the extent of surgery is debated (subtotal vs. total) [24]. Preoperative imaging studies are not recommended and open bilateral neck exploration is the procedure of choice because all parathyroid glands are usually involved. Prophylactic transcervical thymectomy should be done at the

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**Table I**

The RET codon mutation associated with MEN2 syndrome

<table>
<thead>
<tr>
<th>Exon</th>
<th>RET mutation</th>
<th>AIA category</th>
<th>Incidence of PHEO</th>
<th>Incidence of PTH</th>
<th>Hirschsprung's disease</th>
<th>Cutaneous lichen amyloidosis</th>
<th>MEN2 sub-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>V292M</td>
<td>Moderate</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>8</td>
<td>G533C</td>
<td>Moderate</td>
<td>≈10%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>10</td>
<td>C609F/G/R/S/Y</td>
<td>Moderate</td>
<td>4-26%</td>
<td>2-12%</td>
<td>15%</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>10</td>
<td>C611F/R/S/Y/W</td>
<td>Moderate</td>
<td>Up to 25%</td>
<td>2-12%</td>
<td>5%</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>10</td>
<td>C618F/G/R/S/Y</td>
<td>Moderate</td>
<td>12-23%</td>
<td>2-12%</td>
<td>30%</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>10</td>
<td>C620F/R/S/Y</td>
<td>Moderate</td>
<td>9-24%</td>
<td>2-12%</td>
<td>50%</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>11</td>
<td>C630R/Y/F/S</td>
<td>Moderate</td>
<td>10-30%</td>
<td>≈10%</td>
<td>–</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>11</td>
<td>D631Y</td>
<td>Moderate</td>
<td>≈50%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>11</td>
<td>C634F/G/R/S/Y/W/Y</td>
<td></td>
<td>Up to 88%</td>
<td>Up to 30%</td>
<td>–</td>
<td>Up to 36%</td>
<td>MEN2A</td>
</tr>
<tr>
<td>11</td>
<td>S649L</td>
<td>Moderate</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>11</td>
<td>K666E</td>
<td>Moderate</td>
<td>≈10%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>13</td>
<td>E768D</td>
<td>Moderate</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>13</td>
<td>L790F</td>
<td>Moderate</td>
<td>≈10%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>14</td>
<td>V804L/M</td>
<td>Moderate</td>
<td>≈10%</td>
<td>≈10%</td>
<td>–</td>
<td>+ V804 M</td>
<td>MEN2A, MEN2B</td>
</tr>
<tr>
<td>15</td>
<td>A883F</td>
<td>High</td>
<td>≈50%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>MEN2B</td>
</tr>
<tr>
<td>15</td>
<td>S891A</td>
<td>Moderate</td>
<td>≈10%</td>
<td>≈10%</td>
<td>–</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>16</td>
<td>R912P</td>
<td>Moderate</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>MEN2A</td>
</tr>
<tr>
<td>16</td>
<td>M918T</td>
<td>Highest</td>
<td>≈50%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>MEN2B</td>
</tr>
</tbody>
</table>

AIA: American Thyroid Association; MEN: multiple endocrine neoplasia; PHEO: pheochromocytoma; HPT: primary hyperparathyroidism.

1Not included in this table codon mutations that were found in small families with familial MTC (less than 10 cases). Also, duplication, insertion, deletion, and multiple mutations were not included in this table.

2Codon 804 mutations are associated with atypical MEN2B when they associated with tandem mutations on the same allele (double mutation).

3Some authors argue that this mutation is not pathogenic.
### Table III

Tests to be performed in order to detect the presence or the progression of endocrine tumors and therapeutic options in MEN1

<table>
<thead>
<tr>
<th>Affected gland</th>
<th>Test</th>
<th>Age of onset</th>
<th>Threshold</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary</td>
<td>Prolactin, IGF-1 levels/1 yr Other hormones if symptoms</td>
<td>5</td>
<td>↑ prolactin, ↑ IGF-1</td>
<td>Dopamine agonists (prolactinoma), somatostatin analogues (somatotrophinoma), pituitary surgery, radiotherapy</td>
</tr>
<tr>
<td></td>
<td>MRI/3 yr</td>
<td></td>
<td>Adenoma presence or progression</td>
<td></td>
</tr>
<tr>
<td>Parathyroid</td>
<td>Calcium, PTH/1 yr Bone mineral density if HPT Imaging studies only if recurrent HPT</td>
<td>8</td>
<td>Hypercalcemia (&gt; 0.25 mmol/L), bone disease, renal impact</td>
<td>Total or subtotal parathyroid surgery Cinacalcet (under investigation)</td>
</tr>
<tr>
<td>Duodenopancreatic NETs</td>
<td>Imaging studies (MRI, CT), endoscopic ultrasonography/1yr</td>
<td>20</td>
<td>Tumors &gt; 2 cm and/or confirmed progression</td>
<td>Surgery if &gt; 2 cm or confirmed progression</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Fasting glucose, insulin/1 yr</td>
<td>5</td>
<td>Hypoglycemia with ↑ insulin</td>
<td>Surgery ± Diazoxide</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>Fasting gastrin/1 yr</td>
<td>20</td>
<td>↑ gastrin with decreased gastric PH</td>
<td>Proton pump inhibitors, surgery (controversial)</td>
</tr>
<tr>
<td>Other NETs</td>
<td>Glucagon, VIP, PP</td>
<td>8</td>
<td></td>
<td>Surgery ± somatostatin analogues</td>
</tr>
<tr>
<td>For all duodenopancreatic NETs</td>
<td>CgA/1 yr Imaging studies (MRI or CT),</td>
<td>20</td>
<td>Tumors &gt; 2 cm and/or confirmed progression</td>
<td></td>
</tr>
<tr>
<td>Adrenals</td>
<td>Imaging studies (MRI, CT),/1 yr Hypercortisolism and hyperaldosteronism workup if positive imaging studies or symptoms</td>
<td>&lt; 10</td>
<td>Presence, progression, malignancy signs</td>
<td>Surgery if large, progressive, malignant, or functional</td>
</tr>
<tr>
<td>Thymic and bronchial NETs</td>
<td>Imaging studies (CT or MRI)/1-2 yr</td>
<td>15</td>
<td>Presence, progression, recurrence</td>
<td>Surgery, radiotherapy, chemotherapy</td>
</tr>
<tr>
<td>Gastric NETs</td>
<td>Gastroscopy with biopsy/3 yr if Zollinger-Ellison syndrome</td>
<td>Presence, progression</td>
<td>Mucosal resection, surgery</td>
<td></td>
</tr>
</tbody>
</table>

CgA: chromogranin A; CT: computed tomography; HPT: primary hyperparathyroidism; MRI: magnetic resonance imaging; NETs: neuroendocrine tumors; PP: pancreatic polypeptide; ULN: upper limit of normal; VIP: vasoactive intestinal polypeptide.

*Tests proposed in this table are derived from the guidelines issued by the Endocrine Society [1] and they are presented here on an illustrative basis.

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**time of parathyroid surgery as a prophylactic surgery for thymic NETs even though complete thymectomy is not possible with such an intervention. However, thymic NETs have been reported in patients who had undergone prophylactic transcervical thymectomy which means that imaging studies for thymic NETs are still required after prophylactic transcervical thymectomy;**

- treatment of MEN1-associated pituitary tumors is similar to treatment of sporadic pituitary tumors. It is worth to be mentioned that MEN1-associated pituitary tumors were reported to be less responsive to treatment when compared to sporadic pituitary tumors.

- in MEN1-related duodenopancreatic NETs, surgical management represents one of the most striking controversy. On one hand, there is the risk of malignant behavior and metastatic spread. On the other hand, these tumors are invariably multiple and curative surgery is not possible unless extensive surgery (Whipple pancreaticoduodenectomy) is performed; a procedure that has significant immediate and long-term morbidity and mortality. So the benefit-risk ratio should be carefully considered before planning specific therapy. Insulinomas and other rare functional NETs are usually treated surgically provided that the secreting tumor could be localized. Gastrinomas are treated medically except for pancreatic gastrinomas larger than 2 cm that could be surgically resected. However, treatment of gastrinomas remains controversial and should be discussed in multidisciplinary meeting in order to choose the best treatment modality in the context of available resources. Of note, correction of HPT is associated with a decrease of gastrin levels and improvement of Zollinger-Ellison syndrome [25]. Recent studies suggest that watchful waiting could be a suitable option for non-functioning pancreatic NETs < 2 cm [26,27] whereas surgical resection should be considered in patients with large (>2 cm) or progressive tumors (rapid growth over six month interval) due to their metastatic potential;
• adrenal tumors are treated surgically if they are functional, if they are > 4 cm in size, if they progress over time, or if they have suspicious radiological characteristics;
• thymic NETs are treated by surgery if resectable.

Treatment of MEN2-related tumors
In MEN2 prophylactic total thyroidectomy is the mainstay of MTC management with no major complications and good benefit/risk balance. The age of prophylactic thyroidectomy is dictated by the level of aggressiveness (risk) of the RET mutation. According to the guidelines, children with the ATA highest-risk RET mutation should be operated-on as soon as possible in the first months of life (< 1 year), those with ATA high-risk RET mutations should be operated-on at the age of 5 years (or earlier if Ct levels are elevated), and patients with ATA moderate-risk RET mutation should be offered a strict periodic clinical evaluation beginning at the age of 5 years and should have thyroidectomy if Ct levels increase. This strict clinical evaluation should be performed every 6 months and includes a physical examination, neck ultrasound, and Ct levels determination. Actually, in carriers of the ATA moderate-risk RET mutation, more and more physicians wait for Ct elevation to propose thyroidectomy. Also the magnitude of Ct elevation and the results of imaging studies are very helpful in order to determine the extent of surgery.

Neither consistent data, nor clear guidelines exist concerning the need to perform systematic ipsi/contralateral central/lateral lymph node dissection or not. MTC spreads (disseminates) early to lymph nodes and in previous ATA recommendations [28] extensive lymph node dissection was mandatory. But, in the recent recommendations only central compartment lymph node dissection (level VI) is mandatory whereas lateral compartment lymph node dissection (levels II–IV) (recommendations: 24) is optional in absence of lymph node involvement (on pre-operative ultrasound examination) and distant metastases. It was suggested that ipsilateral lateral neck compartments dissection be performed if Ct levels are > 20 pg/mL whereas contralateral lateral neck compartments dissection should be considered if Ct levels are > 200 pg/mL (recommendations: 25).

On the other hand, in the presence of neck disease on preoperative neck ultrasound, the dissection of the ipsilateral lateral neck compartments is mandatory while dissection of the contralateral lateral neck compartment should be considered systematically if Ct levels are > 200 pg/mL (recommendation: 26). In patients with extensive neck, disease external beam radiotherapy may be used as adjunctive to thyroidectomy. For patients with progressive metastatic disease, treatment with tyrosine kinase inhibitors (TKIs) is recommended; two of them (vandetanib and cabozantinib) were approved by the U.S. Food and Drug Administration and the European Medicines Agency to treat MTC.

In all patients with MEN2, PHEO must be excluded prior to any intervention. If PHEO and MTC or PHEO and HPT coexist, surgical treatment for PHEO should be performed first followed by thyroidectomy or parathyroidectomy.

Prognosis

Prognosis of MEN1
Currently, about two thirds of patients with MEN1 die of causes directly related to MEN1. Duodenopancreatic NETs are the
leading cause of mortality because of their malignant behavior. Thymic NETs represents the second cause of mortality in those patients even though they are the most lethal tumor in MEN1 (relative risk of death 4.64 in patients with thymic tumor compared with patients without such tumor) [29].

It is very difficult to predict prognosis in MEN1 patients. Currently, patient characteristic (age, comorbidities), affected organs (duodenopancreatic NETs, thymic NETs), pathological markers (Ki67 and mitosis index), and tumor burden and progression are used collectively to predict prognosis.

**Prognosis of MEN2**

Mortality in MEN2 is directly related to MTC. Ten-year survival rates for patients with stages I, II, III, and IV MTC (MEN2-related and sporadic one) are 100%, 93%, 71%, and 21%, respectively [30]. Death could rarely reveal or complicate PHEO [31].

In contrast to MEN1, MEN2 prognosis is easily predicted by RET mutation location (the affected codon) and completeness of thyroidectomy. Moreover, even in patients with recurrent disease after thyroidectomy there are many biological and morphological means to predict prognosis like Ct doubling time (bad prognosis if less than 6 months), CEA levels (high levels in the presence of moderately elevated calcitonin level indicate poorly differentiated MTC), localization of metastasis, and tumor burden.

**Controversies and perspectives**

Many recommendations lack strength of evidence especially in the field of treatment (absence of randomized controlled trials) but also in the field of prognosis and prediction of tumor behavior.

**In MEN1 patients**

Almost all therapeutic options are somehow controversial: whether to perform subtotal or total parathyroidectomy with autotransplantation? Should pituitary adenoma be treated exactly as sporadic ones or more aggressive treatments should be implemented? When to perform surgery in non-functioning duodenopancreatic NETs? And what’s the best treatment for gastrinoma? Indeed, decisions concerning the risk-benefit ratio of surgery in MEN1-associated duodenopancreatic NETs represent the most difficult issues; more observational or randomized studies are needed to answer these issues. Moreover, there is a striking lack of information about second line treatment in the case of recurrence after surgery or in patients who cannot tolerate surgery. This is especially true in patients with HPT and duodenopancreatic NETs. Some small studies reported good response to Cinacalcet in patients with MEN1-related HPT but this needs to be confirmed by larger studies. Somatostatin analogues have antiproliferative effects in patients with midgut and enteropancreatic NETs but their role in MEN1-related duodenopancreatic NETs is still to be elucidated.

Some patients with MEN1 do not have a mutation in the MEN1 gene and more work is needed to better characterize and understand the cause of MEN1 in those patients. Finally, the need for a prognostic tool in patients with MEN1 cannot be overstated.

**In MEN2 patients**

Randomized studies are more needed in order to determine the time, the extent, and the risk-benefit ratio of lymph node dissection at the time of prophylactic thyroidectomy. Also the utility and long-term results of adrenal sparing surgery in MEN2-related PHEO are still to be explored.

**In both MEN syndromes**

Many imaging functional techniques to appreciate the localization of endocrine tumors and their extension have emerged in the last decade; these techniques have always been tried in small series of patients. It seems necessary to determine the clinical utility, advantages, disadvantages, and cost-effectiveness of these new imaging techniques in patients with MEN-related tumors. Furthermore, new medical treatments (new TKIs, mammalian target of rapamycin inhibitors, Pasireotide) as well as other therapeutic options (peptide receptor radionuclide therapy) are being used to treat metastatic endocrine tumors. It’s extremely difficult to precise the exact indication and right time for these new modalities in MEN patients without an international cooperation (collaboration or consortium) which will be most helpful to plan sufficiently-powered studies.

**Conclusion**

In spite of their imperfection, guidelines are important in the clinical decision-making procedure but multidisciplinary approaches are also very important and this is illustrated in all guidelines for MEN syndromes. The MEN syndromes always lead to lot of anxiety to patients and relatives and high costs for medical institution. So, the risk-benefit ratio of each intervention is of utmost value and should be considered carefully in the context of available resources. We also should not forget that patients and their families must participate in the decision-making procedure especially in the context of our medical uncertainties. Finally, we should emphasize the role of national (the French Group of Endocrine Tumors) and international groups (the European Neuroendocrine Tumor Society) studying endocrine tumors as well as national reference networks providing help in the care of patients with endocrine tumors (RENATEN, TENPATH, TUTHYREF, COMETE, TENGEN).

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References


