

## 6. MEN syndromes

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### ABSTRACT

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MEN1 and MEN2 are rare inherited cancer syndromes which express a variety of endocrine and nonendocrine tumors. The improved knowledge of molecular and clinical physiopathology of MEN syndromes, together with the availability of genetic testing, have led to earlier detection and intervention, with consequent reduction of mortality and morbidity for MEN-associated tumors. Genetic testing has gained a key role in the detection of asymptomatic patients harbouring mutations responsible for these syndrome, and allows institution of early and tailored intervention with a positive impact on the course of disease. Free full text available at [www.tumorionline.it](http://www.tumorionline.it)

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### Introduction

Neuroendocrine tumors (NETs) may occur in association with multiple endocrine neoplasia (MEN) syndromes. In general, a MEN is defined as an autosomal dominant hereditary cancer syndrome characterized by the presence of neoplasms in at least two endocrine tissues. MEN syndromes cause varying combinations of many tumor types which tend to occur repeatedly both in sporadic and familial cases and generally reflect mutations of a critical gene. In general, tumors associated with MENs show multifocality and early onset compared to their counterparts occurring in non MEN patients. Actually, two MEN syndromes are well-defined: multiple endocrine neoplasia type 1 (MEN1) and multiple endocrine neoplasia type 2 (MEN2). This article provides a characterization of MEN1 and MEN2 syndromes and focuses on the importance of genetic counselling in the management of NET patients and in the choice of therapeutic options.

### Multiple endocrine neoplasia type 1 (MEN1)

Multiple endocrine neoplasia type 1 (MEN1) or Wermer syndrome (MIM +131100) causes combinations of over 20 different endocrine and nonendocrine tumors, has high penetrance approaching 95-100% by the age of 60 and demonstrates extremely variable expressivity. Both familial and sporadic forms of the disease are known, although familial cases are much more frequent than sporadic ones. Given the extremely variability of MEN1-associated tumor combinations, no simple definition of MEN1 could encompass all index cases or all families. A practical definition of MEN1 is a case with 2 of the 3 main MEN1-related endocrine tumors (parathyroid adenomas, enteropancreatic endocrine tumors, and pituitary tumors). Familial MEN1 is similarly defined as at least 1 MEN1 case plus at least 1 first degree relative with 1 of those 3 tumors or a known germinal mutation of *MEN1* gene<sup>1</sup>.

More specifically, neuroendocrine tumors associated with MEN1 include: parathyroid tumors, which manifest as hypercalcemia; pituitary tumors, the most common of which is prolactinoma which manifest as oligomenorrhea/amenorrhea and galactorrhea in females and sexual dysfunction and (more rarely) gynecomastia in males; well differentiated neuroendocrine tumors of the gastroenteropancreatic (GEP) tract, which can manifest as Zollinger-Ellison syndrome (gastrinoma), hyperinsulinism (in-

sulinoma), hyperglycemia, anorexia, glossitis, anemia, diarrhea, venous thrombosis, necrolytic migratory erythema and skin rash (glucagonoma), watery diarrhea, hypokalemia and achlorhydria (VIPoma), diabetes, diarrhea/steatorrhea, gallbladder disease, hypochlorhydria and weight loss (somatostatinoma); carcinoid tumors, mainly non-functioning, which can manifest as hypercortisolism, diarrhea, skin rash and acromegaly; and adrenocortical tumors, mainly non-functioning, which can be associated with primary hypercortisolism or hyperaldosteronism. Non-endocrine tumors associated with MEN1 include facial angiofibromas (85%), collagenomas (70%), lipoma(s) (30%), meningiomas (~8%), ependymomas (1%), leiomyomas and pheochromocytomas<sup>2</sup>. Recently, a novel combination of tumors was found in a 68 year-old female with MEN1 that included a cystic pancreatic endocrine neoplasm and multifocal cholesterol granulomas in the breast, pleura and the extremities<sup>3</sup>. Primary hyperparathyroidism (PHPT) is the main MEN1-associated endocrinopathy and represents the first clinical expression of the syndrome in 90% of patients. Gastrinomas are present in approximately 40% of MEN1 individuals and are typically observed in the duodenal submucosa as multiple, small (<1 cm in diameter) lesions. Gastrinomas can lead to Zollinger-Ellison syndrome (ZES) resulting from increased secretion of gastrin from duodenal submucosal tumor<sup>4</sup>. ZES occurs before 40 years of age in 50-60% of cases, with a mean age of onset of 41 years. Despite general awareness of ZES and the large availability of data from literature, the diagnosis of ZES is still delayed by a mean of 3-5 years or even 5-9 years from onset<sup>5</sup>. MEN1-gastrinomas usually include a malignant component, and half have metastasized to lymph nodes or liver before diagnosis. Liver metastases correlates with a poor prognosis, whereas nodal metastases do not seem to negatively influence prognosis<sup>1,6</sup>. Similarly, the thymic carcinoids of MEN1 syndrome tend to be aggressive<sup>7</sup>, and are highly lethal particularly in male smokers<sup>8,9</sup>. Spinal metastasis of carcinoid tumor has been reported in an patient with MEN1<sup>10</sup> and synchronous thymoma and thymic carcinoid has been reported in a woman with MEN1<sup>11</sup>. Bronchial carcinoids, both synchronous and metachronous, are often multicentric. Although bronchial carcinoids show usually an indolent behaviour, they have the potential for local mass effect, metastases and recurrence after resection<sup>12</sup>.

*Molecular genetic pathogenesis* MEN1 syndrome is inherited in an autosomal dominant manner. *MEN1* is the only gene known to be associated with MEN1 syndrome. However, since no genotype-phenotype correlation has been found<sup>13-16</sup>, a known disease-causing mutation cannot predict the expressivity and clinical behaviour of the syndrome. The *MEN1* gene is located at chromosome 11q13 and consists of 10 exons with a 1830-bp coding region that encodes a protein called

menin<sup>1</sup>. Menin is a 610-amino acid protein and is mainly located in the nucleus. Notably, it does not show similarity with any other known protein. *MEN1* mutation usually predicts menin protein absence or truncation, referred to as the "first hit". The presumed unifying mechanism for tumor formation in MEN1 involves loss of menin functions in a tumor precursor cell. The first hit is inherited and therefore is present in every cell of the body, conveying an autosomal dominant predisposition to neoplasia in certain tissues. When the first hit, which remains generally silent until the development of the first tumor, is combined with a somatic or postnatal loss of the copy of *MEN1* (referred to as the second hit) in one cell, neoplastic clonal expansion from that cell is initiated<sup>1</sup>. Recently, putative factors determining MEN1-associated tissue-selective tumorigenesis have been postulated. Menin is widely expressed and may play many different roles in different tissues, and has been reported to be involved in the negative regulation of cell proliferation and DNA repair mechanisms through interactions with a multitude of proteins. In particular, menin's interaction with mixed-lineage leukemia protein-containing histone methyl transferase (MLL-HMT) complex mediates tissue-selective tumor-suppressing and tumor-promoting effects of menin, and as such could be decisive for the predisposition of individual tissues to MEN1-associated tumorigenesis. In tissues in which menin acts as a tumor suppressor, tumorigenesis could depend on the inability of such tissues to adequately compensate for *MEN1* gene loss, whereas the variable clinical presentation of MEN1 in individual patients could be a consequence of additional epigenetic factors and/or modifier genes<sup>17</sup>.

*Genetic counselling* Despite earlier diagnosis of MEN1-associated tumors and improved treatment of clinical manifestations, MEN1 patients have still a significantly higher risk for premature death<sup>18</sup>. Furthermore, longer life expectancy of affected individuals may lead to increased cumulative mortality and morbidity for MEN1-associated malignant tumors, which today account for about 30% of deaths in MEN1<sup>2,19</sup>. Genetic testing allows to identify patients carrying a *MEN1* mutation before the development of clinical signs or symptoms of endocrine disease with a considerable reduction of morbidity and mortality. In a multicenter study on 258 carriers of a *MEN1* mutation, it was demonstrated that "as a result of differential tumor detection, MEN1 carriers born during the second half of the 20th century tend to have their tumors diagnosed earlier than carriers of the same age born in the first half"<sup>20</sup>. When genetically positive patients are carefully studied prospectively, biochemical evidence of neoplasia can be detected up to 10 years before clinically evident disease, allowing for early surgical intervention. Genetically positive individuals should undergo focused cancer surveillance using biochemical investigations and imaging) for

early detection of the potentially malignant neuroendocrine tumors that account for most of the disease-related morbidity and mortality<sup>21</sup>.

### Multiple endocrine neoplasia type 2 (MEN2)

Multiple endocrine neoplasia type 2 (MEN2) is a rare cancer syndrome inherited in an autosomal dominant manner with an estimated prevalence of 1/30,000 in the general population (MIM +171400). In 1993 the proto-oncogene *RET* (REarranged during Transformation) was identified as the only gene responsible for MEN2. MEN2 is classified into three clinical variants: MEN2A, which accounts for about 55% of MEN2, FMTC (familial medullary thyroid carcinoma, 35%) and MEN2B (10%). All three variants show a high penetrance for medullary thyroid carcinoma (MTC). In fact, 90% of MEN2 adult carriers will eventually show evidence of MTC. Furthermore, MTC is usually the first clinical manifestation of most MEN2 patients and usually appears at an earlier age compared to its sporadic, non syndromic counterpart<sup>1</sup>. Specifically, the diagnosis of MEN 2A is based upon the occurrence of two or more specific endocrine tumors (MTC, pheochromocytoma, or parathyroid adenoma/hyperplasia) in a single individual or in close relatives, whereas FMTC is identified in families with four or more cases of MTC in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia<sup>22,23</sup>. MEN2B, which is the most clinically distinctive form and is characterized by a more aggressive behaviour compared to the other two variants, includes the major neoplasms of MEN2A (MTC and pheochromocytoma), plus a marfanoid phenotype and mucosal and intestinal ganglioneuromatosis<sup>1</sup>.

*Genetic counselling* MEN2 is inherited in an autosomal dominant manner. All three variants are caused by missense gain-of-function mutations of the *RET* proto-oncogene involving mainly codons 609, 611, 618, 620, 630, 634, 768, 804, and 918. The probability of a *de novo* gene mutation is 5% or less in index cases with MEN 2A and 50% in index cases with MEN 2B. Approximately, 1-7% of apparently simplex, nonfamilial, MTC cases have germline *RET* mutations including 2-9% with *de novo* germline mutations. Offspring of affected individuals have a 50% chance of inheriting the mutant gene. The specific *RET* mutation may indicate a predilection toward a particular phenotype and clinical course, with a strong genotype-phenotype correlations<sup>24</sup>. To date, more than 50 different MEN2-associated missense mutations have been identified. Sequencing of DNA for *RET* mutation is effective and clinically available. It identifies disease-causing mutations in 95% of MEN2A subjects and in approximately 88% of families with FMTC. The American Thyroid Association (ATA) Guidelines Task Force has classified *RET* mutations based on

their risk for aggressive MTC, identifying four different risk levels. On the basis of this classification, it is possible to predict phenotype and to formulate recommendations regarding the ages at which to perform prophylactic thyroidectomy and begin clinical and biochemical screening for pheochromocytoma and hyperparathyroidism<sup>25</sup>.

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