Multiple Endocrine Neoplasia

Genetics and Clinical Management

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KEYWORDS

- Endocrine neoplasia • Genetics • Clinical management
- Multiple endocrine neoplasia

KEY POINTS

- Early diagnosis of the multiple endocrine neoplasia (MEN) syndromes is critical for optimal clinical outcomes; before the MEN syndromes can be diagnosed, they must be suspected.
- Genetic testing for germline alterations in both the MEN type 1 (MEN1) gene and RET proto-oncogene is crucial to identifying those at risk in affected kindreds and directing timely surveillance and surgical therapy to those at greatest risk of potentially life-threatening neoplasia.
- Pancreatic, thymic, and bronchial neuroendocrine tumors are the leading cause of death in patients with MEN1 and should be aggressively considered by at least biannual computed tomography imaging.
- Patients with MEN-2a or 2b who are from a kindred and have a RET gene mutation identified should undergo total thyroidectomy after a pheochromocytoma is excluded.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

Multiple endocrine neoplasia type 1 (MEN1) is inherited as an autosomal dominant disorder.[1,2] It has a prevalence of 2 to 3 per 100,000[3] and is reported to be present in 0.22% to 0.25% of autopsies.[4] The gene causing MEN1 is located on the long arm of chromosome 11 (11q13)[5,6] and is composed of 10 exons (9 coding).[2,4] The MEN1 gene is a tumor suppressor gene. It encodes a 610 amino acid nuclear protein

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called menin. Abnormalities of this gene result in mutations, deletions, and/or truncations of the menin protein.[4,7,8] The exact mechanism by which alterations of menin result in endocrine tumors is still unclear. Menin interacts with several proteins, many of which have important roles in transcriptional regulation, genomic stability, cell division, and cell cycle control.[2,4,7,8] The crystal structure of menin supports its role as a key scaffolding protein that regulates gene transcription.[9,10]

Patients with MEN1 usually develop primary hyperparathyroidism (HPT) as the initial disorder of the syndrome (90%–100%),[1,11–13] followed by pancreatic neuroendocrine tumors (pNETs) that can either be functional (20%–70%), of which gastrinoma is the most common, or nonfunctional (80%–100%) (pituitary adenomas [20%–65%], adrenal tumors [10%–73%], and thyroid adenomas [0%–10%]).[2,12,14,15] Patients with MEN1 also have a high occurrence of other endocrine and nonendocrine tumors, including carcinoid tumors (thymic 0%–8%, gastric 7%–35%, bronchial 0%–8%, and rarely intestinal), skin and subcutaneous tumors (angiofibromas 88%, collagenomas 72%, lipomas 34%, and melanoma), central nervous system tumors (meningiomas, ependymomas, and schwannomas 0%–8%), and smooth muscle tumors (leiomyomas and leiomyosarcomas 1%–7%).[2,15–26] In early studies, thyroid disease was also reported in patients with MEN1; but in a recent cross-sectional study of 95 patients with MEN1,[27] the rate of co-occurrence of a thyroid incidentaloma was the same as matched non-MEN1 patients (45% vs 51%), respectively. In addition, other nonendocrine malignant tumors are also being reported to occur in MEN1.[11] These tumors include lymphomas, renal cell cancer, melanoma, leiomyosarcoma, thrombotic thrombocytopenia purpura, myeloma, ovarian tumors, gastrointestinal stromal tumor,[28] seminoma, chondrosarcoma, mesothelioma, and thymomas.[11,29–37] However, whether the incidence of these nonendocrine tumors is truly increased or not is unclear.

EARLY DIAGNOSIS OF MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

Before MEN1 can be diagnosed, it must be suspected. Suspicion should be raised in any patient with a family history of endocrine tumors of the pancreas, family members with pituitary or parathyroid disease, or a family history of endocrinopathy; in patients with renal colic with NETs; in any patient with Zollinger-Ellison syndrome (ZES) (20%–25% have it as part of the MEN1 syndrome); with a young age onset of a functional pNET; with multiple pNETs; with HPT with multiple gland involvement or with hyperplasia or with a pNET associated with hypercalcemia or another endocrinopathy.[1,2] In most patients (83%), MEN1 clinically presents after 21 years of age.[38] In the 17% of patients with MEN1 presenting at less than 21 years of age, which should lead to suspicion of the diagnosis, the most frequent abnormalities were HPT (75%), pituitary adenoma (34%), insulinoma (12%), nonfunctional pNET (9%), and gastrinoma (2%).[38] Genetic screening for MEN1 is recommended when an individual has 2 or more MEN1–related tumors, multiple abnormal parathyroid glands before 30 years of age, recurrent HPT at a young age, gastrinoma and HPT or multiple pNETs at any age, plus a family history of kidney stones or endocrine tumors that are part of the syndrome.[39,40] Genetic testing includes sequencing of the entire coding region of the MEN1 gene (exons 2–10) and identifies mutations in about 80% of patients with familial MEN1[1,41,42] (**Table 1**).

PARATHYROID DISEASE IN MULTIPLE ENDOCRINE NEOPLASIA TYPE 1

Primary HPT is the most common endocrine abnormality in MEN1. It reaches nearly 100% penetrance by 50 years of age. HPT is usually the first manifestation of MEN1