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Multiple Endocrine Neoplasia Type 1

[*MEN1, MEN1 Syndrome, Multiple Endocrine Adenomatosis, Wermer Syndrome*]

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Summary

Disease characteristics. Multiple endocrine neoplasia type 1 (MEN1) syndrome includes a varying combination of more than 20 endocrine and non-endocrine tumors. Endocrine tumors (which become evident by overproduction of hormones by the tumor or by growth of the tumor itself) associated with MEN1 syndrome include parathyroid tumors (the main MEN1-associated endocrinopathy with onset in 90% of individuals at 20-25 years of age and manifest as hypercalcemia by age 50 years; hypercalcemia causes lethargy, depression, confusion, anorexia, constipation, nausea, vomiting, diuresis, dehydration, hypercalciuria, kidney stones, increased bone resorption and increased fracture risk, hypertension, and shortened QT interval), pituitary tumors (prolactinoma being most common and manifest as oligomenorrhea/amenorrhea and galactorrhea in females and sexual dysfunction in males), well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract (manifest as Zollinger-Ellison syndrome resulting from a gastrinoma; hypoglycemia resulting from an insulinoma; hyperglycemia, anorexia, glossitis, anemia, diarrhea, venous thrombosis, and skin rash resulting from a glucagonoma; and watery diarrhea, hypokalemia, and achlorhydria syndrome resulting from a VIPoma), carcinoid tumors (non-hormone-secreting and manifest as a large mass after age 50 years), or adrenocortical tumors (associated with primary hypercortisolism or hyperaldosteronism). Non-endocrine tumors associated with MEN1 syndrome include facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, and leiomyomas.

Diagnosis/testing. Clinical diagnostic criteria for MEN1 syndrome include the presence of two endocrine tumors that are either parathyroid, pituitary, or GEP tract tumors. Biochemical testing detects an increased serum concentration of parathyroid hormone and calcium in primary hyperparathyroidism, increased serum concentrations of prolactin from a prolactinoma, and increased serum concentrations of gastrin, insulin,

and VIP from tumors of the GEP tract. Prolactinomas are imaged by MRI, neuroendocrine tumors are detected by somatostatin receptor scintigraphy, and pancreatic endocrine tumors are detected by endoscopic ultrasound.

Molecular genetic testing of *MEN1*, the only gene known to be associated with MEN1 syndrome, detects *MEN1* mutations in about 80-90% of probands with familial MEN1 syndrome and in about 65% of individuals with a single occurrence of MEN1 syndrome in the family.

Management. MEN1 syndrome-associated hyperparathyroidism is treated with subtotal parathyroidectomy and cryopreservation of parathyroid tissue or total parathyroidectomy and autotransplantation of parathyroid tissue; prior to surgery, bone anti-resorptive agents are used to reduce hypercalcemia and limit bone resorption. Prolactinomas are treated with dopamine agonists, of which cabergoline is the treatment of choice. Growth hormone-secreting tumors causing acromegaly are treated by transsphenoidal surgery; medical therapy for growth hormone-secreting tumors includes somatostatin analogues, octreotide, and lanreotide. ACTH-secreting pituitary tumors associated with Cushing syndrome are surgically removed; non-secreting pituitary adenomas are treated by transsphenoidal surgery. Proton pump inhibitors or H2-receptor blockers are used to reduce gastric acid output caused by gastrinomas. Surgery is indicated for insulinoma and most other pancreatic tumors. Long-acting somatostatin analogues can control the secretory hyperfunction associated with carcinoid syndrome. Surgical removal of adrenocortical tumors that exceed three cm in diameter can prevent malignancy. Thymectomy may prevent thymic carcinoid in males, particularly in smokers. Surveillance of individuals who have MEN1 syndrome or are at high risk includes biochemical testing of serum concentrations of calcium (from age eight years), gastrin (from age 20 years), pancreatic polypeptide (from age 10 years), and prolactin (from age five years) and abdominal CT or MRI (from age 20 years) and head MRI (from age five years). Since early detection affects medical management, molecular genetic testing is offered to at-risk members of a family in which a germline *MEN1* mutation has been identified.

Genetic counseling. MEN1 syndrome is inherited in an autosomal dominant manner. Approximately 10% of cases are caused by *de novo* mutations. Each child of an individual with MEN1 syndrome has a 50% chance of inheriting the mutation. Molecular genetic testing can be used for testing at-risk relatives if a disease-causing germline mutation has been identified in an affected family member. Prenatal diagnosis for pregnancies at increased risk is available if the disease-causing allele of an affected family member is identified or if linkage is established in the family.

Diagnosis

Clinical Diagnosis

Multiple endocrine neoplasia type 1 (MEN1) syndrome occurs with a varying combination of more than 20 endocrine and non-endocrine tumors; consequently, no simple definition can encompass all index cases or affected families.

Endocrine Tumors Associated with MEN1 Syndrome

Diagnostic criteria might be considered to be presence of two of the following three endocrine tumors. These tumors may become evident either by overproduction of polypeptide hormones or by growth of the tumor itself.

- **Parathyroid tumors** can manifest as hypercalcemia [primary hyperparathyroidism (PHPT)] as the result of the overproduction of parathyroid hormone by the parathyroid glands.
- **Pituitary tumors** can manifest as oligomenorrhea/amenorrhea and galactorrhea in females and sexual dysfunction and, more rarely, gynecomastia in males resulting from a prolactin-secreting anterior pituitary adenoma (prolactinoma).
- **Well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract** (including tumors of the stomach, duodenum, pancreas, and the intestinal tract) [Klöppel et al 2004] can manifest as the following (from most frequent to least frequent):
 - Zollinger-Ellison syndrome (ZES) (i.e., peptic ulcer with or without chronic diarrhea) resulting from a gastrin-secreting duodenal mucosal tumor (gastrinoma)
 - Hypoglycemia resulting from an insulin-secreting pancreatic tumor (insulinoma)
 - Hyperglycemia, anorexia, glossitis, anemia, diarrhea, venous thrombosis, and skin rash (necrolytic migratory erythema) resulting from a glucagon-secreting pancreatic tumor (glucagonoma)
 - **Watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome)** resulting from a vasoactive intestinal peptide (VIP)-secreting tumor (VIPoma)

Familial MEN1 syndrome is defined as MEN1 syndrome in an individual who has either at least one first-degree relative with at least one of these endocrine tumors **OR** only one organ involvement and an *MEN1* disease-causing germline mutation.

Note: (1) Non-functioning pancreatic endocrine tumors that are difficult to diagnose by biochemical and imaging tests are the most frequent tumors in MEN1 syndrome [Jensen 1999]. (2) Type II gastric enterochromaffin-like (ECL) cell carcinoids are included in the well-differentiated endocrine tumors of the gastro-entero-pancreatic (GEP) tract. They are common in MEN1 and are usually recognized incidentally during gastric endoscopy for ZES [Bordi et al 1998 , Gibril et al 2000].

Non-Endocrine Tumors Associated with MEN1 Syndrome

- **Skin**
 - **Facial angiofibromas:** Benign tumors comprising blood vessels and connective tissue. These consist of acneiform papules that do not regress and

