Multiple Endocrine Neoplasia Syndromes

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Key Points

1) There are three types of Multiple Endocrine Neoplasia (MEN): Type 1 is due to a Menin mutation, and Type 2A and Type 2B are due to Ret mutations.
2) MEN Type 1 has a high penetrance for parathyroid hyperplasia.
3) One-third of patients with gastrinomas have MEN Type 1.
4) MEN Type 2A and 2B are characterized by medullary thyroid carcinoma and pheochromocytomas.

Introduction

Multiple Endocrine Neoplasia (MEN) Type 1 was discovered in 1954 when a previously reported syndrome of pituitary, parathyroid, and pancreatic tumors was discovered to be inherited by a dominant trait. The earliest report was in 1903 of a patient with a pituitary adenoma causing acromegaly and three enlarged parathyroid glands. In the 1960s, MEN Type 2A and Type 2B were described, and the phrase "multiple endocrine neoplasia" was formed.

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Outline

I. Multiple Endocrine Neoplasia (MEN) Type 1

A. Epidemiology:

1. Autosomal dominant mutation in the gene, Menin.
2. Menin acts as a tumor suppressor.
3. Affects 1 in 30,000 people in the USA.
4. Defined by possessing two of three major syndromes listed below.
5. One-third of MEN related deaths are caused by MEN Type 1-associated malignancies.

B. Syndrome

1. Pituitary Tumors

a. 10–60% of patients with MEN type 1
b. Most commonly a prolactinoma (20%)
c. Can also be Adrenocorticotropic Hormone (ACTH)-secreting or Growth Hormone secreting
d. Diagnose with brain Magnetic Resonance Imaging (MRI) and serum prolactin levels
e. Treat with dopamine agonists
f. Monitor with prolactin levels yearly and MRI brain every 3–5 years

2. Primary Hyperparathyroidism

a. Leads to multigland parathyroid hyperplasia. Compare this to the general population, where 80% of primary hyperparathyroidism is due to adenomas
b. High penetrance rate, and therefore 90% of MEN Type 1 patients get parathyroid hyperplasia by age 40, and nearly 100% by age 50
c. Diagnosis: elevated serum calcium and parathyroid hormone levels
d. Surgical Treatment:

i. Subtotal parathyroidectomy (typically 3 1/2 gland excision) with cervical thymectomy
ii. Total parathyroidectomy with autotransplantation of 1/2 gland with cervical thymectomy (most commonly used site is the sternocleidomastoid muscle)

e. Monitor with calcium and parathyroid hormone levels
f. Recurrence is common and may require further resections

3. Pancreatic Neuroendocrine Tumors (PNET)

a. Most common overall: non-functioning PNET
b. Most common functioning PNET: Gastrinoma (~40%)

i. If found to have gastrinoma, evaluate for MEN Type 1. The Menin mutation is present in approximately 1/3 of patients with gastrinoma
ii. Symptoms
    a.) Intractable peptic ulcers due to increased gastrin secretion (Zollinger–Ellison Syndrome)
    b.) Reflux esophagitis
    c.) Chronic diarrhea
iii. Diagnosis:
    a.) Upper endoscopy: confirm peptic ulcer disease
    b.) Fasting serum gastrin > 10× upper limit of normal AND gastric pH < 2
    c.) If fasting serum gastrin < 10× upper limit of normal, need confirmatory tests with secretin stimulation and/or basal acid output
    d.) Imaging:
        i.) Dotatate positron emission tomography (PET) or somatostatin scintigraphy
        ii.) Look for multiple small tumors in the gastrinoma triangle: Junction of cystic duct and common bile duct, junction of head and neck of pancreas, junction of second and third parts of duodenum
iv. Treatment
    a.) Parathyroidectomy—correction of hypercalcemia can improve symptoms
    b.) If symptoms are well controlled—medical management with proton pump inhibitors
    c.) Surgical Treatment:
        i.) May include mucosal resection of duodenum along with distal pancreatectomy.
        ii.) Incredibly difficult to remove all tumors surgically, and this should be used primarily as a debulking procedure.
v. Monitor with gastrin levels and dotatate-PET or somatostatin scintigraphy

c. Other functioning PNETs: insulinoma (~10%), glucagonoma, vasoactive intestinal peptide tumor (also known as VIPoma)

4. Additional Manifestations
    a. Lipomas
    b. Non-functioning adrenal cortical tumors

c. Facial angiofibromas
d. Rare manifestations: pheochromocytoma, carcinoid tumors

C. Diagnosis

1. Most common de novo presentation is recurrent hyperparathyroidism in middle age

a. Patient has history of removal of one parathyroid adenoma in their 20s.
b. In reality, the patient has parathyroid hyperplasia, not parathyroid adenoma.

2. The second most common de novo presentation (25%) is anterior pituitary adenoma.
3. Screening recommendations for patients who have family history of MEN Type 1:

a. Genetic testing for Menin mutation.
b. At age 5: fasting glucose, insulin, prolactin, Insulin-like growth factor (IGLF)-I, brain MRI.
c. At age 8: calcium and PTH levels.
d. At age 20: gastrin, secretin-stimulated gastrin, chromogranin-A, glucagon, proinsulin, and computed tomography (CT), dotatate-PET, or somatostatin scintigraphy.

II. MEN Type 2A and 2B

A. Epidemiology:

1. Autosomal dominant mutation in the gene, Ret
2. Ret is a proto-oncogene
3. Affects 1 in 35,000 people in the USA

B. Syndrome

1. Medullary Thyroid Carcinoma

a. Most common cause of death in MEN 2A
b. Manifests in 90% of patients
c. Surgical Treatment: prophylactic total thyroidectomy and central neck dissection (all lymphatic tissue between sternal notch and hyoid bone, and between the jugular veins)

i. Known MEN 2A patients—perform by age 1–5 years old.
ii. If discovered de novo, after age 10–15, include ipsilateral modified radical neck dissection on affected side due to high incidence of lymph node metastasis.
iii. If discovered de novo, check calcitonin level, and look for distant metastasis. If distant metastases are present, then do not perform thyroidectomy or lymph node dissections.

d. Monitor with calcitonin and carcinoembryonic antigen (CEA) levels, and with neck ultrasounds yearly

2. Pheochromocytoma
    a. This must be treated first before any neck surgery for medullary thyroid cancer
    b. Manifests in 50% of these patients
    c. Diagnosis:
        i. Biochemical tests: plasma or 24-h urine metanephrines
        ii. Imaging tests: CT or MRI abdomen, Meta-iodobenzylguanidine (MIBG) scan
    d. Treatment: alpha blockade and then adrenalectomy
    e. Monitor for recurrence with urine or plasma metanephrines, and CT or MRI abdomen
3. Additional Manifestations
    a. MEN Type 2A
        i. Primary Hyperparathyroidism
            a.) Manifests in 20–30% of these patients
            b.) May be due to single adenoma vs. multigland hyperplasia
            c.) Diagnosis: elevated serum calcium and parathyroid hormone levels
            d.) Surgical Treatment: parathyroidectomy (extent may vary)
            e.) Monitor with calcium and parathyroid hormone levels
        ii. Cutaneous lichen amyloidosis
        iii. Hirschsprung's disease
    b. MEN Type 2B
        1. Mucosal neuromas
        2. Marfanoid habitus

C. Diagnosis
1. De novo presentation may be medullary thyroid cancer or pheochromocytoma
2. If genetic history is known
    a. Genetic testing for Ret mutation of various codons—some are considered more aggressive than others
    b. Prophylactic total thyroidectomy with central neck dissection by age 1–5
        i. By age 1 for level 3 codon mutations-most aggressive, often will have microscopic tumor already by age 1
        ii. By age 5 for level 2 or level 1 codon mutations
    c. Monitor calcitonin, CEA, and neck ultrasounds yearly
    d. Start screening for pheochromocytoma by age 5 with yearly metanephrines and abdominal imaging

Additional Notes

The hereditary nature of Multiple Endocrine Neoplasia syndromes makes it important to consider other family members when treating a child with MEN syndrome. Often parents will be aware that the condition runs in their family. After a child has been diagnosed with MEN, it is important to screen siblings. Consultation with a geneticist will help with preparing for the implications of a positive finding on genetic screening. For example, diagnosis of MEN2A indicates that prophylactic total thyroidectomy is necessary by age 5-years-old. Operation can carry complications such as recurrent laryngeal nerve dissection, or hypocalcemia [1]. A longitudinal study of a large proband with MEN2A syndrome has demonstrated that prophylactic total thyroidectomy leads to long-term protection against thyroid cancer [2].

Treating children with MEN syndrome may reveal some features that are different from the disease in adults. A recent report stated that the marfanoid stature present in adults with MEN2B was not present in a series of children with MEN2B, who actually had short stature [3].

Study Questions

1) The most common pancreatic neuroendocrine tumor in MEN Type 1 patients is:

   a. Insulinoma
   b. Gastrinoma
   c. Non-functioning tumor
   d. Glucagonoma

Answer to Question 1: (c.) Non-functioning tumor. The most common pancreatic neuroendocrine tumor in MEN Type 1 syndrome is a non-functioning tumor. The most common functioning pancreatic neuroendocrine tumor in MEN Type 1 is a gastrinoma.

2) For patients with aggressive mutations of RET in MEN Type 2 syndromes, total thyroidectomy should be performed by age:

   a. 5
   b. 1
   c. 10
   d. 2

Answer to Question 2: (b.) 1. For patients with level 1 or level 2 mutations, which are lower risk than level 3, they should undergo thyroidectomy by age 5. For patients with level 3 codon mutation, which are the most aggressive, they should undergo thyroidectomy by age 1.

3) Which of the following are correct in terms of most common pathology within each MEN syndrome?

   a. Medullary thyroid carcinoma/MEN Type 2A
   b. Gastrinoma/MEN Type 1
   c. Pheochromocytoma/MEN Type 2B
   d. Prolactinoma/MEN Type 1

Answer to Question 3: (a.) Medullary thyroid carcinoma/MEN Type 2A. Primary hyperparathyroidism is the most common manifestation of MEN Type 1, with nearly 90% of patients developing primary hyperparathyroidism by age 40 and nearly 100% by age 50. Medullary thyroid carcinoma is the most common manifestation of MEN Type 2A and 2B, with nearly 90% of patients developing medullary thyroid carcinoma. Pheochromocytoma is also present in MEN Type 2A and 2B, although only 50% of patients will develop it.

References

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Further Reading

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