Multiple endocrine neoplasia

Paul J Newey

Abstract

Multiple endocrine neoplasia (MEN) describes the occurrence of tumours affecting two or more endocrine glands in one patient. Two main forms are recognized: MEN type 1 (MEN1) and type 2 (MEN2). MEN1 is characterized by the combined occurrence of parathyroid, pituitary and pancreatic neuroendocrine tumours, whereas MEN2 features medullary thyroid cancer in association with phaeochromocytoma and parathyroid tumours. Although both MEN1 and MEN2 are autosomal dominant disorders, they have contrasting molecular aetiologies: MEN1 results from inactivating germline mutations of the *MEN1* tumour suppressor gene, whereas MEN2 results from activating mutations in the *RET* proto-oncogene. The clinical features arising in each condition relate to the location of tumour development and/or hormonal hypersecretion, while treatment approaches aim to minimize morbidity and mortality, and preserve quality of life. Genetic testing is a key component of management, not only to confirm the diagnosis in affected patients, but also to identify family members who are at risk of disease but may be asymptomatic. It is recommended that patients 'at risk' of developing MEN1 and MEN2 (i.e. mutation carriers) undergo periodic clinical, biochemical and radiological surveillance to enable the early identification and/or treatment of tumours. Here, a brief overview of MEN1 and MEN2 is provided.

Keywords Genetic testing; hereditary disease; medullary thyroid cancer (MTC); pancreatic neuroendocrine tumour; parathyroid tumour; phaeochromocytoma; pituitary adenoma

Key points

- The possibility of multiple endocrine neoplasia (MEN) should be considered in all patients presenting with apparently sporadic MEN-associated tumours, and a detailed family history obtained to establish evidence of a hereditary disorder
- Genetic testing should be offered to all individuals with a likely clinical diagnosis of MEN1 or MEN2 (i.e. *MEN1* and *RET* mutational analysis, respectively). For MEN2, this includes all patients with medullary thyroid cancer (MTC). Genetic testing should be offered to all first-degree relatives of affected individuals
- Patients at risk of developing MEN1 (i.e. *MEN1* mutation carriers) should be offered periodic clinical, biochemical and radiological screening to enable the early detection of tumours
- Patients at risk of developing MEN2 (i.e. *RET* mutation carriers) should be undergo periodic clinical, biochemical and radiological evaluation, and, where appropriate, be offered early prophylactic thyroidectomy, according to the risk category of *RET* mutation
- Treatment of MEN1 and MEN2 should aim to minimize the morbidity and mortality associated with disease, while maintaining the patient's quality of life. Management is often complex and requires multidisciplinary involvement

Multiple endocrine neoplasia type 1 (MEN1)

Definitions and epidemiology

MEN1 is characterized by the combined occurrence of parathyroid, pituitary and duodenopancreatic neuroendocrine tumours. A spectrum of additional tumours is reported, including thymic and bronchial carcinoids, adrenocortical tumours, and tumours affecting the skin and soft tissues (Table 1). The diagnosis of MEN1 can be established clinically (i.e. patient with $\geq$2 relevant endocrine tumours) or genetically (i.e. an individual with or without clinical manifestations harbouring an *MEN1* mutation).[1] The estimated incidence is approximately 1 in 30,000. It is associated with premature mortality, with around 30–70% of affected patients dying from causes related to the disorder.

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Pathology and pathogenesis

MEN1 is an autosomal dominant disorder caused by germline mutation of the *MEN1* gene, such that first-degree relatives of an affected individual have a 50% chance of inheriting the *MEN1* mutation. However, in around 5–10% of cases, the *MEN1* mutation occurs *de novo* so an affected individual has unaffected parents. The *MEN1* gene is located at chromosome 11q13.1 and encodes the protein menin. Most *MEN1* mutations result in loss of menin function (e.g. nonsense or frameshift mutations), while MEN1-associated tumours typically demonstrate bi-allelic *MEN1* inactivation consistent with a tumour suppressor function. Although menin is reported to influence many cellular processes (e.g. activation and repression of gene transcription, modulation of cellular signalling pathways), the molecular mechanisms leading to tumourigenesis remain ill-defined.

Disease course

MEN1 is a highly penetrant disorder with virtually all patients (>98%) expressing disease by the fifth decade. However, no genotype–phenotype correlation exists, so it is not possible to predict the onset or spectrum of tumours in a given individual. Symptomatic presentations are unusual in early childhood (e.g. <10 years of age), although the earliest reported cases of MEN1-associated hyperparathyroidism, pituitary adenoma and pancreatic neuroendocrine tumour (PNET) are at 4, 5 and 5 years of age, respectively.[1,2] By 21 years of age, the penetrance of these tumours is reported to reach approximately 75%, 35% and 20

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Clinical features of MEN1

Primary hyperparathyroidism (>95%)
- Parathyroid adenoma/hyperplasia (>95%)
- Parathyroid carcinoma (very rare)

Pancreatic neuroendocrine tumours (PNETs) (30–80%)
- Gastrinoma[a] (30–40%)
- Insulinoma (10–30%)
- Glucagonoma (<3%)
- VIPoma (very rare)
- Non-functioning PNET (30–60%)

Pituitary adenomas (30–40%)
- Prolactinoma (20%)
- Somatotropinoma (<10%)
- Corticotropinoma (<5%)
- Non-functioning adenoma (10–25%)

Foregut neuroendocrine tumours (NETs)
- Thymic NET (2–8%)
- Bronchial NET (<5%)
- Gastric NET ('ECLoma'[b]) (10%)

Adrenocortical tumours (10–20%)
- Conn's adenoma (around 1%)
- Cortisol-secreting adenoma (around 1%)
- Phaeochromocytoma (very rare)
- Non-functioning adenoma (10–20%)
- Adrenocortical carcinoma (around 1%)

Miscellaneous tumours
- Lipomas (30%)
- Angiofibromas (85%)
- Collagenomas (70%)
- Meningiomas (around 5%)
- Ependymomas (<5%)
- Breast cancer (increased relative risk reported)

[a] Most gastrinomas are located in the duodenal mucosa.
[b] 'ECLoma' refers to tumours arising from enterochromaffin-like cells, which are observed in patients with hypergastrinaemia caused by Zollinger–Ellison syndrome.

Table 1

–25%, respectively.[2] Hyperparathyroidism is often the first manifestation of disease, although a minority present with a PNET, pituitary tumour or other MEN1-associated tumour (e.g. thymic carcinoid).[2]

Clinical features and treatment

Parathyroid tumours: primary hyperparathyroidism occurs in >95% of MEN1 patients, demonstrates an equal sex distribution, and typically manifests synchronous or asynchronous involvement of all four glands. Patients are frequently asymptomatic with mild hypercalcaemia, although symptomatic disease can occur and relates to hypercalcaemia (e.g. thirst, polyuria, constipation) or disease complications (e.g. nephrolithiasis, osteitis fibrosa cystica). Surgery is the treatment of choice, with most experts advocating subtotal (i.e. removal of ≥3.5 glands) or total parathyroidectomy.[1]

Pituitary tumours: the incidence of pituitary tumours in MEN1 is estimated to be 30–40%, with most occurring as microadenomas (<1 cm diameter). Prolactinomas represent the most common functioning tumour, although somatotropinomas and corticotropinomas also occur. The remainder comprise clinically non-functioning adenomas. Symptoms relate to hormonal hypersecretion or local mass effects (e.g. hypopituitarism, visual field defect). Treatment is the same as for sporadic counterparts (e.g. trans-sphenoidal surgery, dopamine agonist for prolactinoma).

Pancreatic neuroendocrine tumours: clinically significant PNETs occur in around 30–80% of patients with MEN1 and are the leading cause of premature mortality. Patients can harbour multiple tumours, and attempts to correlate imaging findings with symptoms and/or biochemical evidence of hormone hypersecretion can be confounded.[3]

Functioning tumours – gastrinomas occur in 30–40% of patients with MEN1. Untreated, they are associated with gastric acid hypersecretion, recurrent peptic ulceration and haemorrhage (Zollinger–Ellison syndrome). Most MEN1-associated gastinomas are small (<1 cm) and multiple, and occur in the duodenal mucosa. Surgical resection of duodenal gastrinomas is controversial as good long-term outcomes are reported with medical therapy alone (e.g. proton pump inhibitors).[3] Insulinomas affect 10–30% of MEN1 patients and often occur at a young age (around 10–15% penetrance by 21 years of age). Typically, they present with symptomatic hypoglycaemia, and curative surgery is the treatment of choice. Other functioning PNETs (e.g. glucagonomas, VIPomas) occur rarely.

Non-functioning PNETs (NF-PNETS) – these are recognized as the most common PNETs in MEN1, occurring in 30–60% of individuals. Presentations in early childhood are rare, but recent series indicate a prevalence of 10–40% by around 20 years of age. Diagnosis typically relies on imaging (e.g. endoscopic ultrasound, magnetic resonance imaging) as patients are often asymptomatic and tumour markers (e.g. chromogranin A) unreliable.[3] The risk of metastatic disease is related to tumour diameter, with most clinicians recommending surgery for NF-PNETS of >2 cm, although some advocate lower cut-offs.[1,3] Systemic therapies (e.g. somatostatin analogues, tyrosine kinase inhibitors) and locoregional approaches (e.g. cytoreductive surgery, radiofrequency ablation) are used for advanced disease.

Other MEN1-associated tumours: adrenocortical tumours occur in approximately 20% of patients. Most are small (<1 cm) and non-functioning, although a minority are hormone-secreting (e.g. resulting in primary hyperaldosteronism or Cushing's syndrome). Adrenocortical carcinoma is occasionally reported. Thymic and bronchial carcinoid tumours occur in 2–8% of patients with MEN1. Thymic carcinoids, occurring predominantly in men, are associated with an aggressive disease course, while bronchial carcinoids have more favourable outcomes.

Genetic testing

MEN1 genetic testing should be offered to all patients with a clinical diagnosis of MEN1, all first-degree relatives of affected individuals (symptomatic and asymptomatic), and individuals with an increased likelihood of disease (e.g. multiple PNETs, sporadic gastrinoma, recurrent or multigland parathyroid disease). Establishing a genetic diagnosis of MEN1 is important for

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