Multiple endocrine neoplasia type 1

Key facts

- Multiple endocrine neoplasia type 1 (MEN1) is an inherited condition that leads to growth of mainly benign (non-cancerous) tumours of the endocrine glands.
- MEN1 should be distinguished from MEN2, which is a separate genetic condition.
- The features of MEN1 vary depending on the types of tumours that occur, and the hormones produced.
- Features usually present in adulthood; manifestation before teenage years is very rare.
- The most common presenting feature of MEN1 is hyperparathyroidism, with raised calcium levels owing to growth of the parathyroid glands.
- MEN1 is an autosomal dominant condition caused by alterations in the *MEN1* gene.
- Individuals with a variant in the *MEN1* gene should undergo regular surveillance to screen for MEN1-associated tumours and their hormonal effects.
- Early diagnosis, treatment and management improves outcome and quality of life for those affected.
- It is estimated that around 1 in 10,000 individuals are affected by the condition.

Clinical features

- The features of MEN1 vary depending on the types of tumours that occur and the hormones they produce. The three most common tumours to occur are:

Parathyroid tumours

- Onset of hyperparathyroidism usually occurs after the age of 20. Over 90% of patients with MEN1 will develop hyperparathyroidism by the age of 50.
- Growths in the parathyroid gland result in hyperparathyroidism (raised parathyroid hormone (PTH) levels) and hypercalcaemia.
- Hypercalcaemia can lead a wide range of symptoms including thirst, lethargy, aches and pains, muscle weakness and constipation.
- If left untreated, the long-term effects of hypercalcaemia can include osteoporosis and renal stones.

Pancreatic neuroendocrine tumours

- May occur in up to 75% of individuals with MEN1.
- The symptoms will depend on the type of tumour and the hormones that are produced. Most pancreatic neuroendocrine tumours do not produce any hormones in cases of MEN1.
- Gastrinomas are the most common secretory neuroendocrine tumours in cases of MEN1, with excess gastric production leading to acid reflux, indigestion and gastric/duodenal ulcers.
- Insulinomas producing excess insulin can cause symptoms of hypoglycaemia.
- About 10% of patients affected by MEN1 may experience more than one type of pancreatic tumour.
- Some (pancreatic) neuroendocrine tumours have the potential to become malignant and metastasise to local lymph nodes or to the liver, if left untreated.

Pituitary tumours (pituitary adenoma)

- Around 30% of patients affected by MEN1 will develop a pituitary tumour.
- The effect of the tumour will depend on which hormones are produced.
- Tumours may secrete prolactin (causing infertility issues), growth hormone (causing the size of the jawbone, hands and feet to grow) and ACTH (causing the adrenal gland to overproduce cortisol).
- Some tumours may affect vision through compression of the optic nerve.

Diagnosis

- A clinical diagnosis of MEN1 can be made when:
  - » an individual develops two or more MEN1-associated tumours; or
  - » an individual with a family history of MEN1 develops one MEN1-associated tumour.

Genetic basis and genetic testing

- MEN1 is caused by variants in the *MEN1* gene, which are inherited in an autosomal dominant manner.
- Children of an affected individual have a 50% (one-in-two) chance of inheriting the gene variant.
- A proportion of families with MEN1 will not have identifiable variants in the *MEN1* gene.
- Indications for genetic testing and genetic counselling include:
  - » parathyroid multiglandular disease (<35 years);
  - » any pituitary adenoma or insulinoma (<20 years);
  - » pituitary macroadenoma (<30 years);
  - » ≥2 MEN1-related endocrine abnormalities at any age (parathyroid hyperplasia/multiglandular adenomas, pituitary tumours, endocrine tumours of the gastro-entero-pancreatic (GEP) tract, carcinoid tumours, adrenocortical tumours);
  - » ≥1 MEN1-related endocrine abnormality and ≥1 MEN1-related non-endocrine tumours (facial angiofibromas, collagenomas, meningioma);
  - » diagnostic testing in a symptomatic blood relative (≥1 MEN1-related endocrine abnormality and first degree relative with ≥1 MEN1-related endocrine abnormality);
  - » predictive/presymptomatic testing for first-degree relatives of an affected individual; and
  - » affected individuals who are considering prenatal diagnosis.
- Genetic testing is available in the UK and usually provided through specialist clinics or regional genetic centres.

Clinical management

- Regular surveillance is needed to screen for MEN1-associated tumours and their hormonal effects.
- Screening may include a medical review for assessment of symptoms, biochemical screening to check the level of PTH /calcium and other hormones, and imaging of the pituitary/pancreatic gland.
- Parathyroid tumours can be treated by surgical removal of the parathyroid glands, of which there are four. The tumours usually reoccur, so surgeons often remove between three and three and a half glands, with implantation of the remaining portion of gland.
- Treatment of pituitary tumours may require medical treatment or surgery, and in some cases radiotherapy.

- The treatment of pancreatic tumours will depend on the size, type, number and location of the tumours.
- Proton pump inhibitors, which inhibit stomach acid production, are used for medical treatment of gastrinomas.
- Treatment for insulinomas may involve surgical removal of a tumour (if over 2cm), or partial/complete removal of the pancreas.
- Tumours may metastasise to the liver, and may be treated by chemotherapy, newer targeted therapies (for example, tyrosine kinase inhibitors) or radio ablation.

Direction to further reading, guidelines and patient groups

- AMEND (Association for Multiple Endocrine Neoplasia Disorders)

This information is intended for educational use and was current in January 2020. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and Imperial College Healthcare NHS Trust.