

Multiple endocrine neoplasia type 2A

Key facts

- Multiple endocrine neoplasia type 2A (MEN2A) is an inherited condition and a distinct subtype of MEN2 (multiple endocrine neoplasia type 2 – a hereditary endocrine cancer syndrome). Familial medullary thyroid cancer (FMTC) is also a subtype of MEN2 (see FMTC factsheet). MEN2A is suspected when two or more specific endocrine tumours occur (medullary thyroid cancer, adrenal adenoma or parathyroid adenoma/hyperplasia). The extent to which these glands are affected varies from person to person.
- Medullary thyroid cancer is usually the presenting symptom and may have metastasised before diagnosis.
- Onset is typically in early adulthood but may vary.
- MEN2A is an autosomal dominant condition, owing to alterations in the *RET* proto-oncogene.
- The majority (95%) of individuals with the genetic alteration will develop medullary thyroid cancer at some point in their lives.
- Pheochromocytoma occurs in up to 50% of individuals.
- Hyperparathyroidism occurs in 20%-30% and may be due to parathyroid adenoma or hyperplasia.
- Early diagnosis, treatment and management improves outcome and quality of life for those affected with MEN2A.
- MEN2A is a rare inherited condition, affecting approximately 1 in 40,000 individuals.
- Prenatal counselling and testing is available.

Clinical features

The clinical features of MEN2A are due to the onset of medullary thyroid cancer and excess hormone production from adenomas in the adrenal and/or parathyroid glands.

Medullary thyroid cancer (MTC):

- may cause a neck lump or neck pain typically in young adults <35 years old;
- diarrhoea due to raised calcitonin levels;
- may be metastases to lymph nodes, lungs or bones.

Growths in the adrenal gland:

- high blood pressure (persistent or fluctuating), palpitations, anxiety, sweating, severe headaches.

Growths in the parathyroid gland:

- hyperparathyroidism (raised PTH levels) and hypercalcaemia (raised calcium levels);
- thirst, lethargy, aches and pains, muscle weakness and constipation;
- long-term effects can cause osteoporosis and renal stones.

Skin lesions:

- lichen amyloidosis.

Diagnosis

Medullary thyroid cancer (MTC):

- imaging confirming suspicious node/mass/metastases;
- fine needle aspiration or other histology confirming MTC; and
- raised calcitonin level.

Phaeochromocytoma:

- raised plasma metanephrines (catecholamine by-products) +/-; and
- raised 24 hour urine collection for catecholamines.

Primary hyperparathyroidism:

- raised calcium;
- raised parathyroid hormone; and
- presence of parathyroid adenoma or hyperplasia (one or more glands).

Genetic basis

- MEN2A is caused by genetic alterations in the *RET* proto-oncogene.
- This gene encodes a tyrosine kinase receptor. Targeted therapies involving tyrosine kinase inhibitors have recently been developed.
- The *RET* alteration is inherited in an autosomal dominant manner. The specific *RET* alterations are directly related to the MEN2 subtypes and thus to the aggressiveness of MTC and presence of other endocrine tumours.
- Genetic testing can detect >95% of alterations in the *RET* gene.
- An affected individual has one usual and one altered copy of the *RET* gene. Each time an affected person has a child they will pass on either the usual or the altered copy of the gene. Children of an affected individual therefore have a 1-in-2 (50%) chance of inheriting the gene alteration.
- About 95% of affected individuals with MEN2A will have an affected parent and 5% will be due to a de novo genetic alteration. In some cases the parents of an affected individual will be asymptomatic at the time of their child's diagnosis, as the age of disease onset is variable.

Treatment

Medullary thyroid cancer (MTC)



- Total thyroidectomy and neck dissection/removal of lymph nodes as required.
- Lifelong thyroid hormone replacement.
- Tyrosine kinase inhibitors are promising treatments for patients with unresectable (unable to be removed with surgery), locally advanced, or metastatic MTC.
- Phaeochromocytoma.
- Medical treatment of excess catecholamine production (alpha and beta blockade) until blood pressure normalised followed by unilateral adrenalectomy.
- Phaeochromocytoma must be removed before any other surgery undertaken.

Primary hyperparathyroidism

- This usually occurs many years after surgery for the thyroid gland.
- Resection of the affected gland, partial or total parathyroidectomy (with re-implantation of one parathyroid gland).
- Parathyroid surgery may also be performed at time of thyroid surgery, if there is confirmed biochemical hyperparathyroidism or parathyroid adenoma/hyperplasia.

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Clinical management

- Patients with MEN2A should always be managed by a specialist multidisciplinary team. An endocrinologist, an experienced thyroid surgeon (skilled in operating on these rare medullary thyroid cancers) and clinical geneticist/genetic counsellor should be members of the multidisciplinary team.
- Annual screening is recommended by the specialist team to assess for signs of the tumours and their hormonal effects.

Medullary thyroid cancer:

- annual plasma calcitonin level;
- annual thyroid hormone and thyroid stimulation hormone measurements to monitor replacement therapy; and
- annual neck and thorax MRI (usually combined with abdominal scan for phaeochromocytoma development on alternate side).

Phaeochromocytoma:

- annual plasma metanephrines measurement;
- blood pressure; and
- annual abdominal scan (usually combined with neck and thorax imaging for thyroid metastases).

Primary hyperparathyroidism:

- annual plasma calcium test (also to monitor possible hypocalcaemia following surgery to thyroid +/- parathyroids).

Pregnancy:

- phaeo screening up to date;
- specialist endocrine A/N clinic;
- patients and all blood relatives should be offered genetic counselling and *RET* gene testing; and
- children who are shown to have a *RET* genetic alteration should undergo total thyroidectomy from <5yrs age.

Genetic testing

Indications for genetic counselling and testing include:



- a confirmed diagnosis of medullary thyroid cancer;
- a confirmed *RET* genetic alteration (mutation) in a relative;
- diagnostic testing if two or more of the above specific endocrine tumours are present in one patient;
- diagnostic gene testing for a symptomatic blood relative;
- predictive testing for parents, siblings and offspring of someone with a confirmed *RET* gene alteration. For children, this would involve cord blood sample at birth or testing <4-5 years of age. If children are older than 5 years of age, genetic testing is recommended as matter of urgency; and
- prenatal diagnosis.

Genetic testing is available in the UK and usually provided through specialist clinics or regional genetic centres.

This information is intended for educational use and was current in March 2015. For clinical management, it is recommended that local guidelines and protocols are used.

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