Multiple endocrine neoplasia type 2A

Key facts

- Multiple endocrine neoplasia type 2A (MEN2A) is an inherited condition, and a distinct subtype of multiple endocrine neoplasia type 2 (MEN2) - a hereditary endocrine cancer syndrome. Familial medullary thyroid cancer (FMTC) is also a subtype of MEN2.
- MEN2A is suspected when two or more specific endocrine tumours occur together (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 variants in the *RET* proto-oncogene.
- The majority (95%) of individuals with the genetic variant will develop medullary thyroid cancer at some point in their lifetime.
- Phaeochromocytoma occurs in up to 50% of affected individuals; hyperparathyroidism occurs in 20-30% of affected individuals, and may be due to parathyroid adenoma or hyperplasia.
- Early diagnosis, treatment and management improves outcome and quality of life for those affected by MEN2A.
- MEN2A is a rare inherited condition, affecting approximately 1 in 40,000 individuals.
- Prenatal counselling and testing are available.

Clinical features

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

Medullary thyroid cancer (MTC):

- may cause a neck lump or neck pain, typically in adults younger than 35 years of age;
- can result in diarrhoea, due to raised calcitonin levels; and
- may metastasise to lymph nodes, lungs or bones.

Growths in the adrenal gland:

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

Growths in the parathyroid gland:

- may result in hyperparathyroidism (raised PTH levels) and hypercalcaemia (raised calcium levels);
- can cause symptoms including thirst, lethargy, aches and pains, muscle weakness and constipation; and
- if left untreated, long-term effects can cause osteoporosis and renal stones.

Skin lesions:

- can cause the development of 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/or
- raised 24-hour urine excretion of catecholamines.

Primary hyperparathyroidism:

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

Genetic basis and genetic testing

- MEN2A is caused by genetic variants in the *RET* proto-oncogene, a gene that encodes a tyrosine kinase receptor. Targeted therapies involving tyrosine kinase inhibitors have recently been developed.
- The MEN2A-causing *RET* variants are inherited in an autosomal dominant manner. Specific *RET* variants are directly related to the MEN2 subtypes, and thus to the aggressiveness of MTC and presence of other endocrine tumours.
- Genetic testing can detect more than 95% of variants in the *RET* gene.
- Children of an affected individual have a 50% (one-in-two) chance of inheriting the gene variant. About 95% of individuals affected with MEN2A will have an affected parent, with the remaining 5% occurring due to a 'de novo' genetic variant. 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.
- Indications for genetic counselling and testing include:
  - a confirmed diagnosis of medullary thyroid cancer;
  - 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;
  - a confirmed *RET* genetic variant in a relative;
  - prenatal diagnosis; and
  - predictive testing for parents, siblings and offspring of someone with a confirmed *RET* gene variant. For children, this would involve cord blood sample at birth or testing before the age of four or five; for children older than five, genetic testing is recommended as a matter of urgency.
- Genetic testing is available in the UK and is usually provided by specialist clinics or regional genetic centres.

Clinical management

Patients with MEN2A should always be managed by a specialist multidisciplinary team, including an endocrinologist, an experienced thyroid surgeon (skilled in operating on rare medullary thyroid cancers) and a clinical geneticist/genetic counsellor.

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 is normalised, followed by unilateral adrenalectomy.
- Phaeochromocytoma must be removed before any other surgery undertaken.

Primary hyperparathyroidism:

- This usually occurs many years after surgery of the thyroid gland.
- Resection of the affected gland, or parathyroidectomy (total, or partial - 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.

Annual screening is recommended by the specialist team to assess for signs of the tumours and their hormonal effects, which are indicated below:

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:

- phaeochromocytoma screening up to date;
- specialist endocrine antenatal clinic; and
- patients and all blood relatives should be offered genetic counselling and *RET* gene testing, and children who are shown to have a *RET* genetic variant should undergo total thyroidectomy before they reach five years of age.

Direction to further reading and patient groups

- AMEND (Association for Multiple Endocrine Neoplasia Disorders)
- Multiple Endocrine Neoplasia Type 2 and Familial Medullary Thyroid Carcinoma: An Update. Samuel A. Wells, Jr, Furio Pacini, Bruce G. Robinson, Massimo Santoro. The Journal of Clinical Endocrinology & Metabolism, Volume 98, Issue 8, 1 August 2013, Pages 3149–3164

This information is intended for educational use and was current in December 2019. For clinical management, it is recommended that local guidelines and protocols are used.

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