Genomics Education Programme

NHS
Health Education England

Familial medullary thyroid cancer

Key facts

- Familial medullary thyroid cancer (FMTC) is an inherited condition and a subtype of MEN2 (multiple endocrine neoplasia Type 2 – a hereditary endocrine cancer syndrome).
- Individuals with FMTC have a high probability of developing medullary thyroid cancer (MTC) with a lower probability (<5%) of developing the other specific endocrine tumours (adrenal adenoma or parathyroid adenoma/ hyperplasia) usually associated with MEN2.
- It accounts for 10%-20% of all MEN2 cases.
- Genetic testing is essential for all MTC patients, even if there is no known family history.
- The age of onset is usually later than in other types of MEN2 and is typically in middle age.
- FMTC is an autosomal dominant condition, and is due to genetic alterations (mutations) in the RET proto-oncogene.
- Approximately 80% of individuals with a genetic alteration will develop medullary thyroid cancer at some point in their lives.
- Early diagnosis, treatment and management improves outcome and quality of life.
- The prevalence of MEN2 (including FMTC) is estimated to be between 1-9 in 100,000 individuals.
- Prenatal counselling and genetic testing is available.

Clinical features

The clinical features of FMTC are due to the onset of medullary thyroid cancer. Features may include:

- a neck lump or neck pain typically >35 years old; and
- diarrhoea due to raised calcitonin levels.

Diagnosis

Medullary thyroid cancer (MTC)

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

Genetic basis

- FMTC is caused by genetic alterations in the *RET* gene which are inherited in an autosomal dominant manner.
- The particular genetic alterations that cause FMTC mean that the patient has a high probability of developing MTC and a low probability of developing other endicrine 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.

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 potential treatments for patients with unresectable (unable to be removed with surgery), locally advanced, or metastatic MTC.

Clinical management

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

Medullary thyroid cancer screening

- annual plasma calcitonin level;
- annual thyroid hormone and thyroid stimulation hormone measurements to monitor replacement therapy; and
- annual neck and thorax MRI.

Phaeochromocytoma

- annual plasma metanephrines measurement;
- blood pressure; and
- abdominal scan if plasma metanephrines become elevated.

Primary hyperparathyroidism

- annual plasma calcium test.

Pregnancy

- phaeo screening up to date; and
- specialist endocrine A/N clinic.

FMTC patients and all blood relatives should be offered genetic counselling and *RET* gene testing. Children who are shown to have a *RET* genetic alteration should undergo total thyroidectomy from <5 years.

Genetic testing

Indications for genetic counselling and testing include:

- a confirmed diagnosis of medullary thyroid cancer;
- a confirmed *RET* genetic alteration (mutation) in a 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.