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 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.
**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.*