MEN 2 SCREENING PROTOCOL

Clinical Features

MEN2A

Comprises approximately 75% of MEN2.

Medullary Thyroid Carcinoma (MTC) develops in 90% of untreated carriers

Phaeochromocytoma develops in 50% (of which approximately 60% will be bilateral)

Parathyroid hyperplasia/neoplasia and hyperparathyroidism develop in 20-30%

MEN2B

MTC and phaeochromocytoma develop. Parathyroid disease does not.

MTC develops earlier and is more aggressive

Additional features include a Marfanoid habitus and mucosal/intestinal ganglioneuromatosis

Pathogenesis

Germ-line mutations of RET gene produce a constitutively activated receptor-like tyrosine kinase. Mutations affecting the extracellular domain produce MEN2A; mutations of the tyrosine kinase domain produce MEN2B. The genotype determines much of the clinical phenotype, and subsequent risk of neoplasia and metastasis.

Genetic screening for RET mutations

RET mutations are identified in >95% of those with MEN2.

The benefits of screening are:

- Reduced mortality in cases.
- Exclusion of family members when a mutation is detected in the kindred.

Early intervention for MTC and better screening for phaeochromocytoma have reduced mortality.

Genetic screening should be offered to all the following patients:

- Members of a kindred with MEN2

- A patient with a personal/family history of MTC (1-7% of "sporadic" MTC have MEN2)
- A patient with a personal/family history of phaeochromocytoma. Screening for von Hippel Lindau syndrome and Neurofibromatosis type 1 (VHL and NF1 genes) should be offered in addition to RET.

Caveat: Routine screening of RET will only identify the known mutations in exons 10,11 and 13-16. Therefore if a strong suspicion of MEN2 persists, the remaining 15 exons should be sequenced in a research laboratory

Screening is **not** justified in primary or familial hyperparathyroidism.

Risk stratification

The mutated codon and the course of disease in the kindred should be considered together in attributing risk. This helps decide the timing for total thyroidectomy in childhood. Thus those with MEN2B or a mutation in codons 883, 918 or 922 should have thyroidectomy performed within 6 months of birth, while those with other mutations have surgery before 5 years. This should be advised through the genetics service (Dr M Porteous).

In adult practice, any newly discovered case of MEN2 should be advised to have total thyroidectomy, having excluded the presence of phaeochromocytoma first, and referred for genetic counselling.

Biochemical Screening and Imaging

MTC

Calcitonin is an excellent tumour marker and should be assayed before thyroidectomy if possible, and then annually thereafter. Some evidence suggests that the peak calcitonin following calcium/pentagastrin stimulation is more sensitive than a basal calcitonin alone.

During follow-up a rising calcitonin or a palpable mass are indications for imaging. Ultrasound and also CT or MRI are suitable structural imaging modalities, while sestamibi scanning may localise functioning tissue. MIBG scanning may occasionally be useful where other radiopharmaceuticals fail to image.

MTC metastasises to local/mediastinal lymph nodes or peripherally to lung, liver and bone.

Surgery is recommended for local disease (although there are no survival data to support this view). Surgery is not recommended in the presence of metastases (however debulking of tumour may provide palliation from secretory diarrhoea). Parathyroid hyperplasia should be explored for at operation.

Phaeochromocytoma

Annual biochemical screening is necessary in all with RET mutations or in an MEN2 kindred with no identified mutations. 24 hour urinary excretion of normetanephrine & metanephrine is the most sensitive test. A positive test should prompt imaging (CT/MRI and, if positive, MIBG scanning).

Some phaeochromocytomas are non-secretory and imaging is required every 3-5 years by CT or MRI even if biochemical screening negative.

When phaeochromocytomas are detected, pre-operative preparation with α-blockade followed by β-blockade is essential. For unilateral disease a laparoscopic approach is recommended. For bilateral disease either laparoscopic or open adrenalectomy are appropriate.

Hyperparathyroidism

Screening by assaying PTH and calcium (preferably ionized calcium) should be performed annually. Those with codon 634 mutation have an increased risk of parathyroid neoplasia.

No screening is required in MEN2B (codons 883, 918, 922) as hyperparathyroidism does not develop.

Surgery should be performed by an experienced surgeon.

Suggested Follow-up

	Biochemical Screening	*Indication for imaging*	*Imaging*	*Indication for Surgery*
MTC	Annual calcitonin (or stimulated calcitonin)	• Rise in calcitonin • Palpable lump	Ultrasound/CT/MRI, ^{99m}Tc Sestamibi scanning	• At presentation in adulthood **(exclude Phaeo first)**
Phaeo	Annual 24hr urinary metanephrines	• 3-5 yearly • Or if meta-nephrines elevated	CT/MRI, MIBG	• Positive scan
Parathyroid	Annual PTH and ionised calcium			• Development of hyperparathyroidism • **And** renal calculi, osteoporosis, symptomatic hypercalcaemia, or patient preference

References

1. Guidelines for diagnosis and therapy of MEN Type 1 and MEN Type 2. JCEM (2001) 86: 5658-71
2. Preoperative calcitonin levels are predictive of tumor size and postoperative calcitonin normalization in medullary thyroid carcinoma. JCEM (2000) 85: 919-22
3. Primary hyperparathyroidism in multiple endocrine neoplasia type 2A. J Int Med (1995) 238: 369-73
4. A 10-Year Prospective Study of Primary Hyperparathyroidism with or without Parathyroid Surgery. NEJM (1999) 341: 1249-55

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