MEN 1 SCREENING PROTOCOL

Key Points
Multiple endocrine neoplasia type 1 (MEN1) is expressed mainly as parathyroid, enteropancreatic neuroendocrine, anterior pituitary and foregut carcinoid tumours.

- Primary hyperparathyroidism is the most common and usually the earliest endocrine expression of MEN1, occurring in 90% of MEN1 patients by the age of 40 years.
- Gastrin secreting tumors, the most common functional MEN1-associated enteropancreatic neuroendocrine tumors, are a major cause of morbidity and mortality. Approximately 40% of MEN1 patients develop gastrinomas by the age of 50 years. Gastrinomas are often multiple and metastatic at diagnosis. Most are relatively indolent, but ~15% progress to an aggressive malignancy (typically marked by larger tumours (>3cm), higher gastrin levels (>10,000pg/ml) and metastases). Insulinomas occur in 10% of MEN1 cases.
- Pituitary tumours, most commonly prolactinomas (20%), but also mixed (GH+PRL 5%), GH-secreting (5%) and non-functioning (5%), are present in ~40% of MEN1.
- Foregut carcinoid tumours, also associated with MEN1, can be located in the bronchus, thymus or stomach. Carcinoid tumours in MEN1 can be asymptomatic until a late stage and then express malignancy.

Newly Characterised Features of MEN1
- Multiple facial angiofibromas reported in ~90% MEN1 patients.
- Collagenomas (usually thoracic) identified in ~70% of MEN1 cases.

Screening for Tumors in MEN1 Cases

Genetics
Biochemically/clinically confirmed MEN1 cases should be refered to Clinical Genetics for construction of pedigree and identification of at risk/affected family members. Pre-symptomatic testing of individuals with a relative with an identified
menin mutation should be performed by Clinical Genetics who will then refer gene carriers back to Endocrinology for screening and follow up. 10-20% of clearly affected individuals do not have a mutation detectable by current screening methods.

Why

Early screening for MEN1 tumours in known or probable MEN1 mutation carriers might help to decrease MEN1-related morbidity. Disease penetrance by 20 years is >50%, and by 40 years is ~95%.

Tests and schedules to screen for endocrine tumours in definite/probable MEN1 germline mutation carriers

<table>
<thead>
<tr>
<th>Tumour (frequency)</th>
<th>Age at which to begin screening (yrs)</th>
<th>Annual biochemical tests</th>
<th>Imaging tests (every 3 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parathyroid adenoma (90%)</td>
<td>10</td>
<td>Calcium (esp. iCa(^{2+})) PTH</td>
<td>None</td>
</tr>
<tr>
<td>Gastrinoma (40%)</td>
<td>20</td>
<td>Gastrin</td>
<td>None</td>
</tr>
<tr>
<td>Insulinoma (10%)</td>
<td>10</td>
<td>Fasting glucose, insulin</td>
<td>None</td>
</tr>
<tr>
<td>Other enteropancreatic tumours (~20%)</td>
<td>20</td>
<td>Fasting blood for pancreatic peptide screen, (chromogranin-A)</td>
<td>NONE AS YET. USA guidelines suggest octreotide scintigraphy ± CT/MRI. Role of imaging is uncertain as tumours are small and multiple. However, the protocol requires regular review.</td>
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<tr>
<td>Anterior pituitary tumours (40%)</td>
<td>10</td>
<td>Prolactin, IGF1</td>
<td>MRI</td>
</tr>
<tr>
<td>Thymic and bronchial carcinoids (~4%)</td>
<td>20</td>
<td>None (typically non-secretory, but have malignant potential)</td>
<td>NONE AS YET. USA protocols suggest 3yrly CT/MRI, but no data on efficacy. Screening probably not justified by low prevalence. Sensible to do prophylactic thymectomy at parathyroid surgery and perhaps 1x CT thorax in adult life.</td>
</tr>
</tbody>
</table>
i.e. From age 10y (if acceptable) do fasting blood annually and MRI of pituitary every 3 yrs.

- The 10-14 y age group will be seen by Dr Chris Kelnar at the RHSC
- 15y onwards by Endocrinology at the WGH

References
TEM 12:173 (2001)
JCE&M 86: 5658 (2001)
JCE&M 86: 5283 (2001)