Diagnostic Challenges in Multiple Endocrine Neoplasia Type 1 (MEN1) : Usefulness of Genetic Analysis

Professor R. V. Thakker, FRS
May Professor of Medicine
University of Oxford, U.K.

Meet The Experts
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Disclosures: None
Clinical Practice Guidelines for Multiple Endocrine Neoplasia Type 1 (MEN1)

Rajesh V. Thakker, Paul J. Newey, Gerard V. Walls, John Bilezikian, Henning Dralle, Peter R. Ebeling, Shlomo Melmed, Akihiro Sakurai, Francesco Tonelli, and Maria Luisa Brandi

Challenges and controversies in management of pancreatic neuroendocrine tumours in patients with MEN1

Christopher J Yates, Paul J Newey, Rajesh V Thakker

Current and emerging therapies for PNETs in patients with or without MEN1

Morten Frost1,2*, Kate E. Lines1* and Rajesh V. Thakker1

J Clin Endocrinol Metab, 2012, 97: 2990-3011

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Nat Rev Endo, 2018, 14:216-227
Overview - Multiple Endocrine Neoplasia (MEN) Syndromes and MEN type 1 (MEN1)

- Recognition
- Evaluation
- Management
  - Cases (5 patients)
- Summary
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*Thakker et al JCEM (2012)*
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• Recognition

• **Evaluation**: Biochemical, Radiological and Genetic

• Management
  - Cases (5 patients)

• Summary
Biochemical, Radiological and Genetic Testing in Individuals at High Risk of Developing MEN1

<table>
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<tr>
<th>Tumor</th>
<th>Age to begin (yr)</th>
<th>Biochemical test (plasma or serum) annually</th>
<th>Imaging test (time interval)</th>
</tr>
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<tbody>
<tr>
<td>Parathyroid</td>
<td>8</td>
<td>Calcium, PTH</td>
<td>None</td>
</tr>
<tr>
<td>Pancreatic NET</td>
<td>20</td>
<td>Gastrin (+ gastric pH)</td>
<td>None</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>5</td>
<td>Fasting glucose, insulin</td>
<td>None</td>
</tr>
<tr>
<td>Insulinoma</td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Other pancreatic NET</td>
<td>&lt;10</td>
<td>Chromogranin-A; pancreatic polypeptide, glucagon, VIP</td>
<td>MRI, CT, or EUS (annually)</td>
</tr>
<tr>
<td>Anterior pituitary</td>
<td>5</td>
<td>Prolactin, IGF-I</td>
<td>MRI (every 3 yr)</td>
</tr>
<tr>
<td>Adrenal</td>
<td>&lt;10</td>
<td>None unless symptoms or signs of functioning tumor and/or tumor &gt;1 cm are identified on imaging</td>
<td>MRI or CT (annually with pancreatic imaging)</td>
</tr>
<tr>
<td>Thymic and bronchial carcinoid</td>
<td>15</td>
<td>None</td>
<td>CT or MRI (every 1–2 yr)</td>
</tr>
</tbody>
</table>

- **MEN1 mutations**: diverse spectrum and scattered over the coding region, with almost each family having its own unique mutation

Thakker et al, 2012, JCEM; Lemos and Thakker, 2008 Hum Mutation
MEN1 mutational analysis can:

1. aid in confirming the diagnosis

2. identify mutation carriers in a family, who should be screened for tumour development for earlier treatment e.g. non-functioning pancreatic NETs

3. exclude burden of disease and anxiety in the ~50% of non-mutation carriers
Overview - Multiple Endocrine Neoplasia (MEN) Syndromes and MEN type 1 (MEN1)

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Case 1

Primary Hyperparathyroidism in a Young (Man) Person - Suspect MEN1
Investigations and Treatment:

• Hypecalcaemia ($Ca^{++} = 2.72$ mol/l) with raised PTH - Total parathyroidectomy and oral Calcitriol replacement

• Raised plasma glucagon, CT scan shows tumour in tail of pancreas - Distal pancreatectomy. Histology - pancreatic neuroendocrine tumour (NET) immunostains for chromogranin and glucagon

Progress:

• Screened annually for development of MEN1 associated tumours

• Remains well, normocalcaemic without renal stones, and no recurrence of pancreatic NET
Diagnosis: Multiple Endocrine Neoplasia Type 1 (MEN1)
Patient’s Questions

I have children, Will they:

1. Get the same tumours as me

2. What age are they likely to get tumours

3. What is the plan for my children
Answer – 1, Tumour types

Children may not get same tumours as their father, as there is variability of tumour development within a family, and is no genotype-phenotype correlation.

Moreover, studies in 2 identical twins with the same MEN1 mutation revealed that one developed a parathyroid tumour and a prolactinoma, and the other only a parathyroid tumour.

Phenotype genotype correlation not observed in the MEN1 families

Five unrelated families with a 4bp (CAGT) deletion at codons 210 and 211

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<th>Family</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>+</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>+</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>-</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>-</td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>-</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>+</td>
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*Thakker, 1998 JCEM*
Answer – 2, Age of Tumour Development

Age at which tumours develop is also variable, as there is an age-related penetrance for MEN1, with a ~5% of individuals having tumours by age 20 years and >50% by age 40 years.

Age related penetrance for MEN1

Bassett et al, 1998 Am J Hum Genet
Answer – 3, Plan Regular Screening

Screening should be undertaken for all the MEN1-associated tumours in the children.

Two possible options

- MEN1 mutation status ascertained and then undertake regular biochemical and radiological screening for those with the mutation, and reassure and discharge those without the mutation.
- Do not ascertain MEN1 mutation status, but undertake regular biochemical and radiological screening in ALL the children.
Asymptomatic relative of MEN1 patient in whom germ-line mutation identified

Test for MEN1 mutations

Mutant carrier

Age < 40 years

Serum Ca++, PRL and assess for insulinoma

Normal

Abnormal

Re-screen at 6–12 months

Normal

Proceed to further appropriate investigations and treatment

Abnormal

Re-screen at 6–12 months

Non-mutant carrier

Age ≥ 40 years

Serum Ca++, PRL and assess for gastrinoma and acromegaly

Normal

Abnormal

No further investigations

Thakker et al, 2012, J Clin Endo Metab
Patient 2 - Daughter of Patient 1

- MEN1 mutation. Asymptomatic.
- Annual review for next 2 years
- Asymptomatic but oligomenorrhoea on detailed questioning
- Biochemistry: PRL 3676mU/l, cCa\textsuperscript{2+} = 2.64mmol/l, PTH = 6
  Fasting gut hormones - normal
- MRI pituitary: Right sided pituitary adenoma
- MRI abdomen: <2cm mass in neck of pancreas
- Discussed at Multi-Disciplinary Team (MDT) meeting
- Commenced cabergoline. Normal menstrual cycle restored.
- Serial MRI and fasting gut hormones to assess pancreatic lesion
- Over 2 years - increase in tumour size >2cm - surgical referral

Newey et al, JCEM 2010
Patient remains well eight years following surgery with no evidence of tumour recurrence

Newey et al, JCEM 2010
Comment

The case histories from this family with MEN1 help to illustrate the importance of undertaking combined genetic analysis with regular screening for tumours using:

- Plasma biochemistry
- Radiological imaging

Aim is to potentially reduce the harmful effects of metastatic disease and hormonal secretion.
Patient 3 – Family with MEN1

Individual: $2^0$ amenorrhoea due to microprolactinoma, prolactin = 3526 IU/ml (N<360)

Phenotype: MEN1 in a familial context
Patient 3 – Family with MEN1

Individual II.4 does not have MEN1 mutation and represents an MEN1 phenocopy due to sporadic prolactinoma in the context of familial MEN1
Patient 4 - Family with MEN1

Mutational analysis of the MEN1 gene did not identify a mutation
Patient 4 - with MEN1

Mutational analysis of the MEN1 gene did not identify a mutation, but instead patient 4 had a mutation of CDC73 (encodes cell division cycle protein 73, also referred to as parafibromin), associated with the Hyperparathyroidism Jaw Tumour (HPT-JT) syndrome.
Hyperparathyroidism-Jaw Tumour (HPT-JT) Syndrome

- Autosomal dominant disorder characterised by:
  - Parathyroid tumours (80%), often (15%) carcinomas
  - Jaw tumours, ossifying fibromas (>30%)

- Renal abnormalities (15%) eg. Wilm’s tumours, cysts, hamartomas, adenomas, carcinomas
- Uterine tumours (75%)
- Pancreatic adenocarcinomas (<2%)
- Testicular mixed germ cell tumours (<2%)
- Hurthle cell thyroid adenomas (<2%)

HPT-JT maps to chromosome 1q24-q32, location of Cdc73, encoding Cell Division Cycle Protein 73 / Parafibromin
Phenocopy: definition

“The development of disease manifestations that are usually associated with mutations of a particular gene, but instead are due to another aetiology.”

Examples:

*Familial* MEN1 context, in which a patient with one MEN1-associated tumour does not have the familial mutation.

*Patient* with two MEN1-associated tumours, who does not have MEN1 mutation, but has involvement of another gene.

5% of families attributed with MEN1 have phenocopies.

*Turner et al Human Mutation 2010*
Diagnosis of MEN1

* Patient with two or more MEN1-associated tumours

* Familial MEN1 ie: a patient who has one of the MEN1-associated tumours and a first degree relative with MEN1

* Genetic: mutant gene carrier ie an individual who has an MEN1 mutation but does not have clinical or biochemical manifestations of MEN1

*The diagnosis of MEN1 may be confounded by the occurrence of phenocopies
Patient 5 -

Presentation: Cushing’s syndrome (recurrent after >10 years) with asymptomatic hypercalcaemia, elevated serum PTH

Family History: Not known to have MEN1.

Diagnosis: MEN1 on basis of primary hyperparathyroidism plus pituitary tumour causing Cushing’s disease, but no MEN1 mutation detected

Investigation: Cushing’s disease with detectable ACTH, normal MRI, Petrosal sinus sampling - marked central gradient with central / peripheral ratio ACTH >50

Treatment: Transphenoidal hyphosphysectomy. Post-op 9am serum cortisol <50nmol/L, with resolution of Cushingnoid features

Ultrasound & FNA: Thyroid nodule - Cells suspicious of MTC

Plasma calcitonin: 27,500ng/L (normal <15ng/L)

\(^{18}\)FDG-PET Scan: Metastatic MTC with avid uptake in left adrenal gland

CT Scan: Bilateral nodules, 2.0 to 2.5cm in diameter

Plasma urinary (24h) metanephrines: Elevated (2-4 fold increase)

History: No paroxysmal symptoms and normotensive

Diagnosis: Asymptomatic phaeochromocytoma in association with MTC and primary hyperparathyroidism
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*Thakker et al JCEM (2012)*
Patient 5

Revised Diagnosis: MEN2A

Genetic Testing: RET mutation – Cys634Arg, common germline mutation for MEN2A

Cushing’s syndrome in MEN2A: rare & may be due to
- ectopic ACTH secretion from MTC
- adrenal tumour secreting glucocorticoids
- pituitary tumour (Cushing’s Disease)

Steiner et al (1968) Medicine
Implications of Genetic Analysis for His Son

- Son known to have parathyroid hyperplasia
- Found to have RET mutation (Cys63Arg)
- Investigations:
  - plasma calcitonin – normal
  - plasma and urinary metanephrines – normal
  - MRI – bilateral adrenal nodules; pituitary normal
- Treatment: Total thyroidectomy
- History: MTC confirmed
- Progress: annual screening for MEN2 associated tumours. Remains well

MESSAGE: IN PATIENTS WITH MEN, WHO DO NOT HAVE MEN1 MUTATION, LOOK AT OTHER (MEN) GENES FOR MUTATIONS
Summary (1) - Recognition, Evaluation and Management of Multiple Endocrine Neoplasia (MEN) Syndromes and MEN type 1 (MEN1)

• Combined genetic testing and biochemical screening is of value in clinical practice

• There still remain diagnostic challenges due to phenocopies and the involvement of other genes e.g. PARAFIBROMIN, CaSR, and RET/MEN2A in patients who do not have MEN1 mutation
Summary (2) – Genetic and Endocrine Evaluations: Who, When and Where?

Who?

Any individual with:
- Two or more endocrine tumours i.e. MEN
- Development of an endocrine tumour at a young age
- A relative (first degree) with MEN
  (N.B. > 10% of patients will have de novo germline mutations and therefore no familial history)

When?

As early as possible, as children below the age of 10 years may have developed tumours

Where?

Contact Clinical Genetics Departments
ACADEMIC ENDOCRINE UNIT

Andrew Nesbit    Paul Newey
Manish Modi     Charlotte Philpott
Kreepa Koobiall
Tracey Walker    Sian Piret
Sarah Howles
Valerie Babinsky    Caroline Gorvin

Raj Thakker
Kate Lines
Angela Rogers
Fadil Hannan

Mark Stevenson    Gerard Walls
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