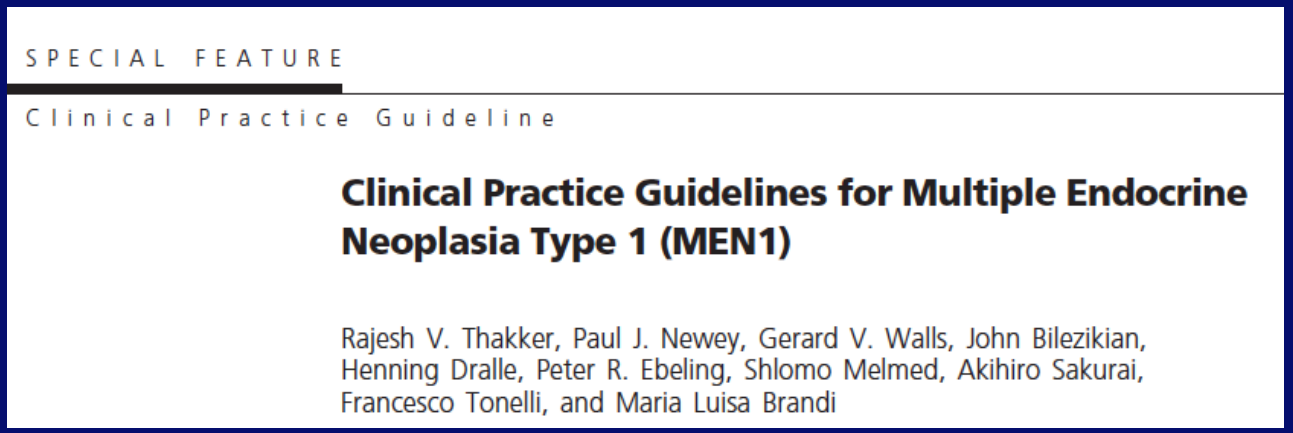
Diagnostic Challenges in Multiple Endocrine Neoplasia Type 1 (MEN1) : Usefulness of Genetic Analysis

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

Meet The Experts
49th Annual Meeting of the Israel Endocrine Society
Tel Aviv, Israel
29-30th April 2018

Disclosures: None

wellcome trust
MRC Medical Research Council
Senior Investigator NIHR



SPECIAL FEATURE

Clinical Practice Guideline

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

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

Review

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

Christopher J Yates, Paul J Newey, Rajesh V Thakker

The Lancet Diabetes & Endocrinology, 2015, 3: 895-904

REVIEWS

Current and emerging therapies for PNETs in patients with or without MEN 1

Morten Frost[1,2], Kate E. Lines[1*] and Rajesh V. Thakker[1]*

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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Two or more endocrine tumours in a patient

	MEN1	MEN2 & 3	MEN4
Tumours			
	Parathyroids (95%) Pancreatic islet (40%) Pituitary anterior (30%)	Medullary thyroid carcinoma, MTC (99%) Phaeochromocytomas (50%) Parathyroids (20%)	Parathyroids Pituitary (anterior) Adrenal, renal, Gonads
Autosomal dominant Inheritance and Chromosome location			
	Yes, 11q13	Yes, 10_{cen}-10q11.2	Yes, 12p13
Gene Product			
	MENIN	RET	CDKN1B (p27,KIP1)

Thakker et al JCEM (2012)

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Overview - Multiple Endocrine Neoplasia (MEN) Syndromes and MEN type 1 (MEN1)

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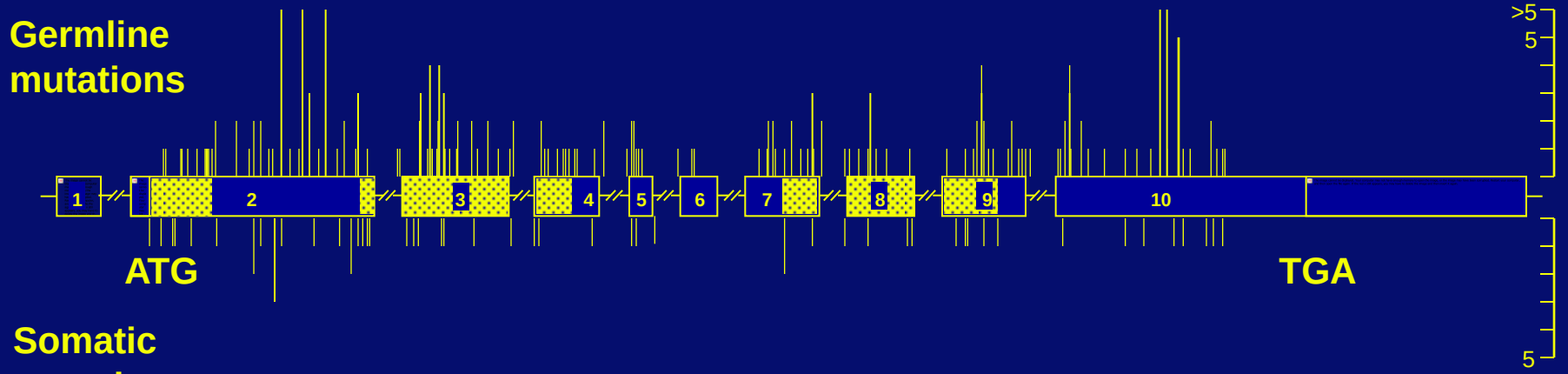
Biochemical, Radiological and Genetic Testing in Individuals at High Risk of Developing MEN1

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

- **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

Genetic : Role of MEN1 Mutational Analysis

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**

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Case 1

Primary Hyperparathyroidism in a Young (Man) Person - Suspect MEN1

Investigations and Treatment:

- Hypecalcaemia (Ca^{++} = 2.72mollL) 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

Family Medical History

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 parathryoid tumour.

Trump et al QJM 1996, Flanagan et al Clin Endo 1996

Phenotype genotype correlation not observed in the MEN1 families

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

	Family				
	1	2	3	4	5
Tumours					
Parathyroid	+	+	+	+	+
Gastrinoma	+	-	+	+	+
Insulinoma	-	+	-	-	-
Glucagonoma	-	-	-	-	+
Prolactinoma	-	+	+	+	+
Carcinoid	+	-	-	-	-

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.

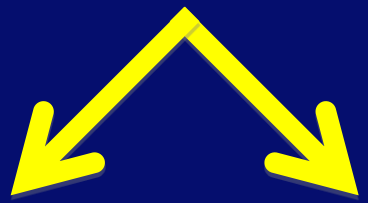
Age related penetrance for MEN1

Bassett et al, 1998 Am J Hum Genet

Answer – 3, Plan Regular Screening

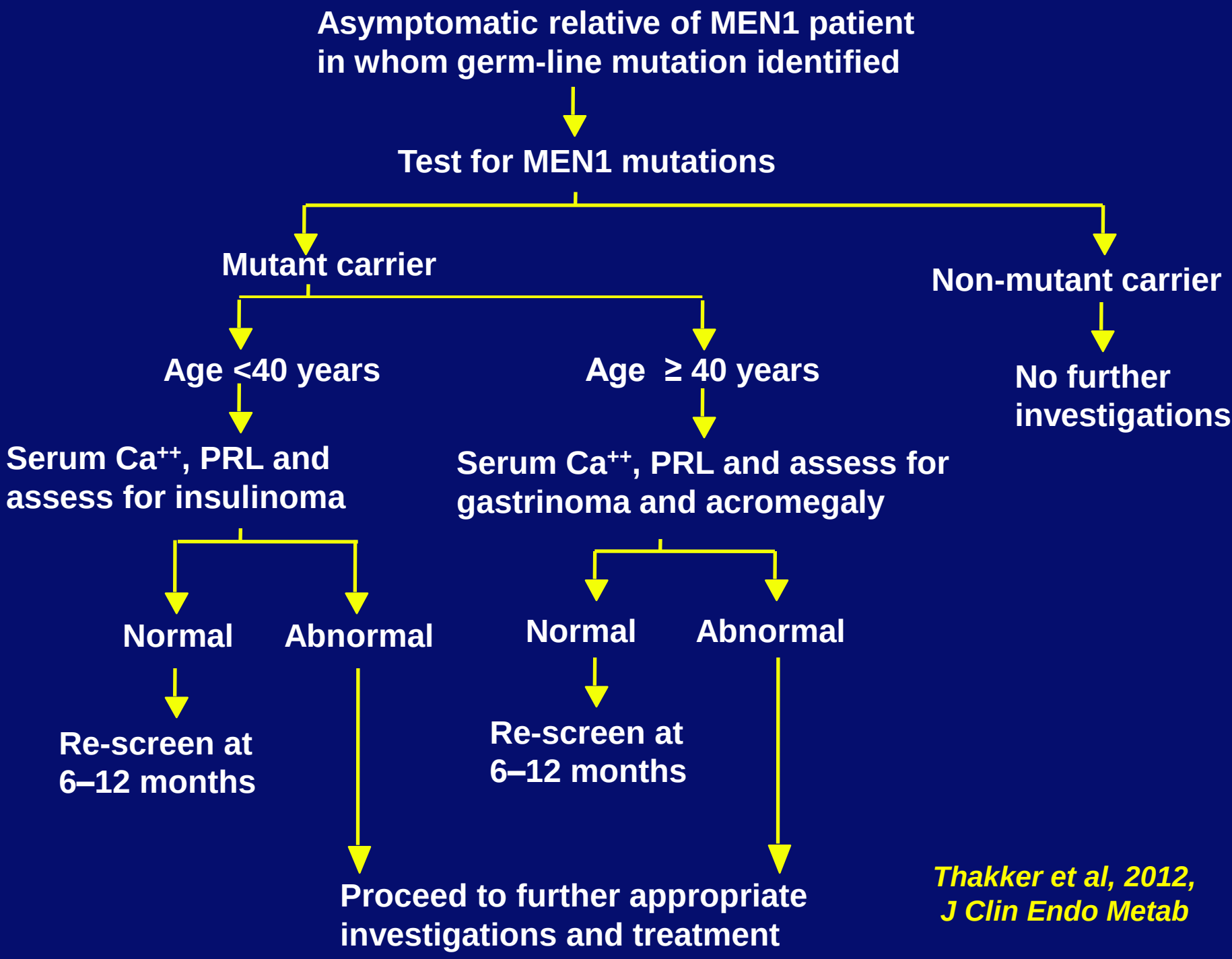
Screening should be undertaken for all the MEN1-associated tumours in the children.

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



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^{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

Non-Functioning Pancreatic NET with loss of menin

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

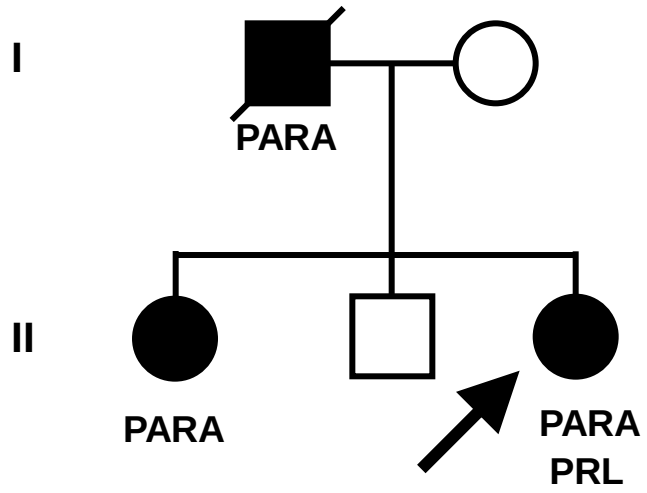
Individual : 2^0 amenorrhoea due to microprolactinoma, prolactin = 3526 IU/ml (N<360)

Phenotype: MEN1 in a familial context

Patient 3 – Family with MEN1

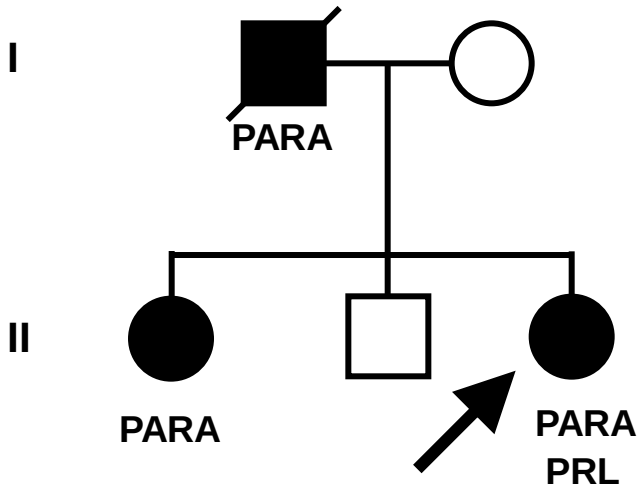
Individual II.4 does not have MEN1 mutation and represents an MEN1 phenocopy due to sporadic prolactinoma in the context of familial MEN1

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 refered 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:

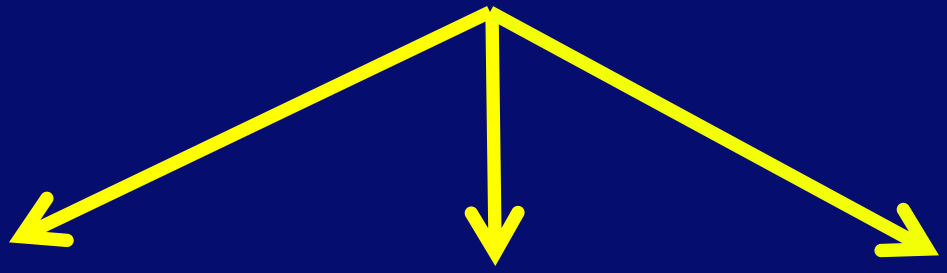
Familial **MEN1 context, in which a patient with one MEN1-associated tumour does not have the familial mutation.**

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)

Thakker et al NEJM 1989, Thakker et al JCEM 2012, Simmonds et al Clin Endo 2012, Naziat et al, Clin Endo, 2013

^{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)

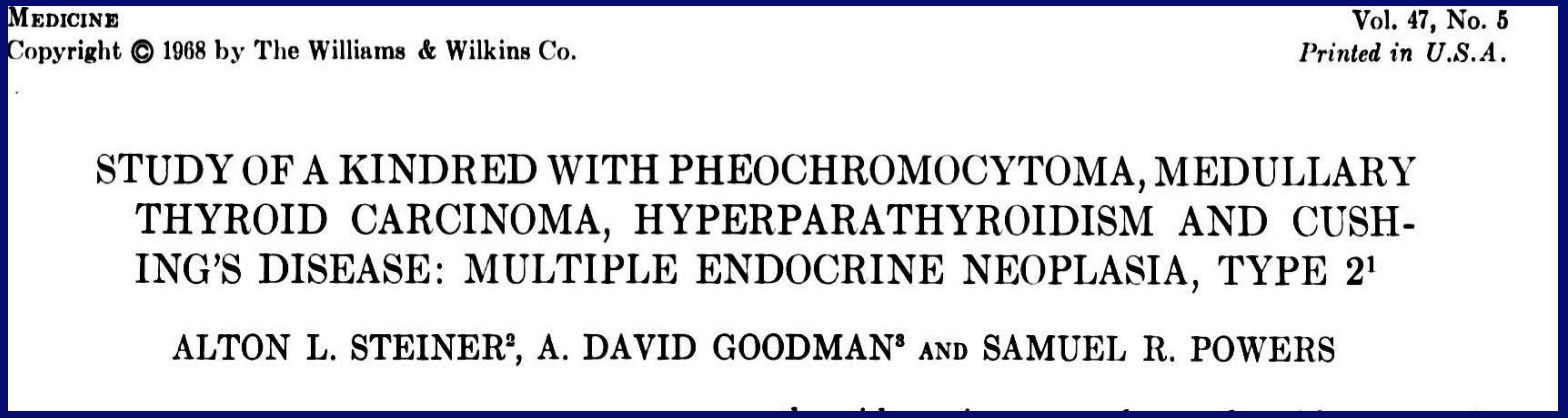
Patient 5

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)



MEDICINE
Vol. 47, No. 5

Printed in U.S.A.

STUDY OF A KINDRED WITH PHEOCHROMOCYTOMA, MEDULLARY THYROID CARCINOMA, HYPERPARATHYROIDISM AND CUSHING'S DISEASE: MULTIPLE ENDOCRINE NEOPLASIA, TYPE 2[1]

ALTON L. STEINER[2], A. DAVID GOODMAN[3] AND SAMUEL R. POWERS

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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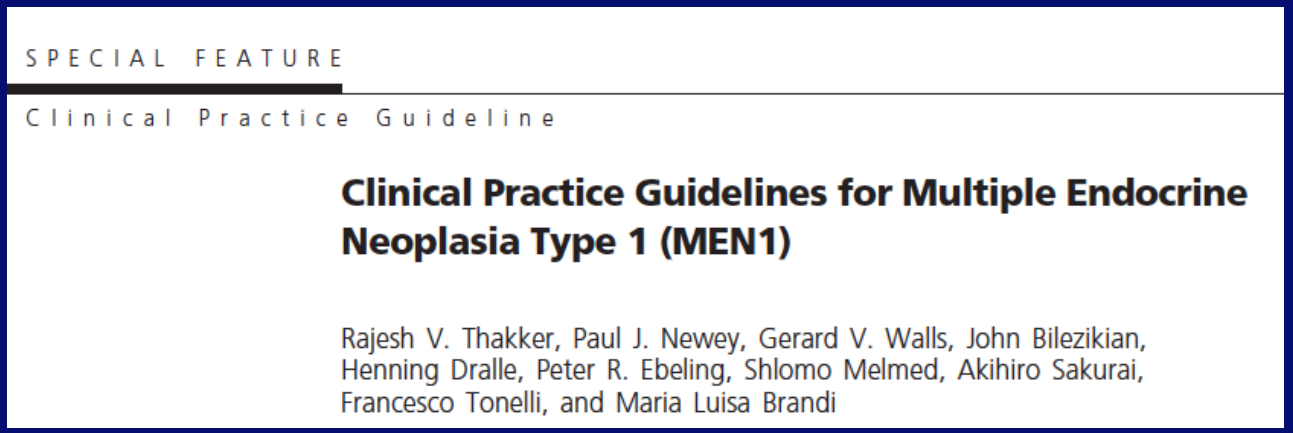

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