Multiple Endocrine Neoplasia
A Case Study

Kate Davies
Senior Lecturer in Children’s Nursing
London South Bank University, UK
Conflicts of Interest

• Nothing to declare
Introduction

What is MEN
Type of MEN
Case study
How should MEN be managed?
Conclusions
What is Multiple Endocrine Neoplasia?

- Encompasses several distinct syndromes
  - Tumours of the endocrine glands

- MEN1
- MEN2
- MEN3
- VHL
How do they occur?

MEN 1 & 2 and VHL

- Autosomal dominant
  - Only one mutation in one pair of genes is needed to cause the condition
  - 50% chance of having a boy or a girl with the same condition
  - Most commonly present in early adulthood and onwards
## How do they occur?

<table>
<thead>
<tr>
<th>MEN1</th>
<th>MEN2&amp;3</th>
<th>VHL</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="MEN1 Diagram" /></td>
<td><img src="image2" alt="MEN2&amp;3 Diagram" /></td>
<td><img src="image3" alt="VHL Diagram" /></td>
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</tbody>
</table>

- **MEN1**: MEN1 gene 11q13
- **MEN2&3**: RET gene 10q11
- **VHL**: VHL gene 3q26-q25

**Become what you want to be**
Genetic screening
Can now target individuals at risk

Genetic screening allows the children from affected families who have NOT inherited the mutation

• Reassured
• Avoid regular clinical monitoring

• Issues re: Informed consent, counselling and confidentiality
Von Hippel Lindau disease

Chromosome 3 – mutation in the tumour suppressor gene

Can identify the gene
  • Pre-symptomatic screening

Autosomal dominant
  • Each child of an affected individual has a 1 in 2 chance (50%) to inherit the gene alteration

Children referred
  • Fellow adult endocrine teams managing in their affected parent
Von Hippel Lindau disease

Incidence
- 1 in 40,000
- Average age of presentation
  - 26 yrs of age

Haemangioblastomas
- Brain, spinal cord, retina

Renal cysts

Phaeochromocytomas

Become what you want to be
Phaeochromocytomas
Neuroendocrine tumour arising from the adrenal medulla
Usually benign, can be malignant
Excretes excess catecholamines
Uncommon cause of ↑BP :: can easily be missed
We have occasional bursts of cats when we are upset or stressed
• Those with phaeos have it all the time
Phaeochromocytomas

Symptoms?
- ↑BP
- Headache
- Perspiration / episodic sweating
- Palpitations
- Anxiety attacks
  - May be incorrectly attributed to anxiety or depression

Can cause life threatening conditions
- Hypertensive crisis
- Mets - Stroke
- Cardiac failure - MI

Become what you want to be
Case study – VHL

Male child Tom
DOB 10.11.01
Family history of VHL
Positive for the familial mutation in exon 3 of the VHL gene
Commenced screening programme
• 2006 age 5yrs
## Clinical screening

### 2007, 2008, 2009
All normal

### 2010
#### January
Urine catecholamine (noradrenaline) slightly elevated
370nmol/day (N=below 194)
Repeat and watch as asymptomatic

#### May
433nmol/day

#### June
MRI adrenal normal

#### October
372nmol/day

### 2011
#### February
477nmol/day

### 2012
Lesion seen on abdominal MRI
Repeat MRI with contrast MIBG scan
There is a 3cm MIBG positive paraganglioma in the upper retroperitoneum interposed between in the aorta, IVC and portal vein. No local invasion seen. Slow increase in size since 2008.

Small areas of soft tissue in the distal aorto-caval region but these are currently indeterminate.

Normal kidneys, adrenals and pancreas

Excision of paraganglioma January 2013, age 11yrs
Clinical management
April 2012

• Paraganglioma
  • Small
  • No plans for surgery
  • Intermittent symptoms and continued raised catecholamines
  • Commence Doxazocin 0.5mg once daily
    • Increase to twice a day after a week if tolerated
    • Continue until surgery planned

• Doxazocin
  • Alpha blockade
    • Reduces BP

Become what you want to be
MRI Abdomen 6.8.14

New 9mm peripherally enhancing left adrenal nodule which demonstrates restricted diffusion likely to represent a small phaeochromocytoma.
Clinical management

2014

- **November** age 13yrs
  - Now wants to be seen without his Mum
  - ? Phaeochromocytoma
  - Tom very stressed and upset
  - Psychological input offered

2015

- Further imaging..
MRI Pancreas 23.2.15

The anterior lesion in the tail of the pancreas is still present and demonstrates an arterial blush.

This remains suggestive of an islet cell tumour.

No other pancreatic lesion is demonstrated.
MRI adrenals 14.7.15

The right adrenal mass in the body of the adrenal has further increased in size now measures 13 mm.

The left adrenal nodule in the lateral limb is stable measuring 15 mm.

Both lesions have similar properties and the appearances are in keeping with small phaeochromocytomas.
Continued management

2015
• July
  • Bilateral phaeochromocytomas
  • Now proceed to surgery
• December – right adrenalectomy

2016
• April – surgical follow up
• As you know he underwent a right laparoscopic adrenalectomy for a pheochromocytoma within the Von Hippel Lindau syndrome in December last year, from which he made a rapid and uncomplicated post-operative recovery.

• On examination today, all incisions have healed well.

• We knew pre-operatively that he had bilateral phaeochromocytomas however the right was the largest and we hoped to proceed with a staged adrenalectomy to preserve adrenal function for as long as possible.

• Unfortunately, post-operative urinary nor-metadrenaline has not decreased substantially although his mother tells me he remains normotensive and asymptomatic.

• I discussed the findings with him and his mother today and I have suggested that he seeks an early appointment with the paediatric endocrine team to discuss the potential for going back on to doxazosin. He particularly would like to avoid further surgery for at least a year. He is of course in his GSCE year currently.
2016

• **May** – paediatric endocrine (PE) follow up
  - Continue here and not the family VHL clinic
  - Headaches / hot flushes / diarrhoea

• **August** – PE follow up
  - Arrangements to be made for L adrenalectomy
  - Commence alpha and beta blockade
  - Discussed adrenal insufficiency post op
    - Dad already on HC

• **September** – Left adrenalectomy
  - Commenced on HC 7.5 / 5 / 5 and Fludrocortisone
Bilateral adrenalectomy • Hydrocortisone replacement
2016

• November – PE follow up
  • Feeling much better

2017

• January – Cortisol day curve
  • Not been feeling well, missing school mornings
  • Had had a recent viral illness
    • HC 10mg tds – felt better
  • Cortisol levels low
  • HC increased to 7.5mg tds

• February – Surgical follow up
  • Discharged home
PE follow up imminent...
How should MEN / VHL be managed?

Screening important
Medical and surgical management
Nursing input
Liaison with adult endocrine teams
Patient support groups
Benefits of Screening in von Hippel-Lindau Disease – Comparison of Morbidity Associated with Initial Tumours in Affected Parents and Children


Departments of Endocrinology and Clinical Biochemistry, Barts and The London NHS Trust, London, UK

What Is Already Known
- Von Hippel-Lindau (VHL) is a rare highly penetrant autosomal dominant syndrome of associated multiple tumours with high morbidity and mortality.
- Genetic testing can identify affected children and enables pre-symptomatic screening of mutation-positive patients.

What New Information Has Been Gained
- Screening allows early treatment and intervention.
- Screening can reduce morbidity and mortality.
- Combined genetic and clinical screening should commence at 5 years of age.
**Genetics**
- Analysis of the index case is key to identifying further members of the family at risk
- Can be done from age 5yrs
  - Enable clinical screening

*Reduction in morbidity compared to their parents*

**Ophthalmology review**
- Fundoscopy screening
- Adrenals
  - Phaeochromocytomas
- Renal carcinomas
  - Now leading cause of death amongst VHL patients
    - Successful treatment for CNS haemangioblastomas
    - Imaging

<table>
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<tr>
<th>VHL</th>
<th>Eyes</th>
<th>Fundoscopy</th>
<th>CNS</th>
<th>Full examination</th>
<th>Fluorescein angiography</th>
<th>5 yrs</th>
<th>Annual</th>
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<td>Renal</td>
<td>Abdominal examination</td>
<td>MRI brain &amp; spinal cord</td>
<td>10 yrs</td>
<td>Annual</td>
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|     |      |            | Adrenal (phaeochromocytoma) | Blood pressure
24-hour urine collections (x3) – catecholamines
(plus corresponding serum metanephrines) | MRI kidneys | 5 yrs | Annual |
|     |      |            |      |                  | US kidneys | 5 yrs | Annual |
|     |      |            |      |                  | MRI adrenals | 5 yrs | 3 yearly |
|     |      |            |      |                  | US adrenals | 5 yrs | Annual |
Patient support

AMEND

- UK Patient support group
- www.amend.org.uk
Conclusion

• Management of children with NETs / VHL very complex

• Importance of screening emphasised
  • Genetics and clinical
    • Inform families
    • Reduce need for screening
    • Reduction in morbidity compared to their parents
    • Can screen from age 5yrs
      • MEN2b genetics from age 1yr

• Shift in management
  • Screening – emphasis on imaging
  • Hydrocortisone management

• Patient support
• Transition
References


Genetics 4 Medics App April 2017 (accessed August 2017)

AMEND website (accessed August 2017)