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Multiple Endocrine Neoplasia A Case Study

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Become what you want to be

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Conflicts of Interest

- Nothing to declare

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Introduction

What is MEN

Type of MEN

Case study

How should MEN be managed?

Conclusions

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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

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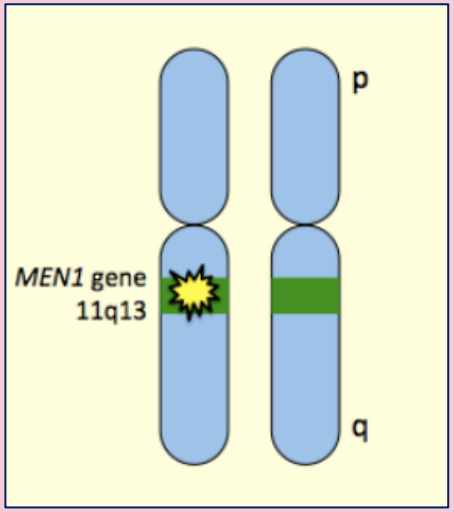
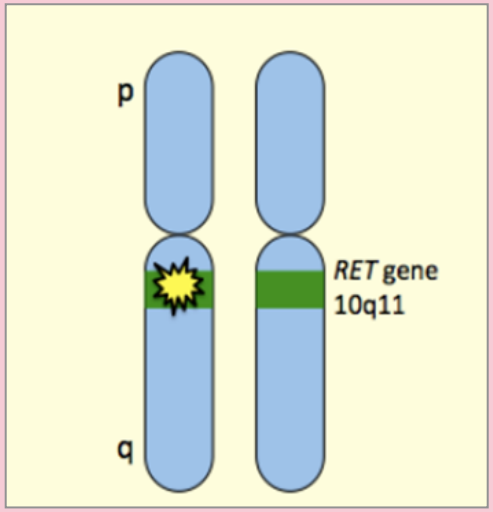
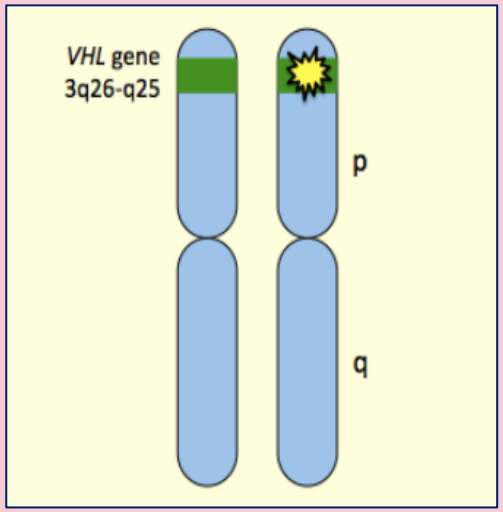
How do they occur?

MEN1	MEN2&3	VHL
		

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

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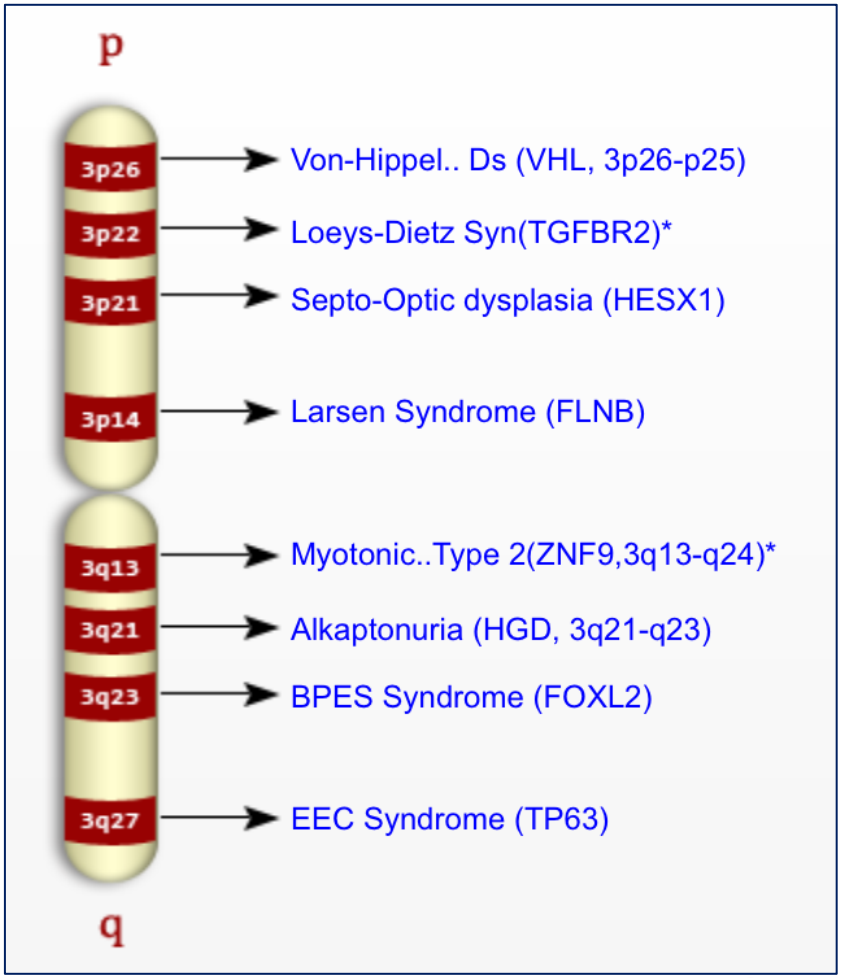
FYI…



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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

Phaechromocytomas

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

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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

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Case study – VHL

Male child Tom

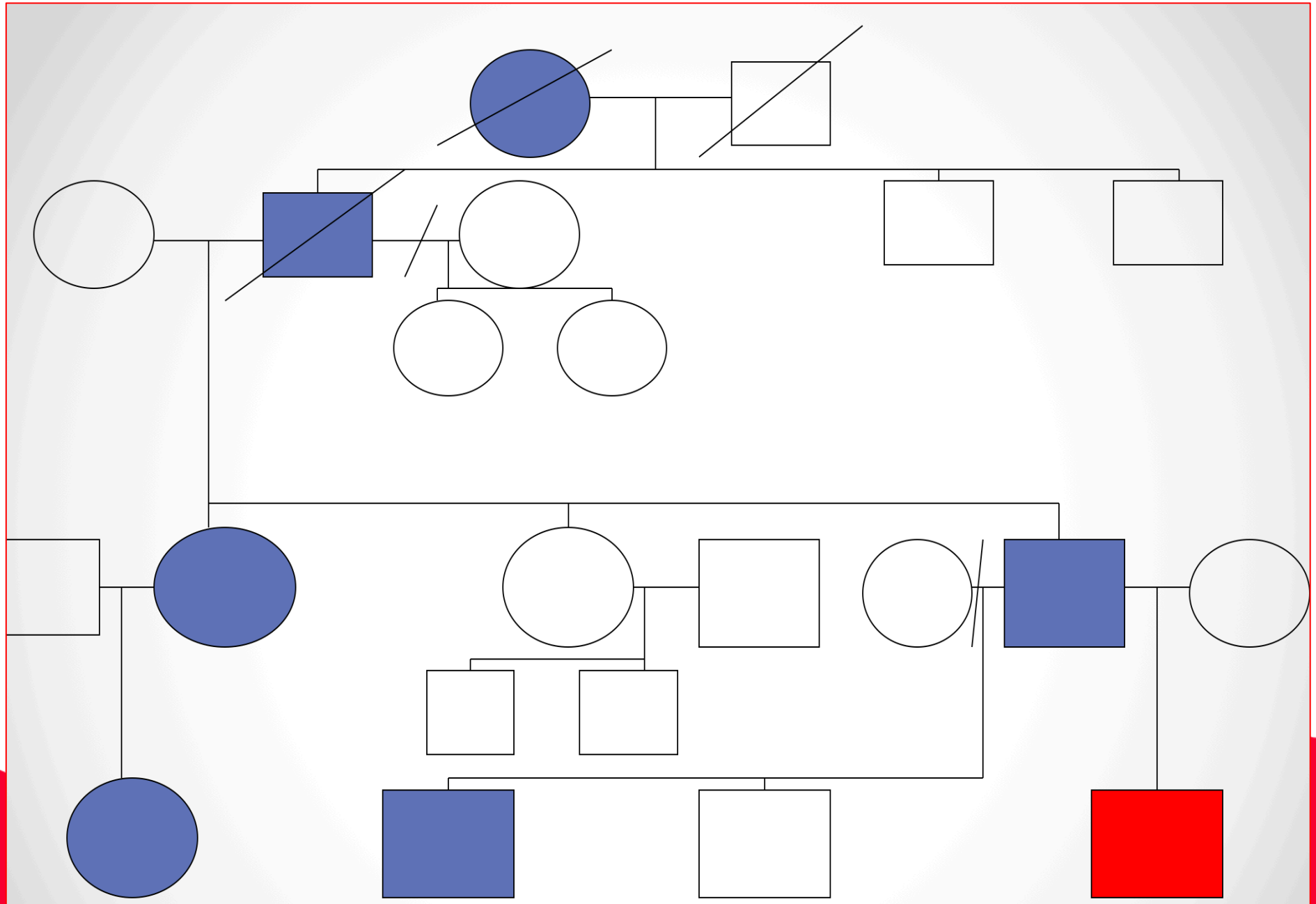
DOB 10.11.01

Family history of VHL

Positive for the familial mutation in exon 3 of the VHL gene

Commenced screening programme

- 2006 age 5yrs



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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

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MRI Abdomen 12.10.12

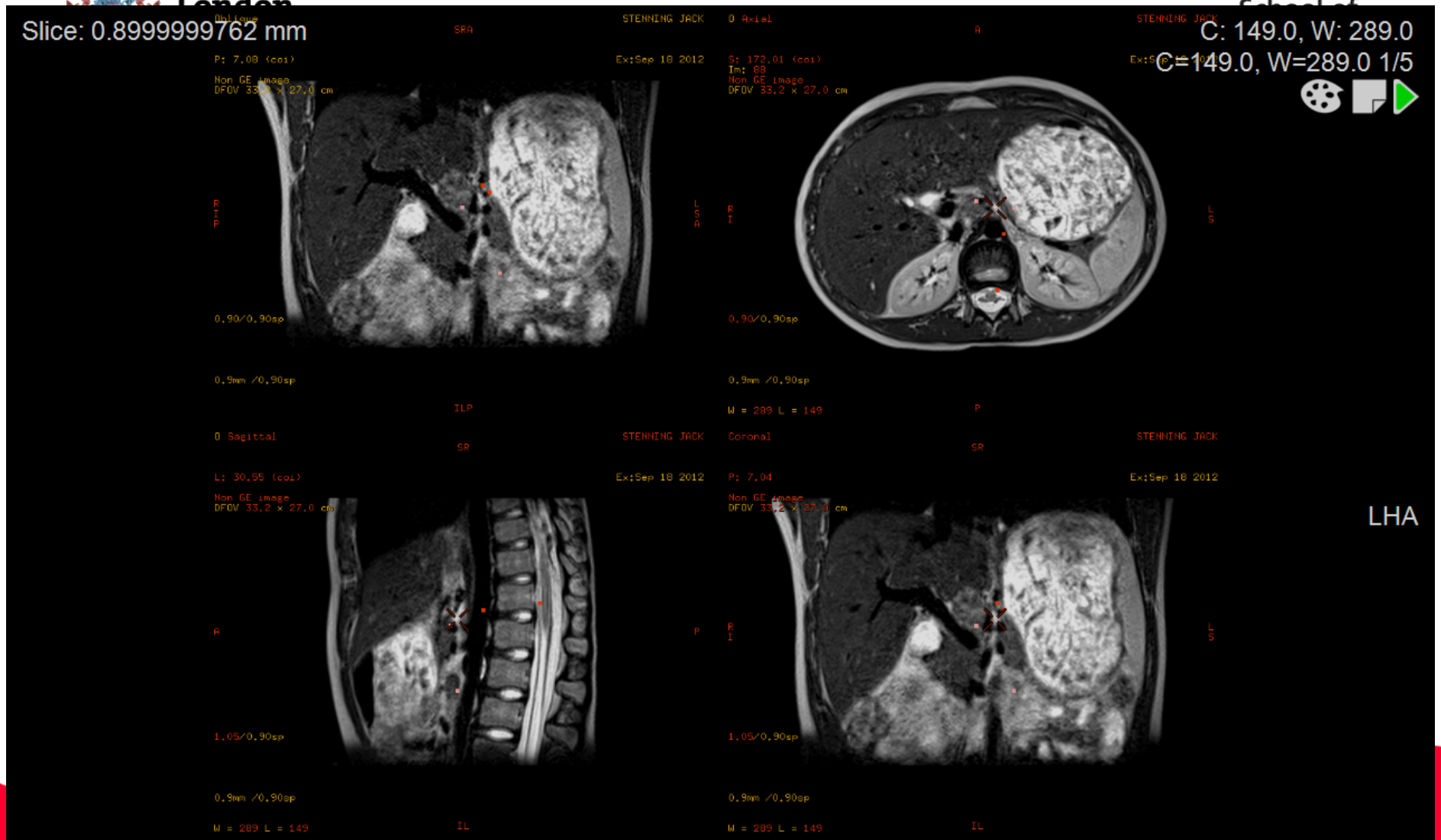
Review of imaging for endocrine VHL MDT 31.10.2012

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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C=149.0, W=289.0 1/5
LHA
Pos: FFS
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3D Saved State - AutoSave
18/09/2012, 14:32:39
FLP
4

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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

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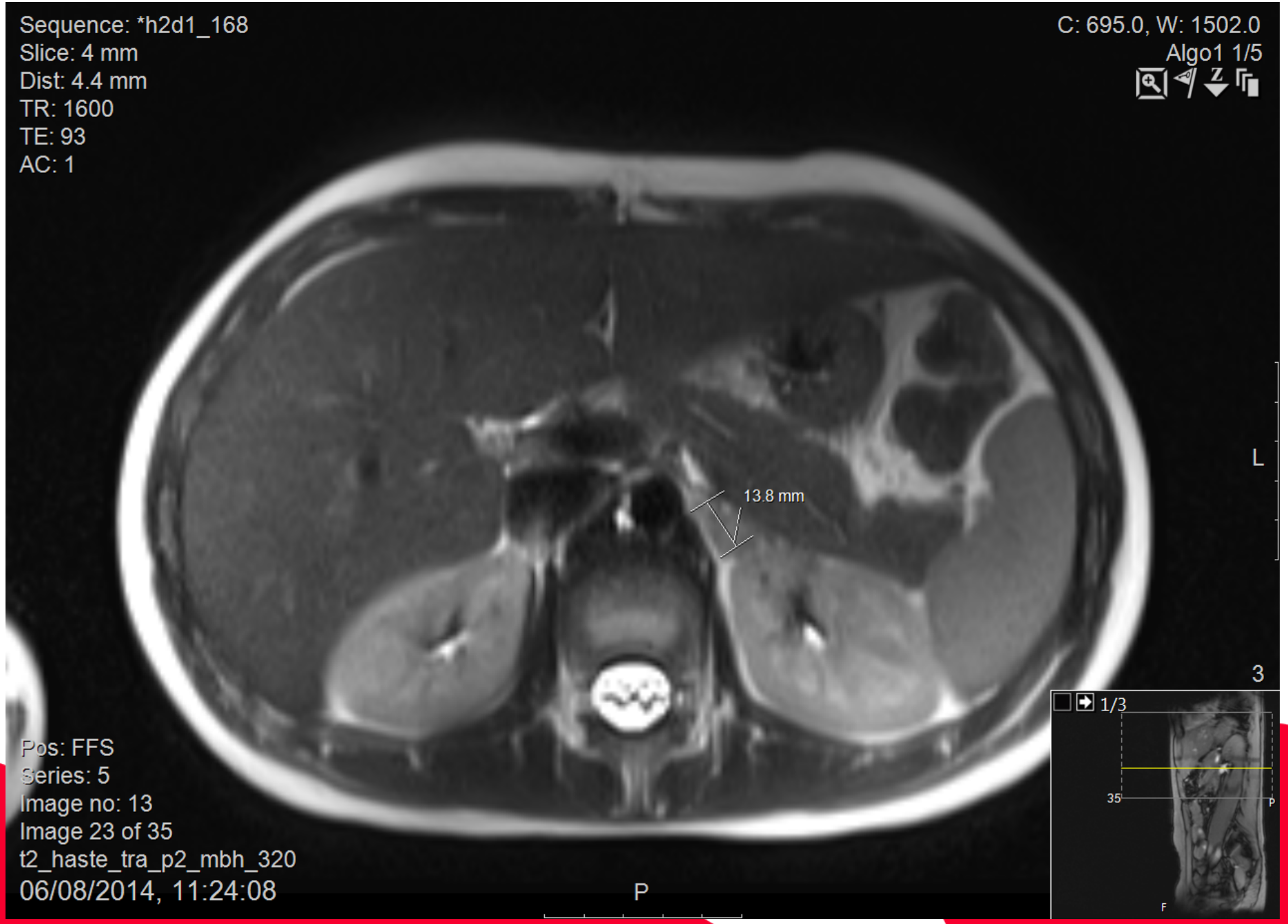
MRI Abdomen 6.8.14

New 9mm peripherally enhancing left adrenal nodule which demonstrates restricted diffusion likely to represent a small phaechromocytoma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C: 695.0, W: 1502.0
Algo1 1/5
13.8 mm
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1/3
35
P
F
Pos: FFS
Series: 5
Image no: 13
Image 23 of 35
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P

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..

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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


Sequence: *fl3d1
Slice: 2.5 mm
TR: 3.94
TE: 1.4
AC: 1
C: 508.0, W: 1064.0
Algo1 1/5
Contrast: Dotarem
8.1 mm
L
10
Pos: FFS
Series: 10
Image no: 29
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23/02/2015, 12:48:04
P
1
L
64
F

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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


Sequence: *fl3d1
Slice: 2.5 mm
TR: 4.09
TE: 1.45
AC: 1
C: 540.0, W: 1088.0
Algo1 1/5
Sync group: 5
Contrast: DOTAREM
L
9
14.3 mm
Pos: FFS
Series: 9
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Image 34 of 72
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P
72
L
F


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TE: 1.45
AC: 1
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Algo1 1/5
Sync group: 5
Contrast: DOTAREM
L
9
14.2 mm
Pos: FFS
Series: 9
Image no: 41
Image 41 of 72
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14/07/2015, 12:03:22
P
72
F

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

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London Ambulance Service NHS Trust

Patient Specific Protocol

PSP Paediatric Steroid Dependent Crisis

This protocol has been specifically prepared for STEROID DEPENDENT CRISIS patients and details the

Instructions for Hospital Doctor

Dear Doctor,

If this patient is brought to hospital as an emergency the following management is advised:

1) Insert an IV cannula
2) Take blood for U&Es, glucose, and perform any other appropriate tests (e.g. urine culture)
3) Check capillary blood glucose level
4) Give 100 mg hydrocortisone intravenously as bolus (unnecessary if patient has already been given IM hydrocortisone)
5) Commence IV infusion of 0.45% sodium chloride and 5% glucose at maintenance rate (extra if patient is dehydrated). Add potassium depending on electrolyte
6) Commence hydrocortisone infusion (50 mg hydrocortisone in 50ml 0.9% sodium chloride via syringe pump)
7) Monitor for at least twelve hours before discharge

IMPORTANT! If blood glucose is < 2.5 mmol/l, give bolus of 2 ml/kg of 10% glucose

If patient is drowsy, hypotensive and peripherally shut down with poor capillary return give 20ml/kg of 0.9% sodium chloride stat.

If in any doubt about this patient's management, please contact the urgent advice numbers

3. Draw up 2mls of

4. Mix the crushed

5. Then draw up 1m

6. Give by mouth as

●●●○○ O2-UK 22:02 100%

Great Ormond Street NHS Hospital for Children

NHS Foundation Trust

My Cortisol

FICENCY

CARD IS ON

ENT THERAPY

Affix photo here

Great Ormond Street NHS Hospital for Children

NHS Trust

Great Ormond Street
London WC1N 3JH

Tel: 020 7405 9200

Gastroenterology, Endocrinology, Metabolic & Adolescent Medicine (GEMA)

Direct Line: 0207-813-8214

Date:
Reference:

Dr
Paediatric Consultant

Dear Dr

RE:

……..is a …. year old ……under the care of …… at Great Ormond Street Hospital. He is a boy/girl with ……, he/she was referred with ……and we have since found he also has cortisol deficiency.

He/She has been commenced on Hydrocortisone at a dose of 2.5mg mane, 2.5mg at lunchtime, and 2.5mg nocte. ……'s mum has had education in his/her management during times of illness and has been trained in giving IM hydrocortisone should the need arise.

I would be extremely grateful if you could arrange for …… to have fast track access at the …… should he/she require emergency IM hydrocortisone. Please let us know on the number below.

Please do not hesitate to contact me should you require more information on 0207 813 8214.

Many thanks,

Yours sincerely

……
Clinical Nurse Specialist

Hospital for Children NHS Trust
ndon Hospitals NHS Trust

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

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PE follow up imminent…

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How should MEN / VHL be managed?

Screening important
Medical and surgical management
Nursing input
Liaison with adult endocrine teams
Patient support groups

Novel Insights from Clinical Experience

HORMONE RESEARCH

Horm Res 2006;66:1–5
DOI: 10.1159/000093008

Received: November 28, 2005
Accepted: March 8, 2006
Published online: April 27, 2006

Benefits of Screening in von Hippel-Lindau Disease – Comparison of Morbidity Associated with Initial Tumours in Affected Parents and Children

M. Priesemann K.M. Davies L.A. Perry W.M. Drake S.L. Chew
J.P. Monson M.O. Savage L.B. Johnston

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

VHL	Eyes	Fundoscopy	Fluorescein angiography	5 yrs	Annual
	CNS	Full examination		10 yrs	Annual
			MRI brain & spinal cord	10 yrs	3 yearly
	Renal	Abdonimal examination	US kidneys	5 yrs	Annual
			MRI kidneys	5 yrs	3 yearly
	Adrenal (*phaeochromocytoma*)	Blood pressure 24-hour urine collections (x3) – catecholamines (*plus corresponding serum metanephrines*)	US adrenal	5 yrs	Annual
			MRI adrenals	5 yrs	3 yearly

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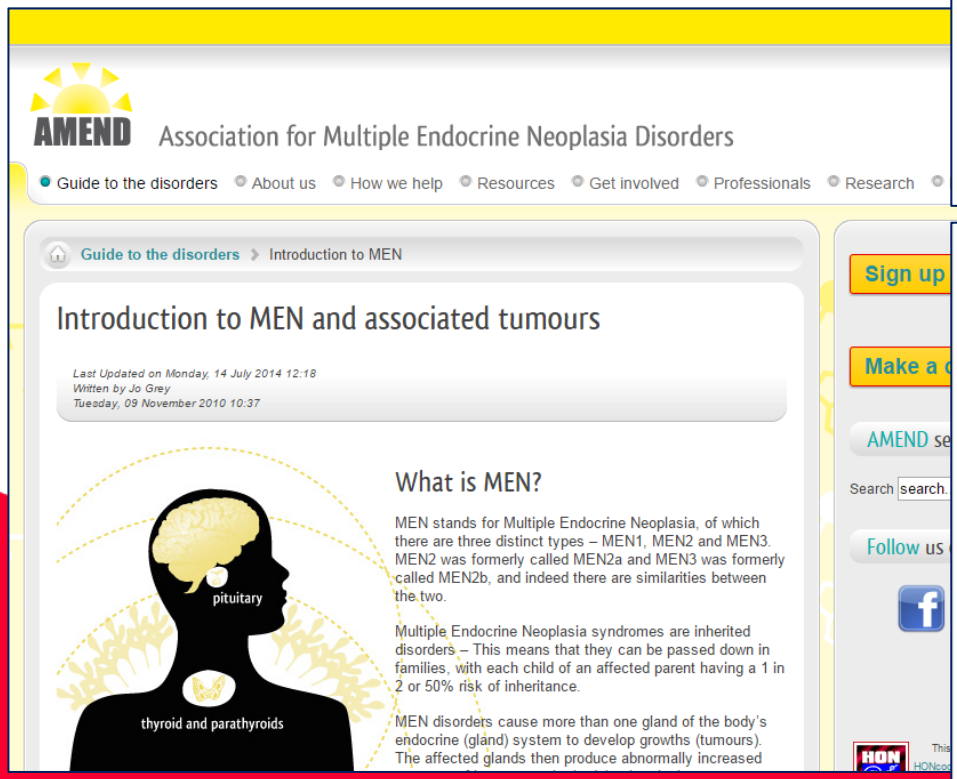
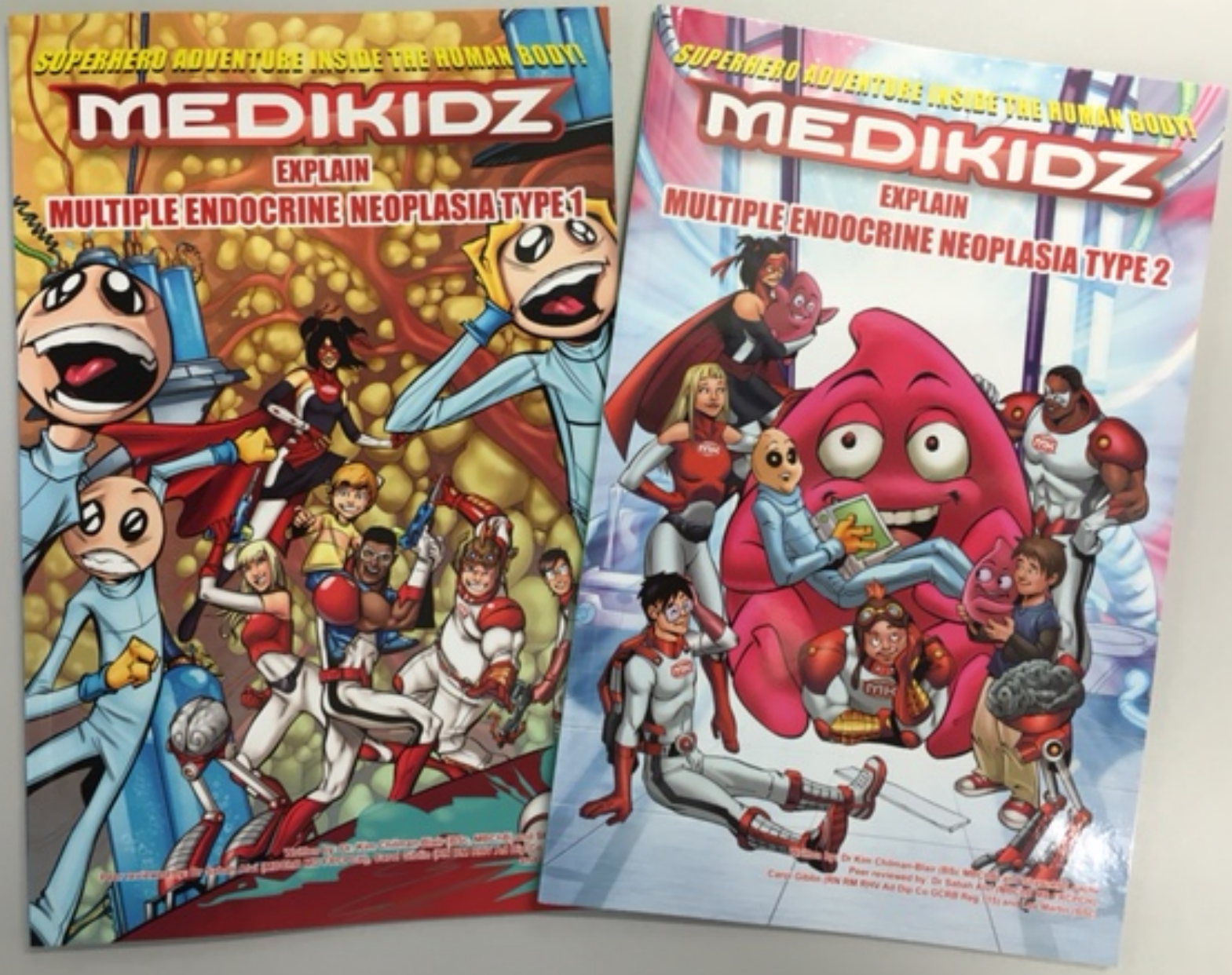
Patient support

AMEND

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




SUPERHERO ADVENTURE INSIDE THE HUMAN BODY!
MEDIKIDZ
EXPLAIN
MULTIPLE ENDOCRINE NEOPLASIA TYPE 1
SUPERHERO ADVENTURE INSIDE THE HUMAN BODY!
MEDIKIDZ
EXPLAIN
MULTIPLE ENDOCRINE NEOPLASIA TYPE 2

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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

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AMEND website (accessed August 2017)