An unusual cause of being able to play basketball well: Diagnosis and management dilemmas

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Western Health, Melbourne
Disclosures

• Previous conference registration grants
  – Novo Nordisk Pharmaceuticals
  – Merck Sharp & Dohme (Australia)
Consent

• Consent obtained from patient
  – Case presentation
  – Displaying images
Presentation

• 26 year old man
• Referred in 2010 by LMO for evaluation of extreme tall stature
Past History

• Deranged liver function tests
  – Neonatal jaundice (conjugated hyperbilirubinaemia)
  – Ultrasound – hepatomegaly, increased periportal echogenicity
  – Liver biopsy (aged 2 yrs) – moderate fatty change
  – F/u paediatrician until age 16

• Fractures
  – Ribs - football practice (aged 16)
  – Scaphoid - fall (aged 21)

• Mild sleep apnoea (aged 18)

• No regular medications
Family History

- Nil significant

Mid parental height
172.5cm +/- 9cm
Development

• Short as a child
• Puberty – 12-13yrs
• Growth spurt – 14-15yrs
• Normal development milestones
• Jaw clicking – 16yrs

• Continued to change
  • Especially face
  • Shoe size 11 → 13 in last 5 years
• Hyperhidrosis
Social History
(at presentation)

- Played a variety of contact sports
  - Trialling for Melbourne Tigers basketball team
- Working full time
- Pursuing tertiary education
- 5-10 cigarettes/day
Examination

• Ht 199 cm, Wt 92 kg
• BMI 23.2 kg/m$^2$
• Asymmetric face
  – Prominent right cheek
  – Protruding right forehead
  – Mild right proptosis
• Prominent jaw
• Pigmentation right chest and lower neck
Examination

- Enlarged hands and feet
- Normally virilised
  - Testicular size 15-20ml
- No organomegaly, skin tags
- No joint swelling, bowing of long bones
- Normal thyroid, cardio-respiratory and neurology examination
# Investigations

## March 2010

<table>
<thead>
<tr>
<th>Blood</th>
<th>Level</th>
<th>Reference Range</th>
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</thead>
<tbody>
<tr>
<td>FBE</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>UEC</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td>2.23</td>
<td>2.15-2.55 mmol/L</td>
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<tr>
<td>Phosphate</td>
<td>1.19</td>
<td>0.8-1.5 mmol/L</td>
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<tr>
<td>Bilirubin</td>
<td>5</td>
<td>4-20 μmol/L</td>
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<tr>
<td>Albumin</td>
<td>43</td>
<td>38-50 g/L</td>
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<tr>
<td>ALP</td>
<td>206</td>
<td>30-120 U/L</td>
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<tr>
<td>GGT</td>
<td>80</td>
<td>5-50 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>19</td>
<td>5-40 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>20</td>
<td>10-40 U/L</td>
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</tbody>
</table>
# Investigations

### March 2010

<table>
<thead>
<tr>
<th>Pituitary Hormones</th>
<th>Level</th>
<th>Reference Range</th>
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<tbody>
<tr>
<td>IGF-1</td>
<td>118</td>
<td>15-64 nmol/L</td>
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<tr>
<td>GH</td>
<td>68.4</td>
<td>&lt; 10 mIU/L</td>
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<tr>
<td>ACTH</td>
<td>14.6</td>
<td>2.0-11.4 pmol/L</td>
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<tr>
<td>Cortisol (AM)</td>
<td>447</td>
<td>138-690 nmol/L</td>
</tr>
<tr>
<td>Prolactin</td>
<td>3619</td>
<td>0-500 mIU/L</td>
</tr>
<tr>
<td>LH</td>
<td>4.3</td>
<td>1.5-8.0 IU/L</td>
</tr>
<tr>
<td>FSH</td>
<td>2.9</td>
<td>1.3-8.4 IU/L</td>
</tr>
<tr>
<td>Testosterone</td>
<td>6.5</td>
<td>12.0-31.9 nmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>0.49</td>
<td>0.10 -4.00 mIU/L</td>
</tr>
<tr>
<td>T4</td>
<td>14.1</td>
<td>9.0-26.0 pmol/L</td>
</tr>
</tbody>
</table>
Investigations

- GH suppression test (75g glucose)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>60 sec</th>
<th>120 sec</th>
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</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.6</td>
<td>6.4</td>
<td>4.5</td>
</tr>
<tr>
<td>GH (mU/L)</td>
<td>71.1</td>
<td>76.5</td>
<td>59.4</td>
</tr>
</tbody>
</table>

- 24hr urinary free cortisol – 428 nmol (100-379)
- 1mg Dexamethasone suppression test – cortisol 29nmol/L
- Testicular ultrasound – right testis microlithiasis with 8mm hyperechoic lesion; left normal
MRI Pituitary
CT Head
Diagnosis
Diagnosis

• McCune-Albright Syndrome (MAS)

*Endocrine issues*
- GH excess – gigantism and acromegaly
- Hyperprolactinaemia
- Hypogonadotrophic hypogonadism

*Bone issues*
- Fibrous dysplasia – disfiguring facial deformities
McCune-Albright Syndrome

• Rare
  – Estimated prevalence 1/100,000 – 1/1,000,000

• Classical triad
  – Fibrous dysplasia
  – Cafe au lait pigmentation
  – Precocious puberty

Dumitrescu et al., Orphanet Journal of Rare Disease, 2008
McCune-Albright Syndrome

• Rare
  – Estimated prevalence 1/100,000 – 1/1,000,000

• Classical triad
  – Fibrous dysplasia
  – Cafe au lait pigmentation
  – Endocrinopathies

Dumitrescu et al., Orphanet Journal of Rare Disease, 2008
Pathogenesis

• Mutation in GNAS1 gene
  – 20q13.2-13.3
  – Substitution Arg$^{201}$
  – Activating mutation

• Alpha subunit of G-protein
  – Stimulates intracellular cAMP production

• Constitutive activation of pathway

Lumbroso et al., J ClinEndocrinol And Meta, 2004
Wilson LC, Trembath RC, J Med Genet 1994
Weinstein et al., J Bone Miner Res, 2007
Genetics

• Sporadic disease

• Post-zygotic mutation
  – Non-inherited

• Clinical presentation depends on which cells carry the mutation
  – Heterogeneous phenotype

Dumitrescu et al., Orphanet Journal of Rare Disease, 2008
Clinical Presentation

Other possible associations: pancreatitis, neuropsychiatric, testicular masses/microlithiasis, malignancy

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Patients (n = 158)</th>
<th>Male (n = 53)</th>
<th>Female (n = 105)</th>
<th>Age at Diagnosis (yr) (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrous dysplasia</td>
<td>154</td>
<td>51</td>
<td>103</td>
<td>7.7 (0–52)</td>
</tr>
<tr>
<td>Café au lait lesions</td>
<td>135</td>
<td>49</td>
<td>86</td>
<td>7.7 (0–52)</td>
</tr>
<tr>
<td>Precocious puberty</td>
<td>82</td>
<td>8</td>
<td>74</td>
<td>4.9 (0.3–9)</td>
</tr>
<tr>
<td>Acromegaly/gigantism</td>
<td>42</td>
<td>20</td>
<td>22</td>
<td>14.8 (0.2–42)</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>23</td>
<td>9</td>
<td>14</td>
<td>16.0 (0.2–42)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>30</td>
<td>7</td>
<td>23</td>
<td>14.4 (0.5–37)</td>
</tr>
<tr>
<td>Hypercortisolism</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>4.4 (0.2–17)</td>
</tr>
<tr>
<td>Myxomas</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td>34 (17–50)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>36 (34–37)</td>
</tr>
<tr>
<td>Rickets/osteomalacia</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>27.3 (8–52)</td>
</tr>
<tr>
<td>Cardiac abnormalities</td>
<td>17</td>
<td>8</td>
<td>9</td>
<td>(0.1–66)</td>
</tr>
<tr>
<td>Hepatic abnormalities</td>
<td>16</td>
<td>6</td>
<td>10</td>
<td>1.9 (0.3–4)</td>
</tr>
</tbody>
</table>

Ringel et al., Medicine, 1996
Collins et al., Orphanet Journal of Rare Disease, 2012
Cafe Au Lait

- 60-89%

- Large with jagged borders
  - Coast of Maine

- Follow Blaschko’s lines

- “Respects” the midline

Dumitrescu et al., Orphanet Journal of Rare Disease, 2008
Coastofmaine.net
Fibrous Dysplasia

- Almost all (~99%)
- Monostotic or polyostotic
- Can affect any bone
- Clinically significant disease appears 5-15 yrs
- Prone to fractures
  - Exacerbated by phosphate wasting
- Pain, nerve compression, deformity
- Highly vascular
- Risk of sarcomatous transformation
  - Rare, ~ 1%
  - Radiation and GH excess can increase the risk

Dumitrescu et al., Orphanet Journal of Rare Disease, 2008
Ruggieri et al., Cancer, 1994
http://www.kjim.org/journal/view.php?number=15960
Treatment – Fibrous Dysplasia

- Surgery in severe deformity or nerve compression
  - Craniofacial disease: recommended to have annual hearing and vision tests

- Bisphosphonate therapy may reduce pain and fracture risk
  - Does not alter disease process itself

Dumitrescu et al., Orphanet Journal of Rare Disease, 2008
Chapurlat et al., J Bone Miner Res, 2006
Kelly et al., Osteoporos Int, 2007
Gigantism/Acromegaly

- Present in 20%
- Due to diffuse hyperplasia
- Almost all associated with skull base fibrous dysplasia
- Can worsen fibrous dysplasia and complications
  - Hearing loss or blindness: GH excess (33%) versus without (4%)
- Treatment difficult
  - Surgery – fibrous dysplasia skull base thickening + vascular
  - Radiotherapy – risk of sarcomatous transformation
- Mainstay of treatment medical
  - Somatostatin analogues and/or dopamine agonists

Collins et al., Orphanet Journal of Rare Disease, 2012
Akintoye et al., Journal of Clinical Endocrinology & Metabolism, 2006
Salenave et al., Journal of Clinical Endocrinology & Metabolism, 2014
Back To The Patient...
Management Issues

- **Hyperprolactinaemia**
  - *Cabergoline 0.5mg x2/week* → *Quinagolide 75 μg/daily*

- **GH Excess**
  - *Lanreotide 60mg monthly*

- **Hypogonadotrophic hypogonadism**
  - *Improved with treatment of hyperprolactinaemia*

- **Fibrous dysplasia**
  - *Initially asymptomatic, no treatment*
  - *Developed facial pain* → *Pamidronate 60mg*
Progress

Lanreotide 60mg/m
Cabergoline 1mg/w

Lanreotide 120mg/m

Lanreotide 90mg/m

Lanreotide 120mg/m
Quinagolide 75μg/d
Back To The Literature...
Pegvisomant

- Growth hormone receptor antagonist
- Effective in biochemical and clinical improvement
- Established in treatment guidelines for Acromegaly
  - Approved in USA since 2003
- Limitations
  - Cost, injection, potential pituitary tumour growth, liver function abnormality

Dumitrescu et al., Orphanet Journal of Rare Disease, 2008
Clemmons et al., Journal of Clinical Endocrinology & Metabolism, 2003
Neggers et al., Nature Reviews Endocrinology, 2009
Pegvisomant – MAS (1)

McCune-Albright Syndrome and Acromegaly: Effects of Hypothalamopituitary Radiotherapy and/or Pegvisomant in Somatostatin Analog-Resistant Patients

Françoise Galland, Peter Kamenicky, Hélène Affres, Yves Reznik, Dominique Pontvert, Yves Le Bouc, Jacques Young, and Philippe Chanson

• Retrospective analysis
• 6 patients
  – 5 patients: fractionated Radiotherapy (RT) (45-55 Gray)
  – 3 patients: pegvisomant (2 with previous RT), 10-20mg/d
• Measures: GH/IGF1, clinical features

Galland et al., Journal of Clinical Endocrinology & Metabolism, 2006
Results

• All 3 pegvisomant
  – Normalised IGF-1
  – No increase in size of pituitary
  – Symptom & glucose tolerance improved

• After RT
  – Reduction IGF-1, none normalised
  – Symptom & glucose tolerance improved
  – Sarcomatous transformation seen in 1 patient, outside radiation field

Galland et al., Journal of Clinical Endocrinology & Metabolism, 2006

![Graph of GH and IGF-1 SDS levels](image)
Pegvisomant – MAS (2)

Pegvisomant for the Treatment of gsp-Mediated Growth Hormone Excess in Patients with McCune-Albright Syndrome

Sunday O. Akintoye, Marilyn H. Kelly, Beth Brillante, Natasha Cherman, Sarah Turner, John A. Butman, Pamela G. Robey, and Michael T. Collins

• Double-bind, placebo-controlled, crossover
• 5 patients
• 20mg/d, 12 weeks
• Primary measure: normalisation IGF-1

Akintoye et al., Journal of Clinical Endocrinology & Metabolism, 2006
Results

• 4/5 patients normalised IGF-1
  • Average 63% reduction in IGF-1
• No significant difference in symptoms
• As a group, no change in pituitary volume
  – 1 patient pituitary enlarged (~0.7 mL to 2.2 mL)

Akintoye et al., Journal of Clinical Endocrinology & Metabolism, 2006
Pegvisomant – MAS (3)

All cases MAS with GH excess (112 patients)

Treatment success
- Surgery - 3/22 patients
- Radiotherapy - 4/29 patients
- SA +/- DA - 18/56 patients
  - Macroadenoma - 3/21 patients
- Pegvisomant - 10/13 patients
  - 2 non-compliant

Salenave et al., Journal of Clinical Endocrinology & Metabolism, 2014
Back To The Patient...
Progress

Pegvisomant 10mg/d
Progress

• Most recent update (6/8/14)
  – IGF-1 36 nmol/L (12-30), Prolactin 1290 mIU/L (45-375)
  – Facial pain improved
    • Intermittent tinnitus right ear
    • No change on repeat MRI

• Annual hearing testing – Mild conductive loss on right
• Annual visual field testing – Normal
• Repeat testicular US – no change
  – Urology follow up
• Significant disruption to his life
  – Depression/anxiety
    • Sertraline 50mg and psychology
  – Not working or studying
Take Home Messages

• McCune-Albright syndrome should be considered in cases of tall stature, especially in the presence of bony deformities or skin pigmentation

• Gigantism/Acromegaly can be difficult to treat
  – Medical management may be the only practical option
  – Pegvisomant is an important consideration as third line therapy

• Fibrous dysplasia can be difficult to manage
  – Bisphosphonates may reduce pain and fracture risk, but do not appear to influence deformity
References

Acknowledgements

- Prof Peter Ebeling
- A/Prof Shane Hamblin
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- Dr Priya Sumithran
- Dr Sarah Catford
- Dr Azni Wahab
- Medical Imaging Department, Western Health
- Pfizer – for subsidising the cost of pegvisomant on compassionate grounds