A Case of Glucose Tolerance

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Mrs AZ

57 year old female
Married, 3 children
Book-keeper for family business
Early Childhood

- Born in Croatia, 1957
- Non-consanguineous parents
- Normal developmental milestones
- Umbilical hernia Age 6
Adolescence

- Completed Year 10
- Average grades
- Hearing impairment
- Recurrent otitis media
Obstetric history

• 1974, Daughter
  – Bilateral carpal tunnel syndrome
    • CTR surgery Aged 19

• 1976, son
  – Pre-eclampsia
Obstetric history

• 1986, Daughter
  – IOL, forceps assisted
  – Worsening carpal tunnel syndrome
  – Multiple failed epidural insertion

• Early post partum tubal ligation
  – Failed intubation
1986, Acromegaly

Referred to private endocrinologist for evaluation of acromegalic features

- Coarse facial features
- Broad hands and feet
- Enlarging head circumference
- Arthralgias
# Investigations

<table>
<thead>
<tr>
<th>Time</th>
<th>Glucose (mmol/l)</th>
<th>GH (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>4.4</td>
<td>29</td>
</tr>
<tr>
<td>0</td>
<td>Glucose 75g</td>
<td></td>
</tr>
<tr>
<td>+60</td>
<td>6.4</td>
<td>2.3</td>
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<tr>
<td>+120</td>
<td>5.6</td>
<td>0.6</td>
</tr>
<tr>
<td>+150</td>
<td>5.5</td>
<td>&lt;0.6</td>
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</table>

**CT pituitary**
- No evidence of pituitary adenoma
- Partially empty pituitary fossa

IGF 1 and MRI were not available

*Normal Basal GH < 5ng/ml*
Referred for neurosurgical opinion

“…. Marked acromegalic features slowly oncoming for ten years or so...”

[15 October 1986]

“..... After a good deal of thought and a couple of sessions of discussion with Mrs AZ it seems reasonable to me that we proceed along a surgical line and she accepts this.”

[20 October 1986]
Transsphenoidal exploration

• 29/12/1986
  – Rt sided 4mm lesion presumed to be adenoma
  – “torrential venous haemorrhage”; “poor visibility”
  – Subtotal excision
  ➔ Histopathology: no definite tumour

• 5/1/1987
  – No definite adenoma visible
  ➔ Histopathology: no definite tumour
## Post-operative

<table>
<thead>
<tr>
<th>Time</th>
<th>Glucose (mmol/l)</th>
<th>GH (ng/ml)</th>
<th>FT4</th>
<th>TSH</th>
<th>Prolactin</th>
<th>FSH</th>
<th>LH</th>
<th>Cortisol</th>
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<tbody>
<tr>
<td>-20</td>
<td>4.5</td>
<td>5.5</td>
<td>18</td>
<td>0.45</td>
<td>5</td>
<td>5.7</td>
<td>6.8</td>
<td>450</td>
</tr>
<tr>
<td>0</td>
<td>Glucose 75g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+60</td>
<td>5.0</td>
<td>0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+120</td>
<td>4.4</td>
<td>&lt;0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2004, Aged 47

• Re-referred with reduced peripheral vision
  – ?Acromegaly recurrence

• Clinical exam
  – Acromegalic facial features
  – Thickened skin
  – Splaying of teeth
  – Macroglossia
  – Hypertension
  – *Clawed hands*
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<th>Glucose (mmol/l)</th>
<th>GH (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-5</td>
<td>4.6</td>
<td>9.8</td>
</tr>
<tr>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>+60</td>
<td>5.9</td>
<td>1.2</td>
</tr>
<tr>
<td>+120</td>
<td>5.5</td>
<td>0.6</td>
</tr>
</tbody>
</table>

**IGF-1** 9 (11-31mIU/L)
Progressive symptoms

1. Vision
   - Sun glare
   - Reduced night vision
   - Tunnel vision
2. Contractures
3. Nerve entrapment syndromes

– Persistent carpal tunnel syndrome

– Ulnar neuropathy
  • Decompression 2008

– Cervical central canal stenosis, moderate – severe
  • C3/C4 discectomy and fusion 2007

– Advanced and extensive multilevel lumbar canal stenosis and foraminal narrowing
4. Progressive hearing loss
   – Mixed conductive and sensorineural
5. Obstructive sleep apnoea (moderate)
6. Valvular heart disease
   – Aortic valve sclerosis
   – Mitral annular calcification
7. Hepatomegaly
8. Functional disability
Diagnostic dilemma

- Acromegalic facial features
- Enlarged hands and feet
- Recurrent carpal tunnel syndrome
- Hypertension
- OSA
- Hepatomegaly

- Contractures
- Clawing hands and feet
- Ophthalmic disease
- No evidence of GH excess
- No pituitary adenoma
- No metabolic complications including diabetes mellitus and dyslipidaemia

Multiple specialty unit involvement

- Endocrinology, Rheumatology, Neurology, Orthopaedic Surgeons, Ophthalmology, Cardiology, Respiratory, Neurosurgeons
Where to go from here?
Pseudo-acromegaly

Heterogenous group of disorders with acromegaloïd appearance in the absence of elevated GH or IGF-1 levels.
Pseudo-acromegaly

- Pachydermoperiostosis
- Acromegaloid facial appearance
- Insulin-mediated acromegaloidism
- Mixonidil induced pseudoacromegaly
- Chromosome 11 pericentric inversion
- X tetrasomy
- Berardinelli-Siep Congenital Lipodystrophy
- Multiple Haemartoma Syndrome
1) Pachydermoperiostosis

- Primary hypertrophic osteoarthropathy
- Elevated PGE2 levels
  - HGPD, SLCO2A1 gene mutations

Liu et al. NEJM 2014
Rastogi et al. Indian J Radiol Imaging 2009
2) Acromegaloid Facial Appearance

3) Insulin mediated Pseudo-acromegaly

Flier et al. JCEM 1993
Diagram 1. Diagram showing post-receptor defect first proposed by Karim Dib et al. with preservation of Insulin receptor and IGF-1. The signal mediated by PI 3-kinase is disrupted, a signal generated by the compensatory hyperinsulinemia is diverted toward the mitogenic pathway, potentiating the effects of insulin and other growth factors. (Taken from Diabetes Mellitus: A Fundamental and clinical text 3rd edition)
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Mrs AZ
Mrs AZ

- GH
- IGF-1
- Collagen synthesis
- Collagen Degradation

"GH/IGF-I excess"

- local IGF-I production
- proteoglycan synthesis
- glycosaminoglycan synthesis
- cell replication
Confirmation of diagnosis, 2011

1) Urine mucopolysaccharide screen
   • Total glycosaminoglycans (GAG) = 22.9mg/mmol (<15.4)
   • Dermatan sulphate elevated

2) Enzyme analysis
   • Alpha- L- Iduronidase activity = 7pmol/min/mg (15-134)

3) Genetic testing (IDUA gene)
   • Compound heterozygous mutation
     – p.Q70X mutation; 12 nucleotide duplication in exon 7

Mucopolysaccharidosis Type 1
Mucopolysaccharidosis

- Lysosomal Storage Disorder
- Glycosaminoglycans (GAGs) are degraded by specific enzymes within lysosomes
- Deficiency of a specific lysosomal enzyme resulting in accumulation of GAGs within lysosomes
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Deficient Enzyme</th>
<th>Genetic Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPS I</td>
<td>Alpha L Iduronidase</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>MPS II</td>
<td>Iduronase 2 sulphatase</td>
<td>X-Linked recessive</td>
</tr>
<tr>
<td>MPS IV</td>
<td>Galactose 6 sulphatase</td>
<td>Autosomal Recessive</td>
</tr>
<tr>
<td>MPS VI</td>
<td>Arylsulphatase B</td>
<td>Autosomal Recessive</td>
</tr>
</tbody>
</table>
MPS 1 (Hurler Scheie Syndrome)

- Mutation in IDUA gene resulting in Alpha-L-Iduronidase deficiency
  - Accumulation of GAGs: dermatan sulfate, heparan sulfate

- First described by Hurler in 1919
  - Milder phenotype was later identified by Scheie in 1962

- Chronic, progressive, life-threatening disease

- Incidence of MPS 1 = 1 in 111,000 live births per year
  - Total MPS incidence = 1 in 22,500 per year
  - Acromegaly incidence = 1 in 250,000 per year

Muenzer et al. Rheumatology 2011
Meikle et al. JAMA 1999
Moore et al. Orphanet J Rare Diseases 2008
Facial dysmorphisms

Clarke et al. GeneReviews 2011
Dysostosis Multiplex
Musculoskeletal

Cimaz et al. Paed Rheumatology 2009
Lampe et al. Rheu Dis Clin N Am 2013
High risk of spinal cord compression

- Atlanto-axial instability
- Thickened dura and hypertrophy of ligamentum flavum
- Multilevel cervical or lumbar foraminal stenosis

→ Caution when undergoing anaesthesia
→ Avoid high risk contact activities
1) Corneal clouding
2) Retinal degeneration
3) Optic atrophy
4) Glaucoma

Summers et al. Rheumatology 2011
Other manifestations

- **Respiratory**
  - Upper airway obstruction
  - OSA
  - Restrictive lung disease
  - Tracheomalacia

- **Cardiac**
  - Cardiomyopathy
  - Valvular heart disease
  - CAD

- **Gastrointestinal**
  - Hepatomegaly
  - Splenomegaly
  - Umbilical and inguinal hernias

- **CNS**
  - Hydrocephalus
  - Seizures
  - Behavioural disturbance
  - Progressive mental retardation

- **ENT**
  - Recurrent otitis media
  - Hearing loss
  - Enlargement of pharyngeal soft tissues

*Clarke et al. GeneReviews 2011*
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*Clarke et al. GeneReviews 2011*
Phenotypic variability

- Severe
- 70.7%
- Marked cognitive delay
- Onset <1yo
- Rapidly progressive
- Life expectancy <10yo
- Early death commonly from cardiac failure compounding preceding respiratory complications

Moore et al. Orphanet J Rare Diseases 2008
Giugliani et al. Genetics and Molecular Biology 2010
Phenotypic variability

Hurler-Scheie Syndrome

- Intermediate
- 22.8%
- Mild cognitive defect
- Progressive
- Life expectancy <25yo
- Death from cardiac or respiratory failure

Moore et al. Orphanet J Rare Diseases 2008
Giugliani et al. Genetics and Molecular Biology 2010
Scheie Syndrome

- Attenuated
- 6.6% (detection bias)
- Normal intelligence
- Near normal life expectancy
- Significant morbidity from musculoskeletal, ocular, pulmonary and cardiac defects
Mrs AZ - Progress

Metabolic Disease Unit,
Royal Melbourne Hospital

• Aldurazyme Enzyme replacement therapy as of June 2012

• Improvements
  – Reduced contractures
  – Improvement in hepatomegaly
  – Improvement in OSA
  – Blood pressure
  – Reduce back pain – off analgesics
  – Stabilisation of vision and hearing
Case summary

57 year old female with late diagnosis of Scheie Syndrome (attenuated MPS I) which proved difficult to differentiate from Acromegaly on presentation.
Key Points

• Mucopolysaccharidosis is a lysosomal storage disorder with varying degrees of severity, in which the attenuated form can mimic Acromegaly.

• Mucopolysaccharidosis can be distinguished from Acromegaly by the lack of metabolic complications (diabetes) and the significant burden of musculoskeletal and ophthalmic disease.

• Diagnosis of Mucopolysaccharidosis can allow early administration of disease modifying therapies, and recognition of patients at high anaesthetic risk.
Take home message

DDx Acromegaly = DDx Pseudo-acromegaly

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- Multiple Haemartoma Syndrome
- Mucopolysaccharidosis
Acknowledgements

Professor Gerard de Jong
Dr Sylvia Lim-Tio
Professor Andrew Symons
References

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17. Cimaz et al. Joint contractures in the absence of inflammation may indicate mucopolysaccharidosis. Pediatric Rheumatology 2009, 7:18