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A good response to GH therapy – why?
Overview

• Key Objectives
  – Difficulties surrounding the diagnosis
• What is Growth Hormone Deficiency
• Case Study
• Growth hormone therapy in UK
• Specialist clinics at Great Ormond Street Hospital
• Transition
Growth Hormone Deficiency

- Many reasons why a child may present with short stature
- Most common reason why a child presents with short stature:
  - Constitutional delay of growth and puberty
  - Idiopathic short stature
  - Genetic short stature
- Important reason:
  - Growth hormone deficiency (GHD)
  - 1-4000 children
Short Stature

- Genetic
- Pubertal and growth delay
- SGA
- Dysmorphic syndromes
  - Noonan
  - Prader Willi
  - Turner
  - Laron
- SHOX deficiency
- Growth Hormone Deficiency (GHD)
- Hypothyroidism
- Cushing’s syndrome
- GH Resistance
- Chronic paediatric diseases
- Psychosocial deprivation
Causes of GHD

- Due to the pituitary gland not being able to produce enough GH to facilitate the growth process

**Acquired**
- CNS tumours: 
  - craniopharyngioma
  - germinoma
  - optic glioma
- Histiocytosis
- Cranial irradiation
- Head injury
- Inflammatory/granulomatous diseases
- Total body irradiation

**Transient**
- Psychosocial deprivation
- Prepubertal
- Hypothyroidism

**Genetic**
- GH-1 mutations
- GHRH receptor mutations
- Pit-1, Prop-1 mutations

**Congenital**
- GHRH deficiency
- Structural defects:
  - septo-optic dysplasia
  - agenesis of the corpus callosum
  - single central incisor
  - holoprosencephaly
- Intrauterine infection
## Diagnosis
### Growth Hormone Stimulation Tests

<table>
<thead>
<tr>
<th>Insulin-tolerance test</th>
<th>Arginine test</th>
<th>Clonidine test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong> 0.05–0.1 units/kg intravenously; lower dose if evidence of panhypopituitarism</td>
<td><strong>Dose</strong> 0.5g/kg intravenously over 30 mins</td>
<td><strong>Dose</strong> 0.15mg/m² orally</td>
</tr>
<tr>
<td><strong>Sampling</strong> GH, cortisol, glucose at 0, 15, 30, 45, 60, 90 mins; monitor blood glucose every 5 minutes</td>
<td><strong>Sampling</strong> GH at 0, 30, 60, 90, 120, 150 mins</td>
<td><strong>Sampling</strong> GH at 0, 30, 60, 90, 120, 150, 180 mins</td>
</tr>
<tr>
<td><strong>Complication</strong> Severe hypoglycaemia, seizures</td>
<td><strong>Complication</strong> Nausea, irritation at iv site</td>
<td><strong>Complication</strong> Potential hypotension</td>
</tr>
<tr>
<td><strong>Requirement</strong> Doctor at bedside throughout test, blood glucose &lt;2.2mmol/L</td>
<td></td>
<td><strong>Requirement</strong> BP monitoring</td>
</tr>
<tr>
<td><strong>Contraindication</strong> Age &lt;5 years, epilepsy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Diagnosis

### Glucagon test

<table>
<thead>
<tr>
<th>Item</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>15μg/kg intramuscularly; maximum dose 1mg</td>
</tr>
<tr>
<td><strong>Sampling</strong></td>
<td>GH, cortisol, glucose at 0, 30, 60, 90, 120, 150, 180 mins</td>
</tr>
<tr>
<td><strong>Complication</strong></td>
<td>Hypoglycaemia, particularly in young children, nausea</td>
</tr>
<tr>
<td><strong>Requirement</strong></td>
<td>Doctor in attendance throughout test</td>
</tr>
<tr>
<td><strong>Contraindication</strong></td>
<td>Epilepsy in young children</td>
</tr>
</tbody>
</table>

- **Glucagon Stimulation Test**
- **Confirmed by a peak GH level below 20mU/L (7 ng/ml)**
  - Short stature
  - Slow growth
  - Delayed bone age
International Consensus

- Growth Hormone testing
  - Glucagon
  - Insulin Tolerance Test
  - Arginine
  - Clonidine
  - Other...
Quick quiz 1

• What is NOT true about growth hormone deficiency?
  
  – A
  • A head injury could cause GHD
  
  – B
  • 15mcg/kg of Glucagon is given IM during a Glucagon stimulation test
  
  – C
  • The GH peak on testing should be above 7ng/ml
  
  – D
  • The incidence is approximately 1- 4000 children
Answer - C

- The peak on GH testing should be BELOW 7ng / ml
  - Department of Health NICE Guidelines
    - International Consensus..?
Case Presentation

Tom is a 5 year old boy presenting with short stature

Presented to hospital when 3
History

- Male
- Born in 2004
- White British
- No consanguinity
- Birth weight: 3.49kg
- Gestation: Term + 6
- Parents height
  - Mother: 168.6cm
  - Father: 178.0cm
Past Medical History

• Tom was diagnosed with a Leptomeningeal low grade glioma in 2008 when he was 3 years old
  – Tumour was in the posterior fossa region
• Growth data during oncology treatment
  – Fell down the centiles
Post Fossa Tumours

- **Cerebellum**
  - Controls the movement of voluntary muscles, balance, posture and in co-ordinating movements

- **Brainstem**
  - Co-ordinates functions such as breathing, BP, HR
  - Contains Reticular Formation
    - responsible for consciousness, drowsiness and attention
Low Grade Glioma

• Benign tumours
  – Brain cells –
    • Astrocytes

• Can arise anywhere in the brain or spinal cord

• Treatment
  – Surgery
  – Radiotherapy – older children
  – Chemotherapy

• Potential late effects
  – Growth, hormonal
  – Behavioural changes
    • Learning problems
    • Difficulties with co-ordination
  – Hearing and visual disturbances
Past medical history

- Family history of breast cancer
  - Mother – BRCA2 positive – screening programme started
- Tom treated with:
  - Surgery
    - VP Shunt
  - Low grade glioma chemotherapy protocol
  - Completed October 2009 when Tom was 5
    - Vincristine
    - Carboplatin
June 2009 – Tom is nearly 5

Hypertension
- Hydralazine
- Nifedipine

Ophthalmology normal

Neurology – under assessment
- Seizures
- Neuropathy

Residual disease still present

‘Growth arrest’ since starting chemotherapy over the last year

No direct endocrine intervention needed currently, but to review growth velocity and any pubertal progress
Subsequent clinic visits

- **October 2009 (5yrs)**
  - Prepubertal

- **April 2010 (5.5yrs)**
  - Has completed chemotherapy
  - Hearing deficit
  - Renal tubal toxicity
  - Physiotherapy and occupational therapy
  - Goes to nursery

- **October 2012 (8yrs)**
  - Borderline 3rd centile on most scores on neurocognitive assessment
  - Challenging behaviour
    - Mum blames on early puberty, but no physical evidence
  - ‘Not growing as well as he should’
  - Referral for Glucagon, TRH and LHRH test
Clinical Investigations

Previous baseline investigations

<table>
<thead>
<tr>
<th>Name of Test</th>
<th>Range</th>
<th>08.10.09</th>
<th>18.11.10</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4 pmol/L</td>
<td>10.8 - 19.0</td>
<td>16.3</td>
<td>13.8</td>
</tr>
<tr>
<td>TSH mU/L</td>
<td>&lt;6</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Prolactin mU/L</td>
<td>59 – 271</td>
<td>109</td>
<td>163</td>
</tr>
<tr>
<td>Cortisol nmol/l</td>
<td></td>
<td>579</td>
<td>425</td>
</tr>
<tr>
<td>LH IU/L</td>
<td>0.7 – 6.5</td>
<td>0.3</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>FSH IU/L</td>
<td>0.1 – 5.8</td>
<td>1.2</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td>Testosterone nmol/L</td>
<td></td>
<td>&lt;0.69</td>
<td>&lt;0.69</td>
</tr>
<tr>
<td>IGF-1ng/ml</td>
<td>52 – 297</td>
<td>47</td>
<td>64</td>
</tr>
<tr>
<td>IGF-BP3mg/L</td>
<td>1.3 – 5.6</td>
<td>1.80</td>
<td>2.66</td>
</tr>
</tbody>
</table>
Pituitary Function tests
February 2013 (8.3yrs)

Glucagon Test: 15mcg/kg (0.43mg) IM

<table>
<thead>
<tr>
<th>T = (Min)</th>
<th>-30</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.7</td>
<td>4.6</td>
<td>6.5</td>
<td>5.7</td>
<td>4.4</td>
<td>4.0</td>
<td>4.1</td>
<td>4.2</td>
</tr>
<tr>
<td>Growth Hormone (μg/L)</td>
<td>0.2</td>
<td>0.4</td>
<td>1.9</td>
<td>0.7</td>
<td>1.6</td>
<td>4.2</td>
<td>1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>268</td>
<td>469</td>
<td></td>
<td></td>
<td>508</td>
<td>659</td>
<td>582</td>
<td></td>
</tr>
</tbody>
</table>
Pituitary Function tests – 8.3yrs

**LHRH test**

<table>
<thead>
<tr>
<th>T=</th>
<th>0</th>
<th>20</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (IU/L)</td>
<td>0.7</td>
<td>6.8</td>
<td>5.5</td>
</tr>
<tr>
<td>FSH (IU/L)</td>
<td>1.7</td>
<td>3.4</td>
<td>3.8</td>
</tr>
</tbody>
</table>

- Pubertal response?

**TRH test**

<table>
<thead>
<tr>
<th>T=</th>
<th>0</th>
<th>20</th>
<th>60</th>
<th>Ref range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4 (pmol/L)</td>
<td>10.2</td>
<td></td>
<td></td>
<td>12-22</td>
</tr>
<tr>
<td>TSH (mU/L)</td>
<td>1.3</td>
<td>12</td>
<td>9.8</td>
<td>&lt;6.0</td>
</tr>
</tbody>
</table>

- Normal response

Pubertal Staging: 1 1 1 02 02
Difficulties surrounding the diagnosis

• Puberty interfering?
• Long follow-up to ascertain GHD
• Continued follow-up in multi clinics
  – Accurate auxology?
  – DNA to any clinics
Treatment

- Decision to start GH
  - February 2013
    - 0.4mg daily s/c
      - 0.025mcg/kg/day

- Zomajet Vision X
  - Ferring

- Needle free device
  - Transjection

- 10 mg, 4 mg vials
- Fridge
- Reconstitution
Response to Treatment – June 2014 – 9.65yrs

- Good response
  - ? Early puberty
    - G2
    - P2
    - A1
    - TV 4
- GnRH analogue commenced Nov 2013
  - Decapeptyl 11.25mg every 10 weeks
- GH dose increased to 0.8mg daily
  - Further follow up at the end of this year
Summary

• Complex child with obvious need for follow up in a neuro-oncology endocrine clinic
• Regular strict follow-up enabled early diagnosis of GHD
• Good prognosis for catch-up growth, along with regression / halting early puberty with GnRH analogue
Growth Hormone Therapy in the UK

- Decision to prescribe GH made by hospital Consultant
- Liaise with GP / homecare companies / local funsing authorities
- Prescribe in line with NICE guidelines
- Patient choice of GH device
  - 12 devices
- 6 licensed indications for GH in the UK
- Continue until end of linear growth or HV <2cm/yr
  - Transition
GH paediatric licensed indications - dosing

- GHD
  - 0.025mg – 0.05mg / kg / day
- TS
  - 0.045mg / kg / day
- SGA
  - 0.035mg / kg / day
- CRI
  - 0.05mg / kg / day
- PWS
  - 0.035mg / kg / day
- SHOX deficiency
  - 0.045 – 0.05mg / kg / day
Quick quiz 2

• What is NOT a licensed indication for GH in the UK?
  – A
    • Turner Syndrome
  – B
    • Idiopathic Short Stature
  – C
    • Chronic Renal Failure
  – D
    • SHOX deficiency
Answer - B

• Idiopathic short stature not a licensed indication for growth hormone therapy in the UK
  – UK NICE GUIDELINES
    • GHD
    • TS
    • PWS
    • CRI
    • SHOX
    • SGA
Specialist clinics – growth hormone

- Neuro-Oncology Endocrine
- Septo-Optic Dysplasia
- Turner Syndrome
  - Congenital Hypothyroidism
  - Adrenal
  - DSD
  - Thyroid surgery
  - General endocrinology
Neuro-Oncology-Endocrine

• ‘Late Effects’
  – Meet early on in oncology journey
• Chemotherapy
• Radiotherapy
• Long term steroid treatment
• Growth
• Puberty
• Ophthalmology
• Neurology
• Audiology
• School
  – Neurocognition
Growth hormone treatment: ‘Late Effects’

- Particularly susceptible if received craniospinal irradiation
- 85% of cancer survivors
  - Young
  - Intensive treatment
  - CNS tumours
    - Cognitive
    - Neuropsychological
    - Endocrine impairment
- Evidence that chemotherapy alone can affect growth and puberty
- Commence GH when active disease still present?
Tom’s treatment

- **Surgery**
- **Chemotherapy**
  - Vincristine
    - Peripheral neuropathy
  - Carboplatin
    - Auditory dysfunction
    - Renal dysfunction

*Hypothalamic pituitary axis can be affected even in the absence of radiotherapy*
Quick quiz 3

• How long do you think children who have had a brain tumour should be followed within endocrinology?
  – A
    • During their oncology treatment only
  – B
    • From diagnosis until transition
  – C
    • When they have reached puberty
  – D
    • Until they have stopped growth hormone treatment
Answer - B

- Theoretically from diagnosis until they are discharged from paediatrics and into adult services and long-term rehab
  - Neurology
  - Gynaecology
  - Endocrinology
- Long term monitoring of growth and puberty
  - Other hormone deficiencies
- Transition
2004 Consensus guidelines

- Re-evaluating the need for GH treatment
- Re-evaluation of GH and IGF-1 at end of linear growth
Quick quiz 4

• How long should the transition process take?
  – A
    • 5 minute chat just before child turns 18
  – B
    • When the child has finished taking GH
  – C
    • As soon as the child turns 13
  – D
    • At least 3 years
Answer - D

- Transition discussions
  - Put to child and family early
  - Discuss long term goals
  - Introduce adolescent teams / adult physicians
Conclusion

• Children treated with brain tumours
  – Intense follow up – diagnose GHD early
• Advise intense CNS input
  – Good rapport with child and family
  – Build confidence
  – Encourage compliance
    • Good response to GH
    • Discuss transition
Thank you