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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

Insulin-tolerance test

Dose	0.05–0.1 units/kg intravenously; lower dose if evidence of panhypopituitarism
Sampling	GH, cortisol, glucose at 0, 15, 30, 45, 60, 90 mins; monitor blood glucose every 5 minutes
Complication	Severe hypoglycaemia, seizures
Requirement	Doctor at bedsite throughout test, blood glucose <2.2mmol/L
Contraindication	Age <5 years, epilepsy

Arginine test

Dose	0.5g/kg intravenously over 30 mins
Sampling	GH at 0, 30, 60, 90, 120, 150 mins
Complication	Nausea, irritation at *iv* site

Clonidine test

Dose	0.15mg/m^2 orally
Sampling	GH at 0, 30, 60, 90, 120, 150, 180 mins
Complication	Potential hypotension
Requirement	BP monitoring

Diagnosis

Glucagon test

Dose	15μg/kg intramuscularly; maximum dose 1mg
Sampling	GH, cortisol, glucose at 0, 30, 60, 90, 120, 150, 180 mins
Complication	Hypoglycaemia, particularly in young children, nausea
Requirement	Doctor in attendance throughout test
Contraindication	Epilepsy in young children

- 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..?

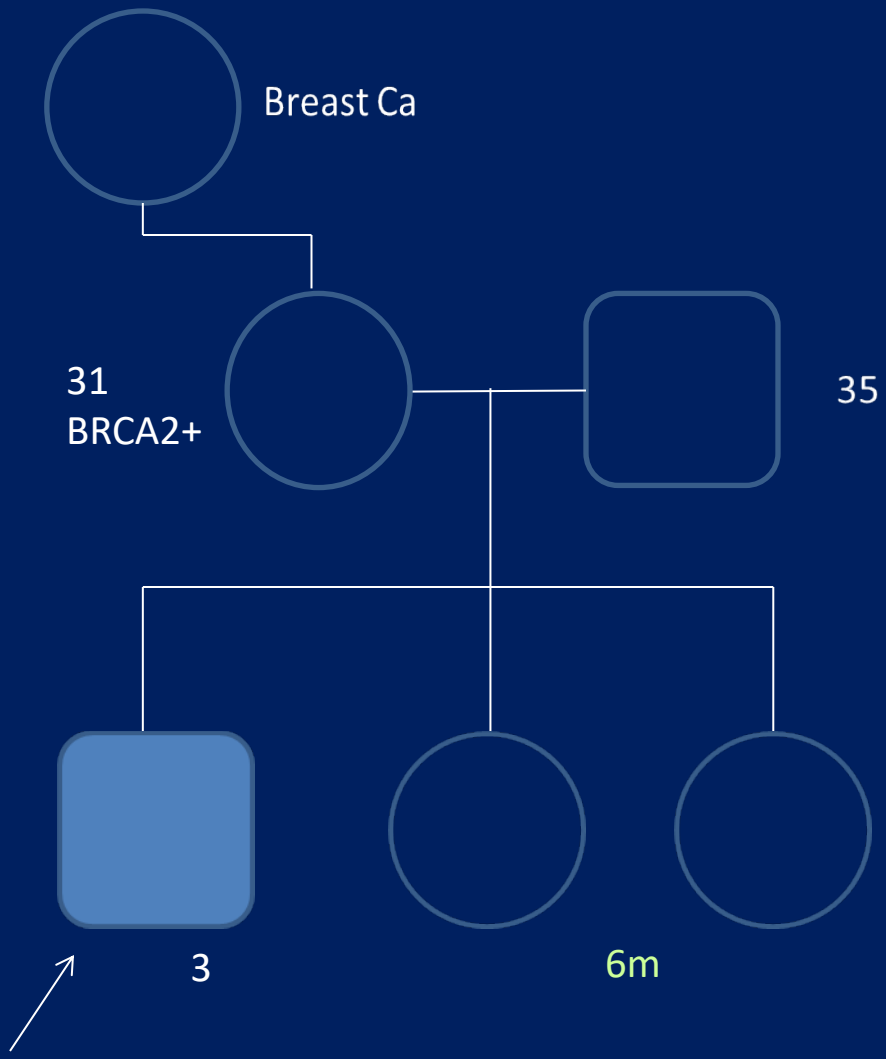
Case Presentation

Tom is a 5 year old boy presenting with short stature

Presented to hospital when 3

History

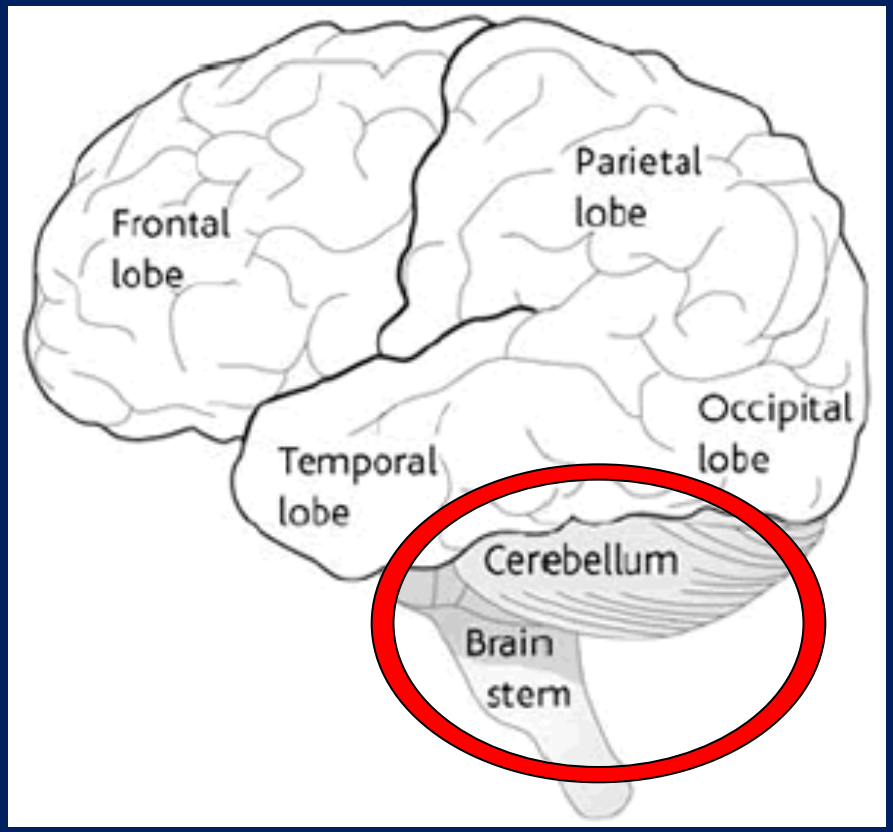
- Male
- Born in 2004
- White British
- No consanguinuity
- Birth weight: 3.49kg
- Gestation: Term + 6
- Parents height
  - Mother: 168.6cm
  - Father: 178.0cm



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

Presentation to Neuro-Oncology-Endocrine Clinic

- 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

Name of Test	Range	08.10.09	18.11.10
FT4 pmol/L	10.8 - 19.0	16.3	13.8
TSH mU/L	<6	2.9	2.7
Prolactin mU/L	59 – 271	109	163
Cortisol nmol/l		579	425
LH IU/L	0.7 – 6.5	0.3	<0.2
FSH IU/L	0.1 – 5.8	1.2	<0.2
Testosterone nmol/L		<0.69	<0.69
IGF-1ng/ml	52 – 297	47	64
IGF-BP3mg/L	1.3 – 5.6	1.80	2.66

Pituitary Function tests February 2013 (8.3yrs)

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

T = (Min)	- 30	0	30	60	90	120	150	180
Glucose (mmol/L)	4.7	4.6	6.5	5.7	4.4	4.0	4.1	4.2
Growth Hormone (µg/L)	0.2	0.4	1.9	0.7	1.6	4.2	1.6	0.4
Cortisol (nmol/L)	268	469				508	659	582

Pituitary Function tests – 8.3yrs

LHRH test

T=	0	20	60
LH (IU/L)	0.7	6.8	5.5
FSH (IU/L)	1.7	3.4	3.8

– Pubertal response?

TRH test

T=	0	20	60	Ref range
FT4 (pmol/L)	10.2			12-22
TSH (mU/L)	1.3	12	9.8	<6.0

- Normal response

Pubertal Staging: 1 1 1 02 02

Difficulties surrounding the diagnosis

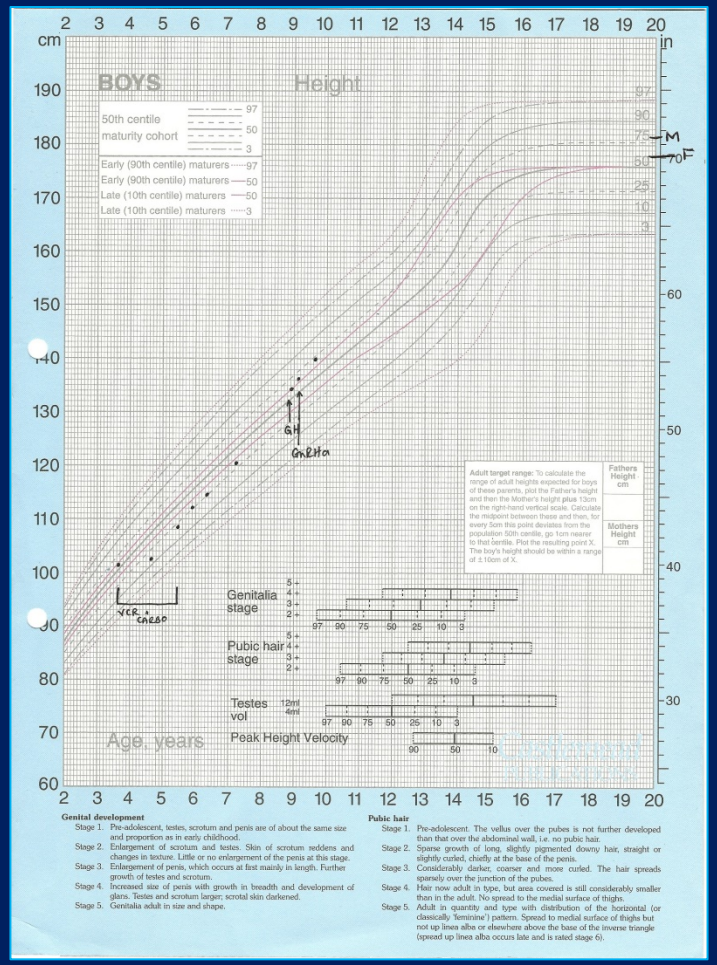
- Puberty interfering?
- Long follow-up to ascertain GHD
- Continued follow-up in multi clinics
  - Accurate auxology?
  - DNA to any clinics

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

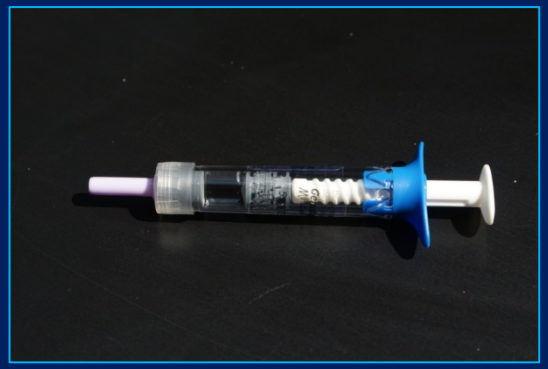
Growth Hormone Therapy in the UK

- 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

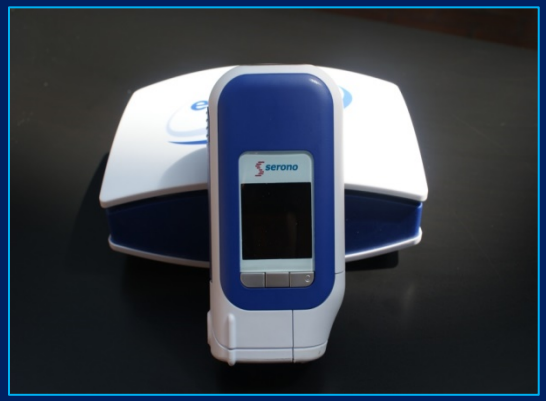
GH paediatric licensed indications - dosing

- 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

GH devices




NordiFlex PenMate®
Test medium (15 mg) Norditropin NordiFlex®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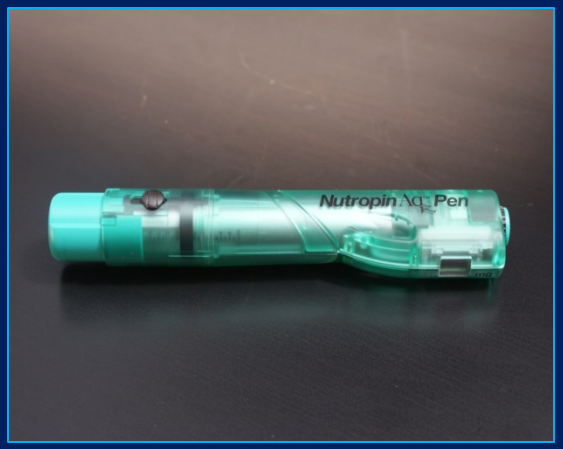
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Quick quiz 2

- 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

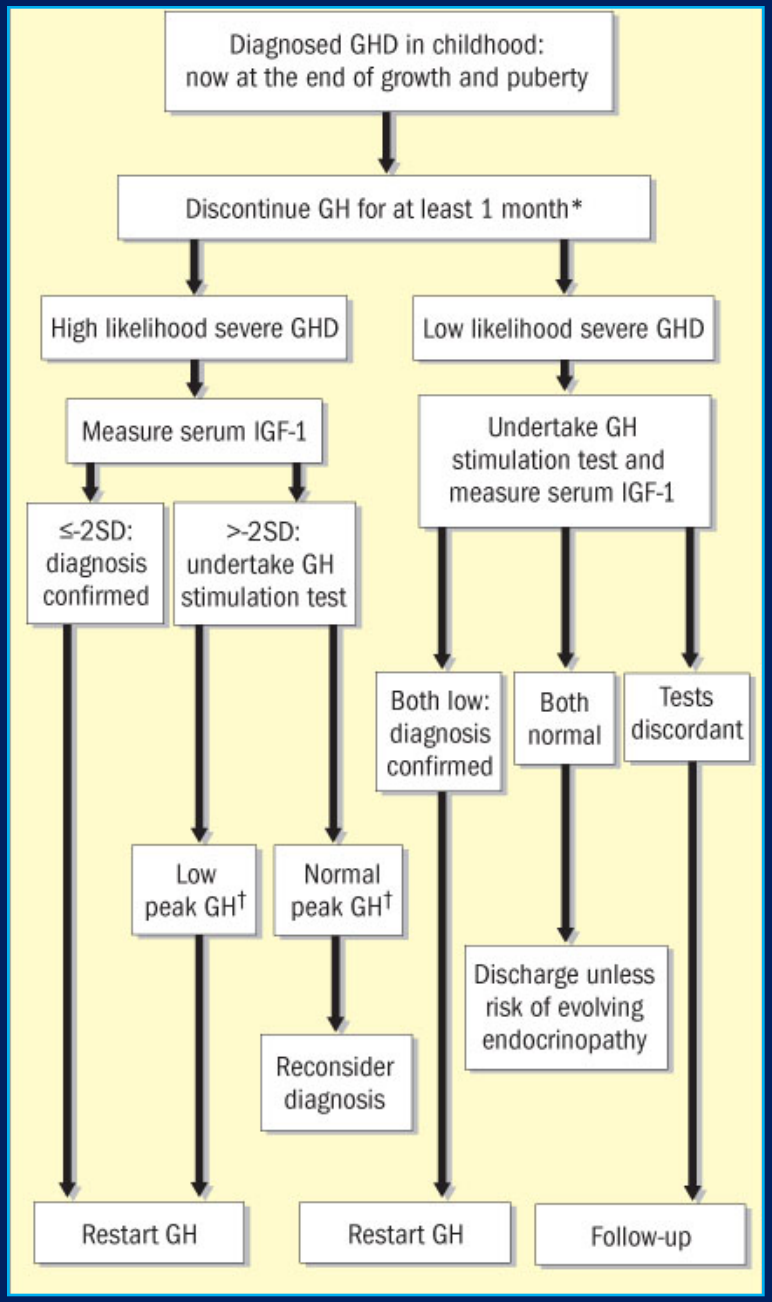
Quick quiz 3

- 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

Transition - ESPE Guidance



- 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