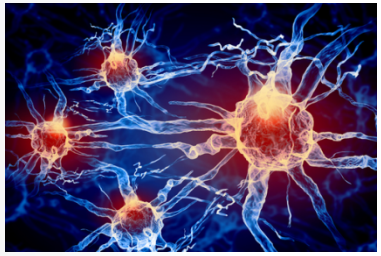
Workshop on GHD



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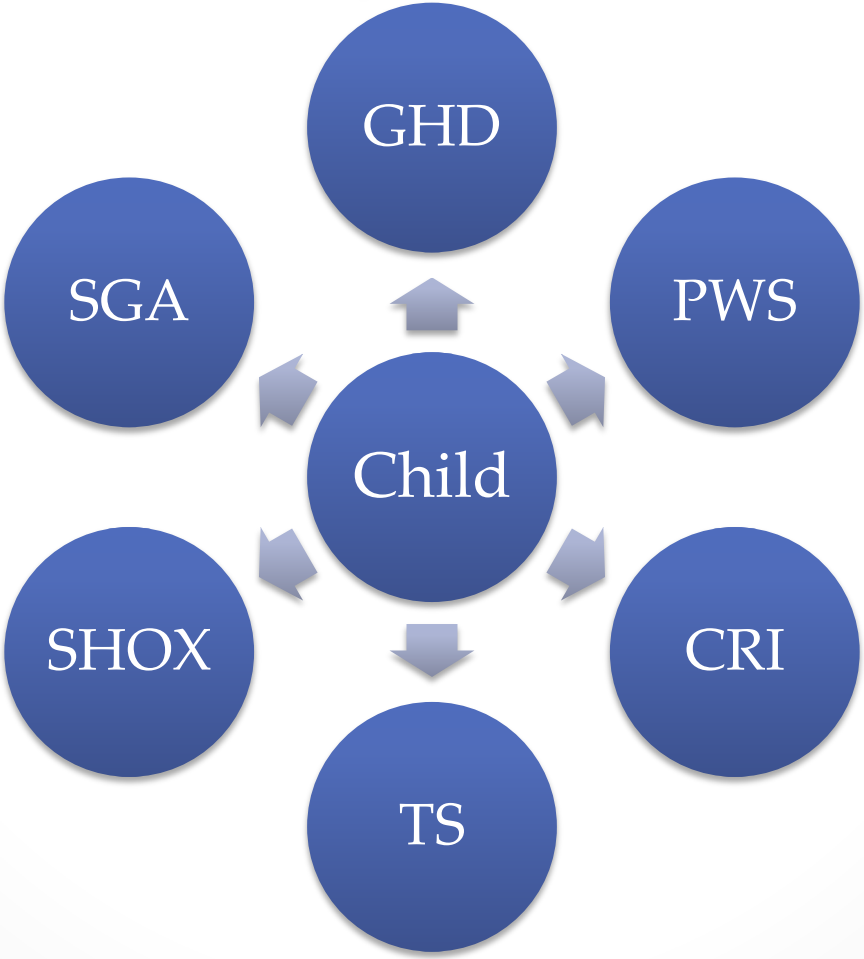
London South Bank University

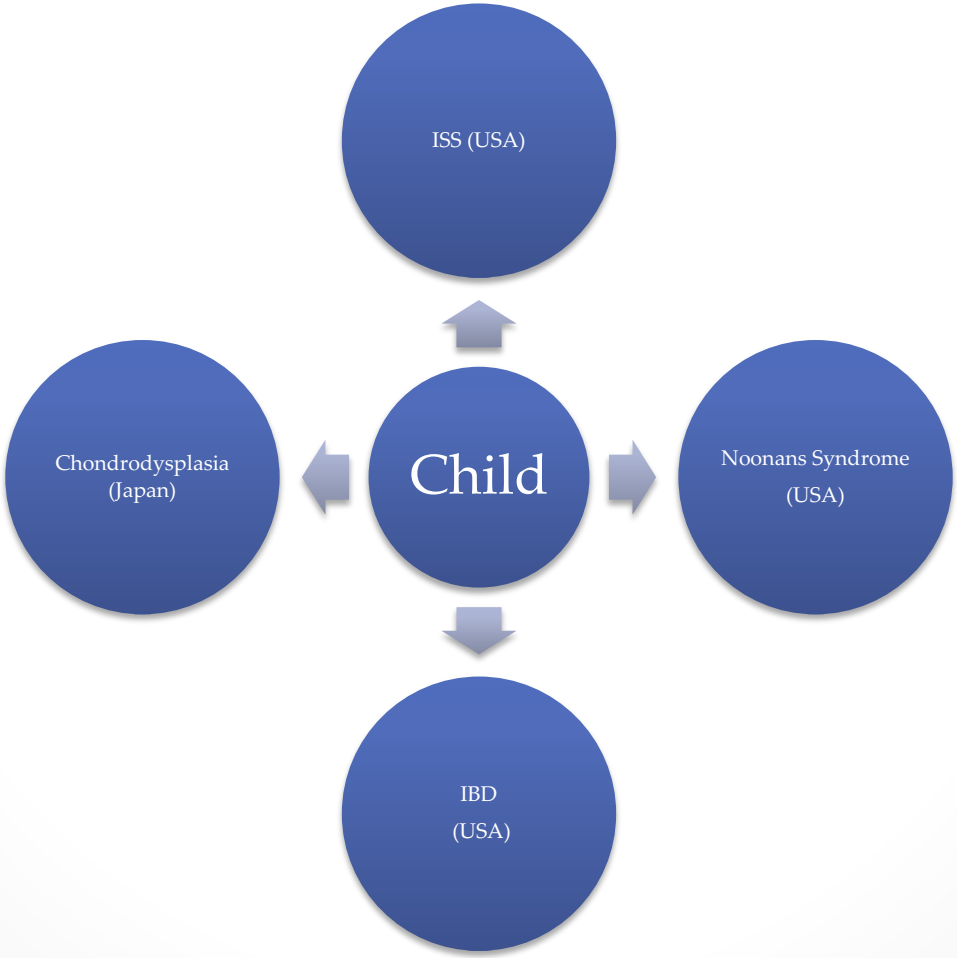
Introduction

- Different reasons why children need GH in comparison to adults
- Confusions re diagnosis and whether to treat
- Case studies

Growth hormone in children (UK license)



GH in children - international

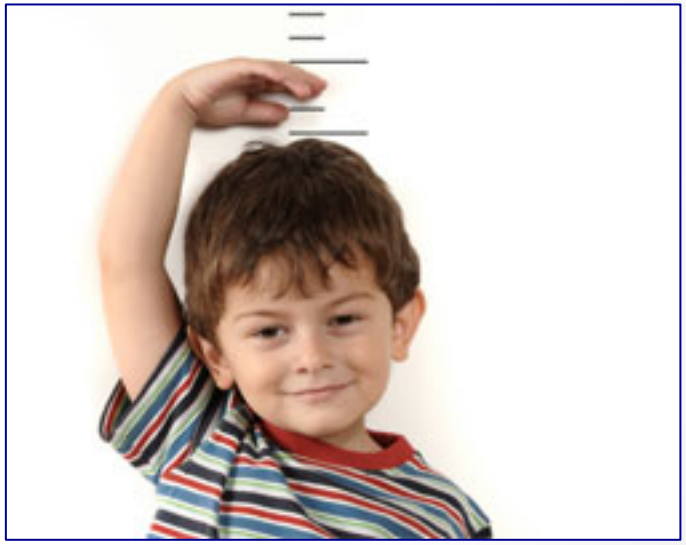


Case study 1

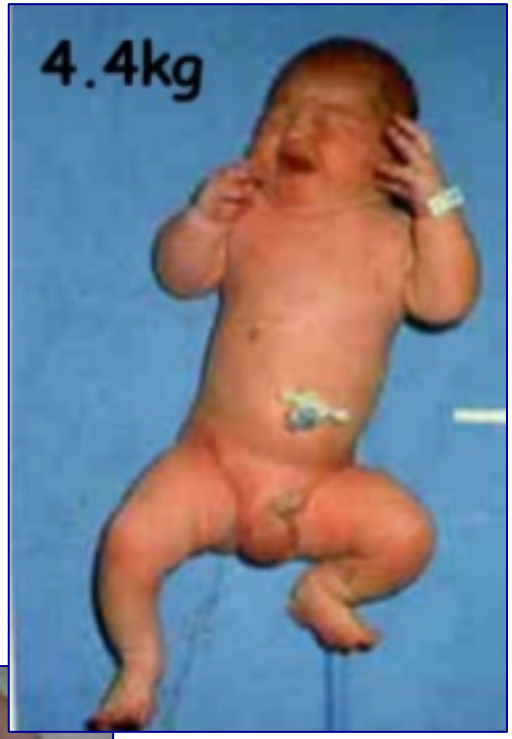
GHD?

Age 1.61years March 2010

- Noticed to be short by Practice Nurses
- Referred to Paediatric Endocrinologist
  - When did the Practice Nurse refer?
  - Who referred to them?
    - Parents
    - Health Visitor
- Full history
  - SGA
- Auxology
- Parents height
- Baseline bloods
- Follow up in 4 months

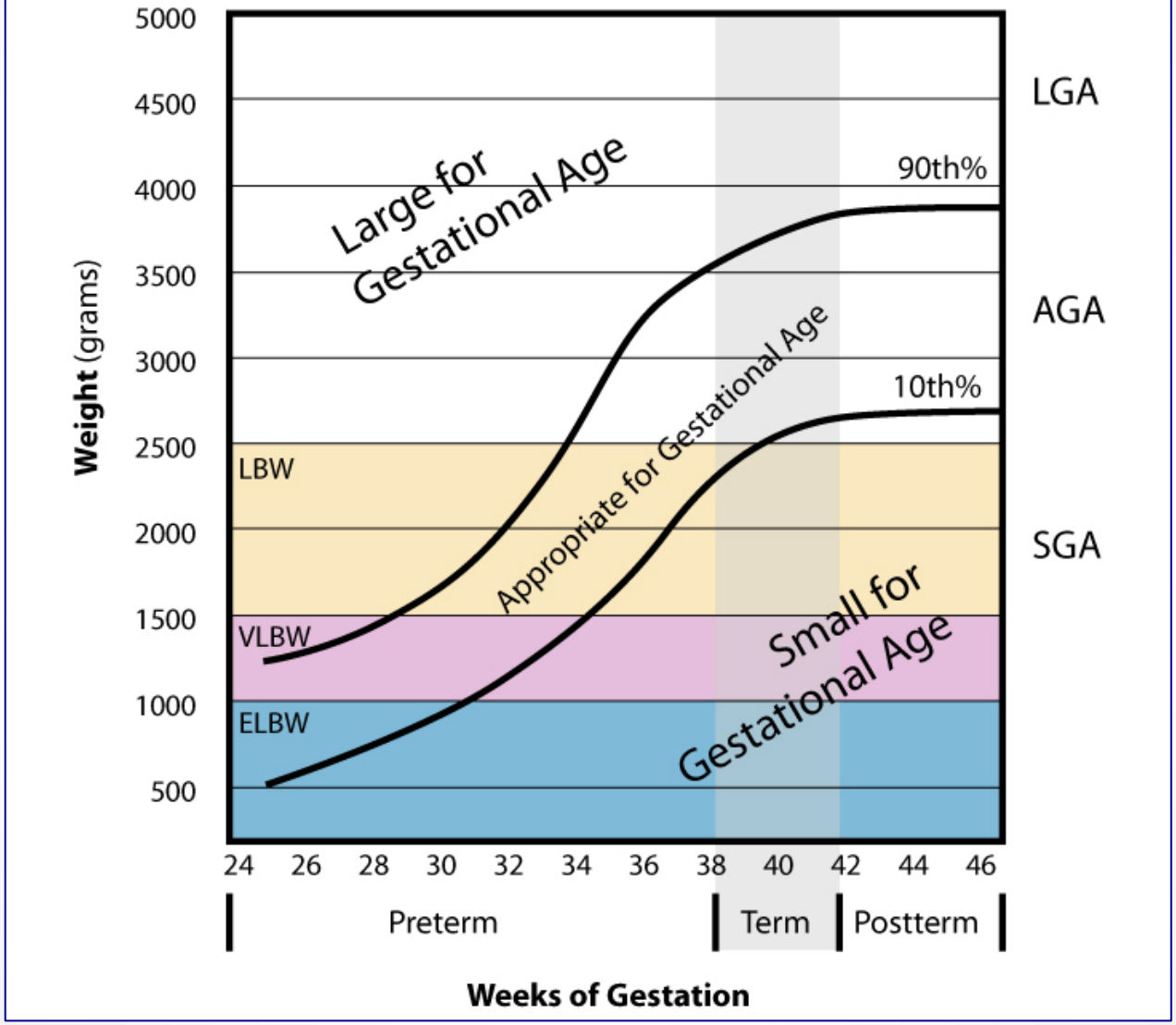


SGA



- SGA
  - Small for gestational age
    - Weight below 10th percentile
- AGA
  - Weight between 10 and 90th percentiles (between 2.5kg and 4kg)
- LGA
  - Weight above 90th percentile
- IUGR
  - Deviation in expected growth pattern
    - Not all IUGR babies are SGA

SGA


5000
4500
4000
3500
3000
2500
2000
1500
1000
500
Weight (grams)
LGA
AGA
SGA
90th%
10th%
Large for Gestational Age
Appropriate for Gestational Age
Small for Gestational Age
LBW
VLBW
ELBW
24
26
28
30
32
34
36
38
40
42
44
46
Preterm
Term
Postterm
Weeks of Gestation

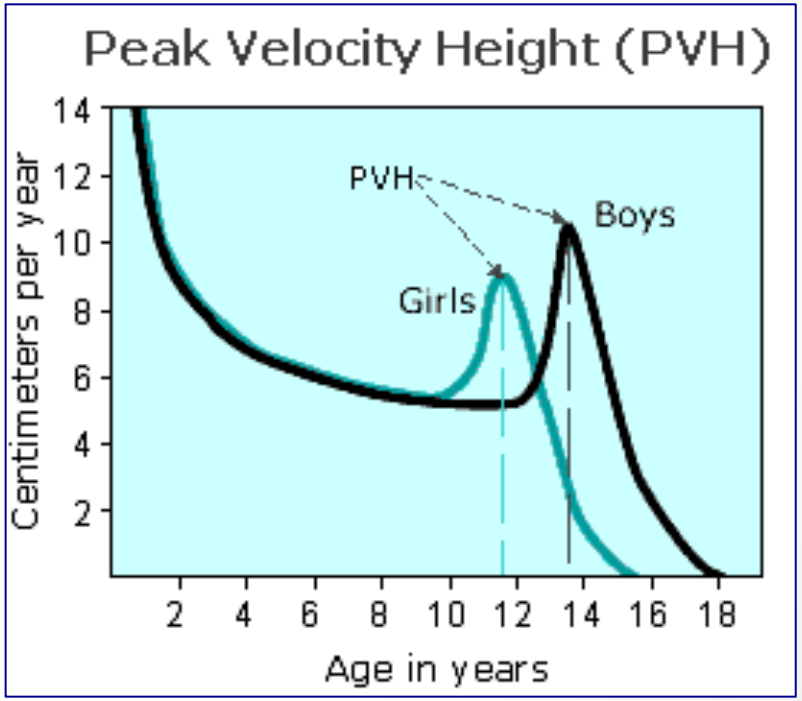
SGA

- Cause
  - Foetal
    - Chromosomal
    - Genetic syndromes
    - Intrauterine infection
  - Placental
    - Impaired function
      - Malnutrition
      - Hypoxaemia
      - Acidaemia
  - Maternal
    - Chronic illness
      - Renal disease
      - Hypertension
    - Smoking / alcohol / drugs

- High dose GH therapy for a period of 2 years induces catch up growth
- Catch down growth has been reported if treatment is discontinued in childhood
- At risk of hypoglycaemia
- GH: 0.035mg/kg/day
- Start at age 4 years

Age 2.27 years
July 2010

- Baselines all normal
- Decided to watch height velocity
  - 8.6cm/yr
- Follow up 4 months



Age 2.61 years
November 2010

- Height velocity now 11.9cm/yr
- Watch and wait
- Follow up 6 months

Age 3.11 years June 2011 (one year in the system)

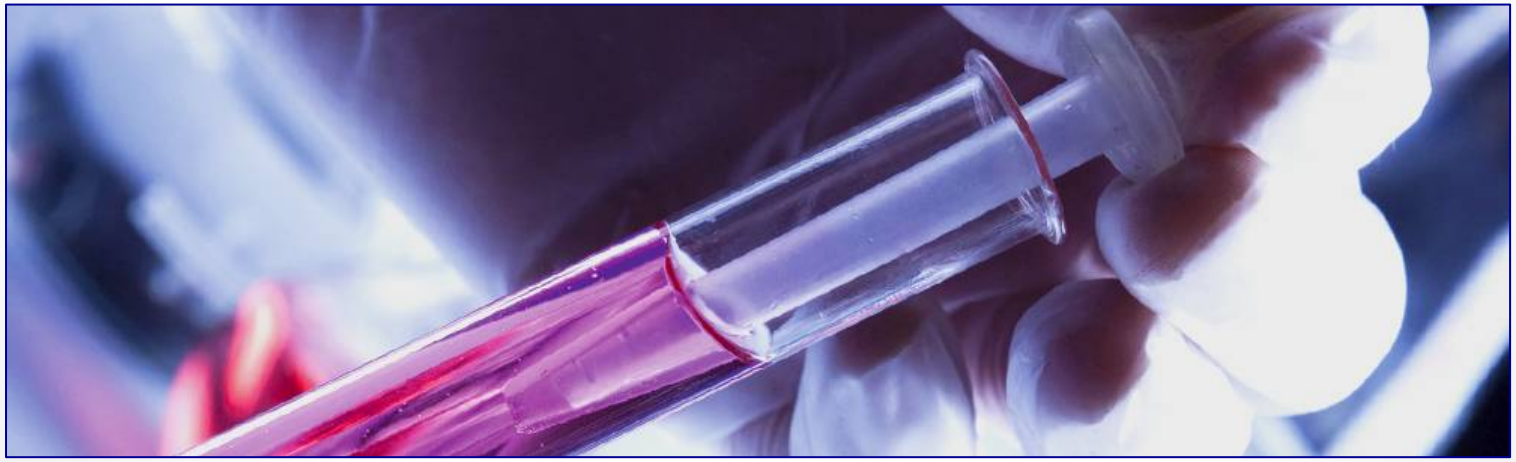
- Height velocity 4.6 cm/yr
- More baseline bloods
  - Normal
- Follow up 6/12
- Still too young for SGA GH treatment

Discussion

- What do you think the appropriate course of action is to take now?

Age 3.63 years December 2011

- Height velocity 6 cm/yr
- Decision made to undertake Glucagon stimulation test
  - ? See if GHD



February 2012

- Glucagon stimulation test
  - Brought into the day ward
- Return to clinic when results ready

Age 4.15 years
June 2012
(two years in the system)

- Found to be GHD!
- Full range of GH devices shown and demonstrated to the child and family
  - Licensed indications
  - DVDs given to family to take him if indecisive
  - CNS contact details given
- Parents called CNS two weeks later with device choice

Glucagon Stimulation Test 15 December 2012

Time	GH µg/L	Cortisol nmol/L	Glucose mmol/L	Bedside Glucose mmol/L
0	5.9	187	3.5	4.2
60	4.23	525	3.0	3.7
90	4.4	374	3.2	4.1
120	2.4	269	3.0	3.6
150	3.13	227	2.9	3.4
180	3.24	223	2.7	3.4

GH devices


NordiFlex
PenMate
Test medium (15 mg)
Norditropin NordiFlex

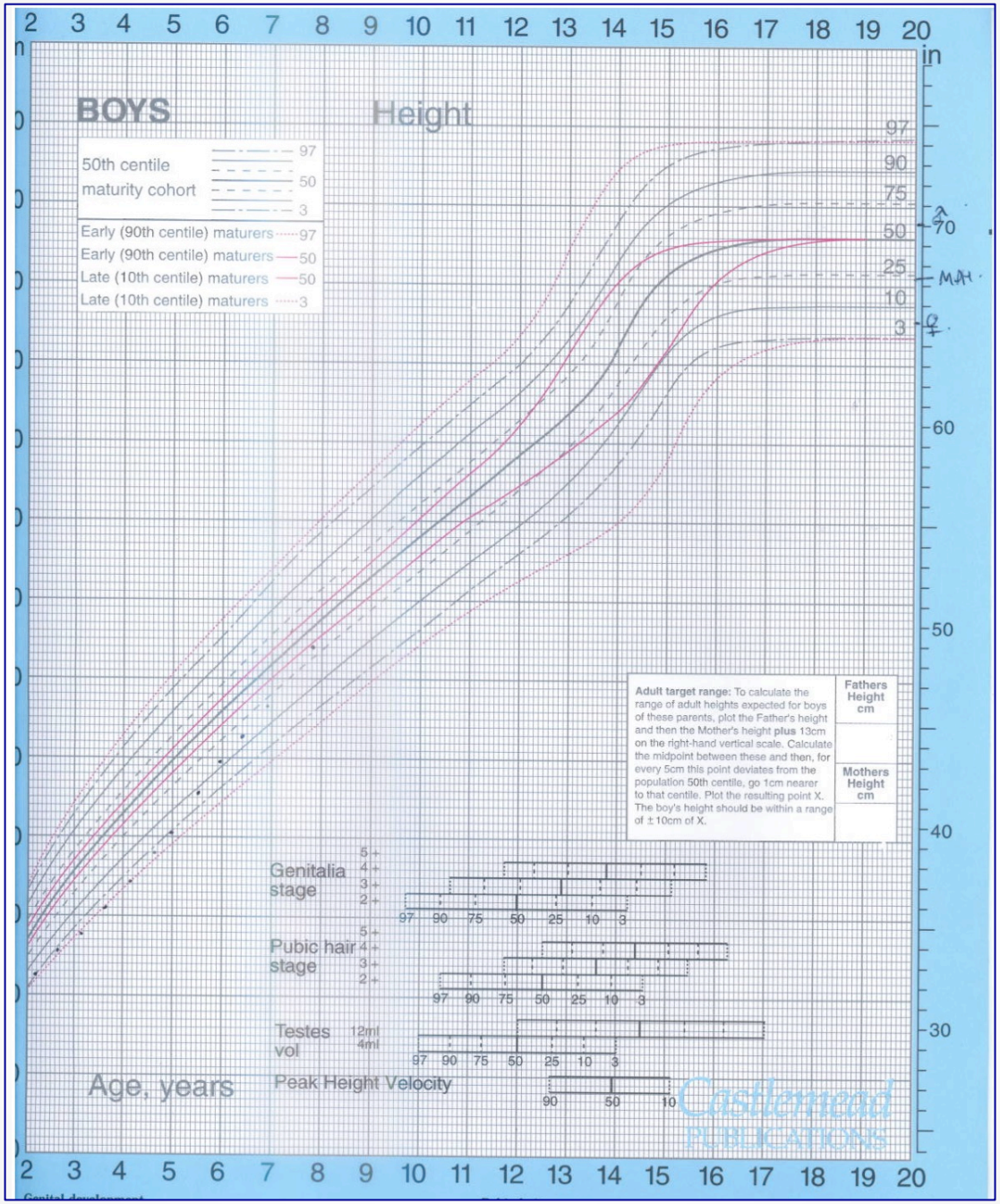

VISION X


NORDI
penmate
NORDI
pen


Introducing the NEW
HumatroPen™
• Precision Dosing
• Flexibility to dose in small units
• Available in 3 colour coded pens
HumatroPen™
6 mg
HumatroPen™
12 mg
HumatroPen™
24 mg


SurePal™ 10


Nutropin AQ Pen


BOYS
Height
50th centile
maturity cohort
97
50
3
Early (90th centile) maturers 97
Early (90th centile) maturers 50
Late (10th centile) maturers 50
Late (10th centile) maturers 3
97
90
75
50
25
10
3
Adult target range: To calculate the range of adult heights expected for boys of these parents, plot the Father's height and then the Mother's height plus 13cm on the right-hand vertical scale. Calculate the midpoint between these and then, for every 5cm this point deviates from the population 50th centile, go 1cm nearer to that centile. Plot the resulting point X. The boy's height should be within a range of ±10cm of X.
Fathers Height cm
Mothers Height cm
Genitalia stage
Pubic hair stage
Testes vol
12ml
4ml
Peak Height Velocity
Age, years
Castlemead PUBLICATIONS

GH prescribing

- 4/52 prescription from the hospital
- CNS sends to relevant homecare company
- Letter to GP asking them to take on shared care, and continue prescribing of GH

- Patient will start around one month later

- VARIES FROM HOSPTIAL TO HOSPITAL

-

Patient journey

- From start to finish

AT LEAST TWO YEARS

POTENTIAL BARRIERS

- Missing clinic appointments
- Full clinics – delay in next appointment
- Waiting list for glucagon test
- Samples go missing
- Family indecisive re GH choice
  - Want to come in again and see device
- Delay in prescription being done
- Delay with health care company
- Funding requests from CCG
- GP refusal to prescribe

Discussion

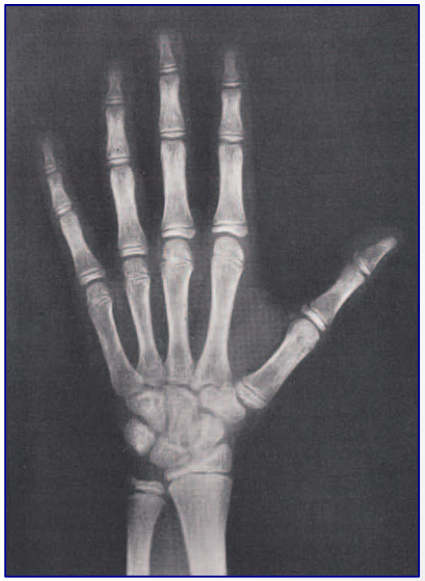
- How do you think the patient journey for this child could have been made better?
- What factors do we need to consider before starting GH therapy in children?

Guidelines for GH therapy – BEFORE starting

- Pubertal assessment and bone age
  - Growth potential?
- Subnormal HV
- Pre-treatment HV
  - HV after 1 year of treatment can be assessed
- Full commitment from family
- Involvement of CNS
  - Counselling the child and family
  - Assessing likelihood of compliance
  - Patient choice of devices
  - Teaching the daily injection

Guidelines for GH therapy - DURING

- Given subcutaneously in the evening, 7 days a week
- 4 monthly clinic visits
  - Auxology and pubertal staging
- Compliance
- Home visit if HV disappointing
- 6-12 monthly IGF-1 measurement
  - Dosage and compliance
- Annual bone age
- Discontinue GH at completion of growth (HV <2cm/yr)
- Re-test prior to transition



GHD - Children

Acquired

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

Transient

- Psychosocial deprivation
- Prepubertal
- Hypothyroidism

Genetic

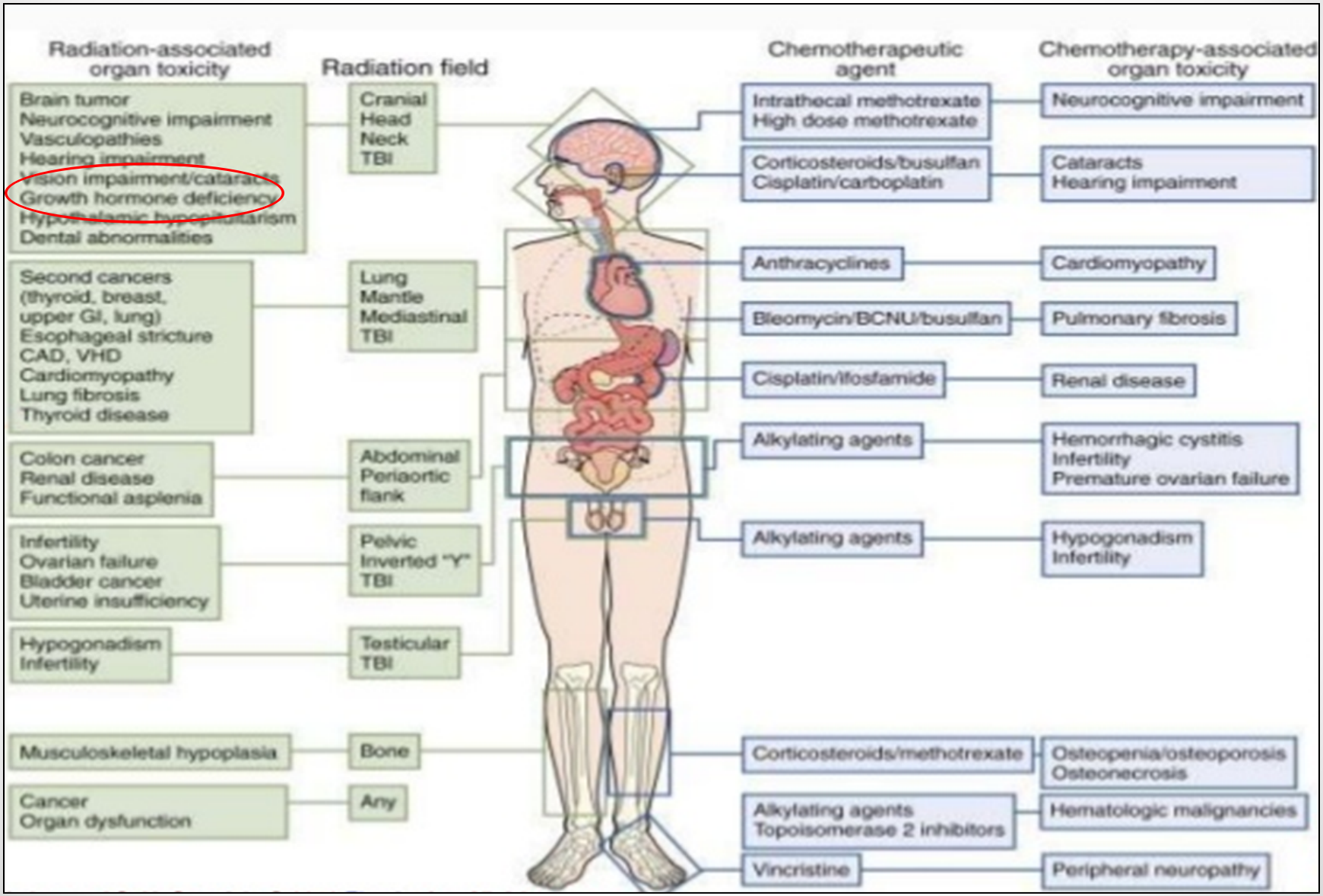
- GH-1 mutations
- GHRH receptor mutations
- Pit-1, Prop-1 mutations

Congenital

- GHRH deficiency
- Structural defects:
  - *septo-optic dysplasia*
  - *agenesis of the corpus callosum*
  - *single central incisor*
  - *holoprosencephaly*
- Intrauterine infection

- Due to the pituitary gland not being able to produce enough GH to facilitate the growth process
- Confirmed by a peak GH level below 20mU/L (7ng/ml)
  - Short stature
  - Slow growth
  - Delayed bone age

Cancer treatment



Overall Late Effects of Brain Tumours

Late Effect	Risk Factors	Surveillance
Dental problems	- Radiotherapy to field, including jaw (base of skull, cervical spine)	- Regular dental review
Hearing loss	- Platinum chemotherapy - +/- Radiotherapy to field, including middle ear (especially posterior fossa)	- Enquire re: speech and language development
Neuro-endocrine and growth	-Tumours in area of hypothalamus or pituitary - Cranial radiotherapy	-Regular anthropometric monitoring -Regular endocrinology review -Pituitary function tests
Secondary tumours	-Radiotherapy -Chemotherapy, particularly epipodophyllotoxins and alkylating agents -Pre-disposing syndromes eg: NF1	-High index suspicions of skin lesions (especially skin cancers, meningiomas, glial tumours) within radiotherapy fields -Patient education and regular examination of skin lesions
Shunts (blocked or infected)		- Inform patient of potential complications and symptoms
Thyroid function	- Radiotherapy to field, including thyroid (base of skull, cervical spine)	-Clinical screening -Annual thyroid function tests
Alopecia	- Radiotherapy to field including scalp	- Clinical examination

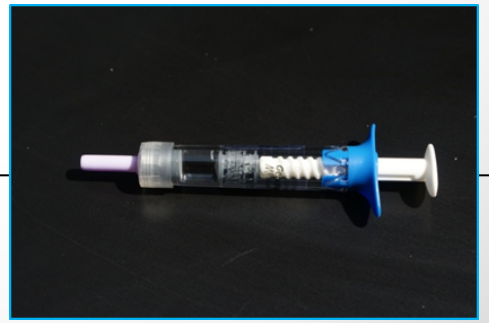
Hormone deficiencies..

- Most deficiencies are probably caused by the tumour itself, as much as surgery, radiotherapy or chemotherapy

- It can be difficult to know the exact causes and effects, but current research suggests..

Growth Hormone Deficiency

- The result of both tumour and radiotherapy
- Occurs more quickly after higher (rather than lower) radiation doses
- Older children, who's growth and development is nearly finished, may get away without therapy in childhood
- The importance for it in adulthood is still under review:
  - General health, muscle and bone strength, quality of life



Case study 2

Typical Paediatric GHD?

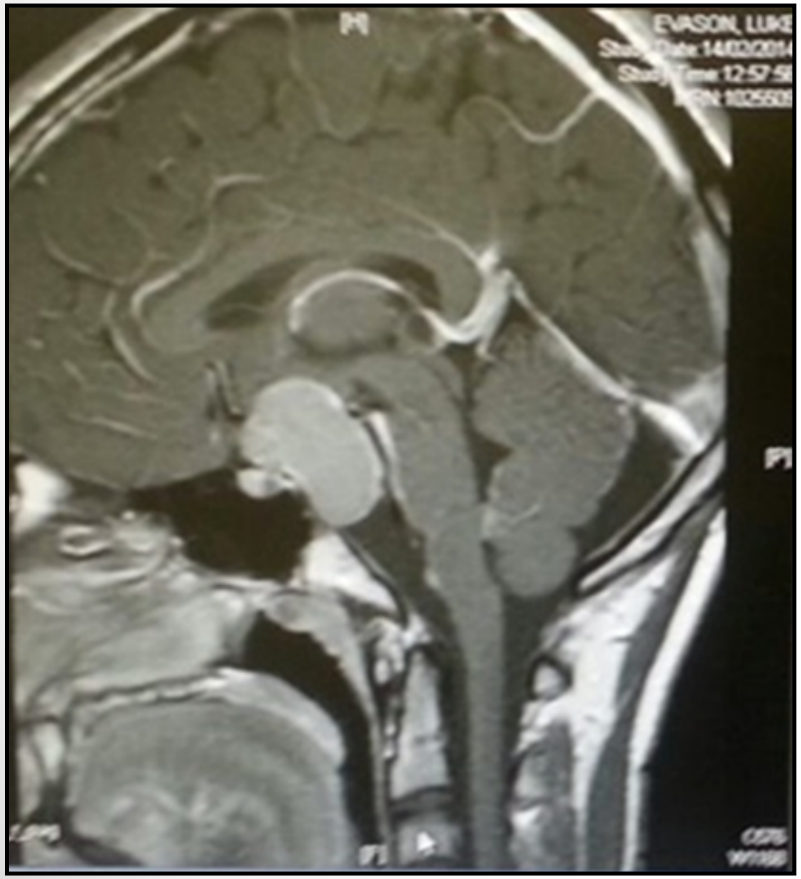
History

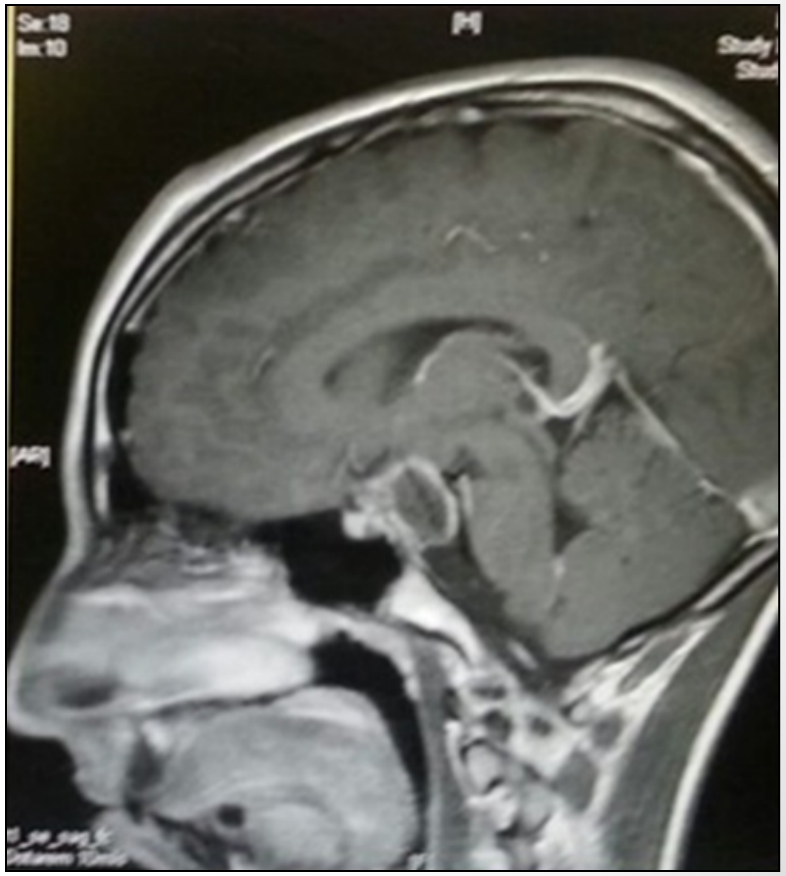
- 17 year old boy – Tom
- 4 year history of fatigue
  - Had swine flu age 13yrs, and 'never regained energy'
  - Complained of headaches, but 'ignored as family history of migraines'
- Presented with a 6 week history of peripheral visual field loss – left, then right

Discussion

- Should Tom have been referred to an adult or a paediatric clinic?
- Diagnosis?

Brain MRI - Craniopharyngioma



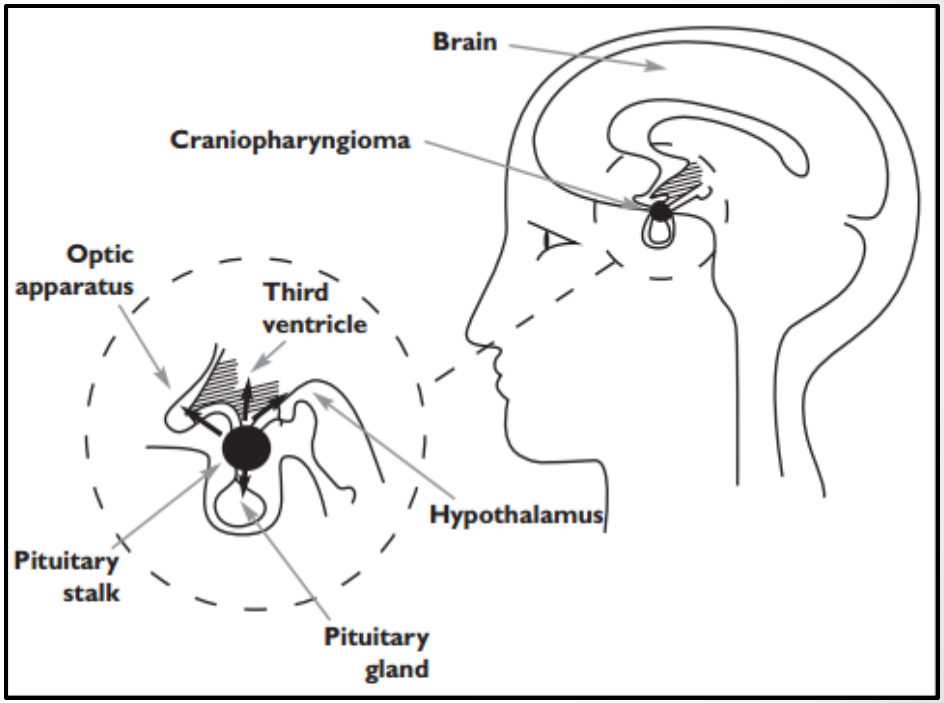


Brain MRI results

- Mostly cystic post-chiasmatic suprasellar mass, with a small solid calcified component anteriorly and on the right side.
- It elevates the anterior visual pathways and slightly favours the right side without eroding through the floor of the third ventricle
- Appearances are typical of a craniopharyngioma

Craniopharyngioma

- Benign brain tumour
- Thought to form and grow from some misplaced cells in the brain close to the pituitary gland
- Presentation varies
  - Most commonly occurring symptoms are headaches and blurred vision

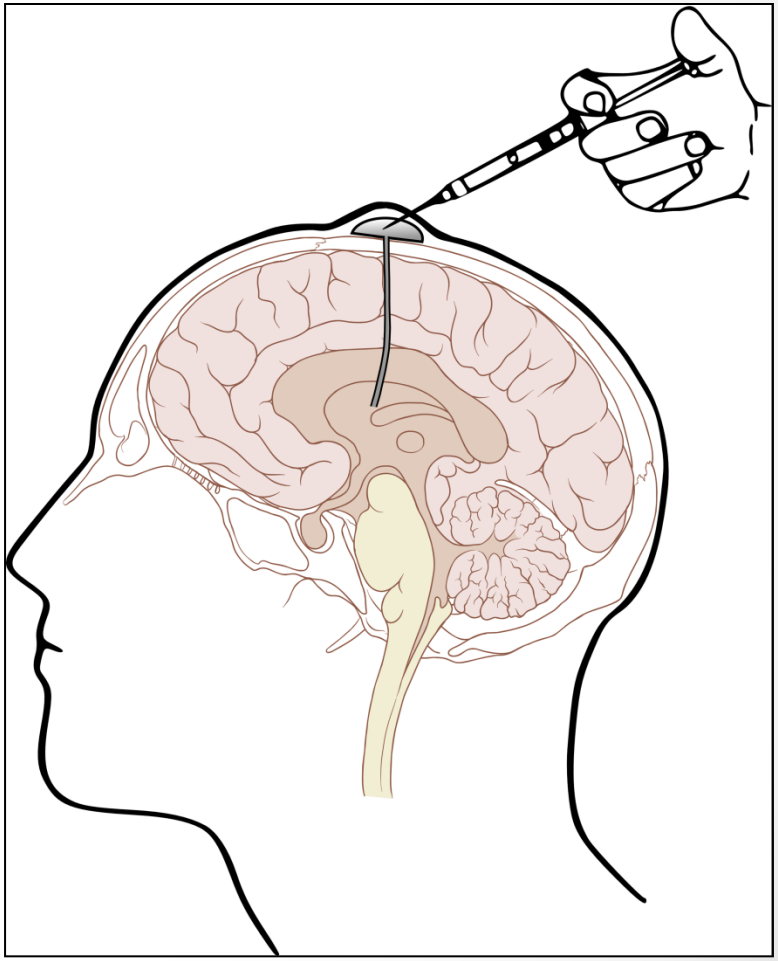


Surgery

- 5 March 2014
  - Cyst aspiration
    - 12mls of fluid
  - Right sided ommaya reservoir inserted
  - Bi-temporal hemianopia recovered following surgery within 24 hours

Ommaya reservoir

- Intraventricular catheter system
  - Can be used for aspiration of cerebro spinal fluid (CSF), or delivery of drugs
  - Indwelling catheter into one of the lateral ventricles in the brain



Post op endocrine assessment

- Insulin Tolerance Test 14 March 2014
- Intact pituitary reserve except severe growth hormone deficiency
- Good peak cortisol
- Normal thyroid function
- Normal gonadal function
- No diabetes insipidus

Insulin Tolerance Test - results

T =	- 0h20m	0h00m	0h20m	0h30m Glucogel	60m	90m	1h20m
Glucose (mmol/L)	5.2	5.0	3.4	2.5	6.3	8.4	7.8
GH (mcg/L)	<0.05	0.06		0.88	1.54		0.08
Cortisol (nmol/L)	377	469		307	319	226	162

- Growth hormone therapy commenced April 2014
- Nordipen 1.0mg daily s/c

Discussion

- Should Tom be starting GH?
- Paediatric or adult dose?
  - Near end of puberty
  - Minimal growth left

Neurosurgical follow up

- Post operative MRI scan
  - Small solid component at the anterior wall of the cyst
  - Intimately associated with the pituitary stalk, the carotid vessels and the optic chiasm
- Complete surgical excision would be difficult
  - Either transphenoidal or transcranial
- Radiotherapy proposed
  - April 2014 – Proton beam therapy, Jacksonville, Florida
    - Tom too old under NHS guidance as over 16
      - Family planned to raise funds for treatment in USA
      - Eligible for clinical trial
        - Month of pre treatment tests = treatment paid for

Further post operative follow up

- 27 March 14
  - Sperm cryopreservation
- 6 May 2014 - Florida
  - Standard Short Synacthen Test
    - Cortisol: 0840 180nmol/l → 0900 380nmol/l
    - FT4 0.7ng/dl, TSH 0.7mIU/ml
- Commenced:
  - Hydrocortisone (oral) 5mg three times a day
  - Thyroxine (oral) 75mcg once a day

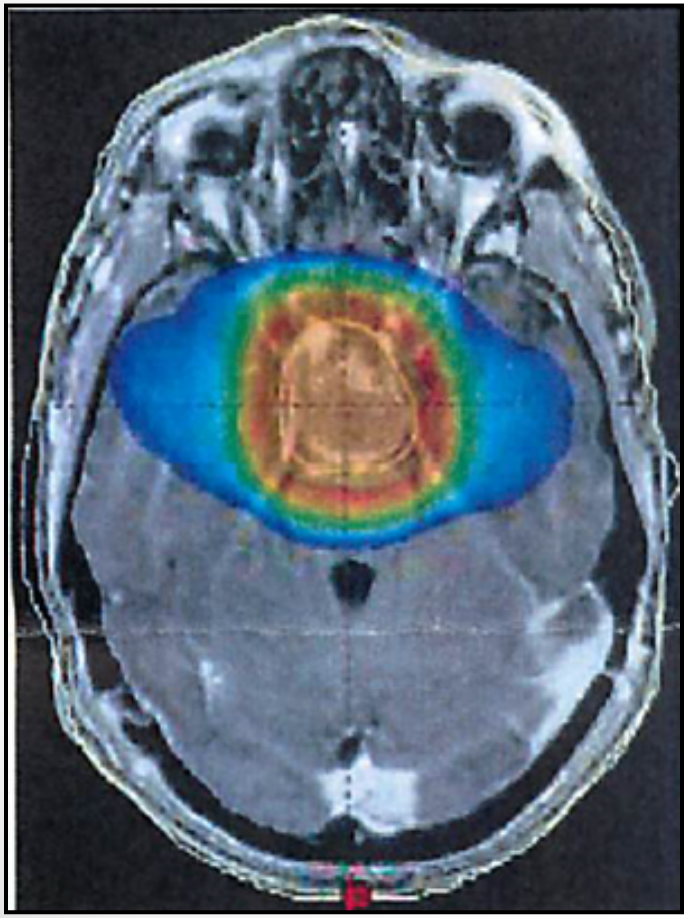
Proton beam treatment

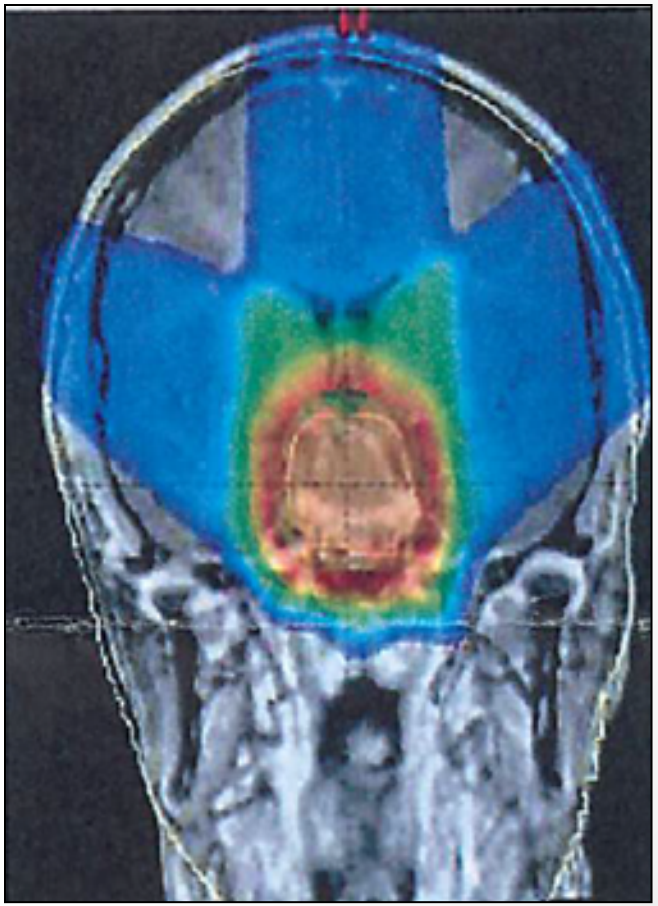
- Type of external beam radiotherapy that uses ionizing radiation
- Tumour is targeted with a beam of protons
- Protons
  - Damage the DNA of the cells, halting the reproduction
  - Due to their large mass
    - Little lateral side scatter in the tissue
    - All have a certain range
      - Very few go beyond that distance
- ? Overall benefit over conventional radiotherapy

Proton beam treatment

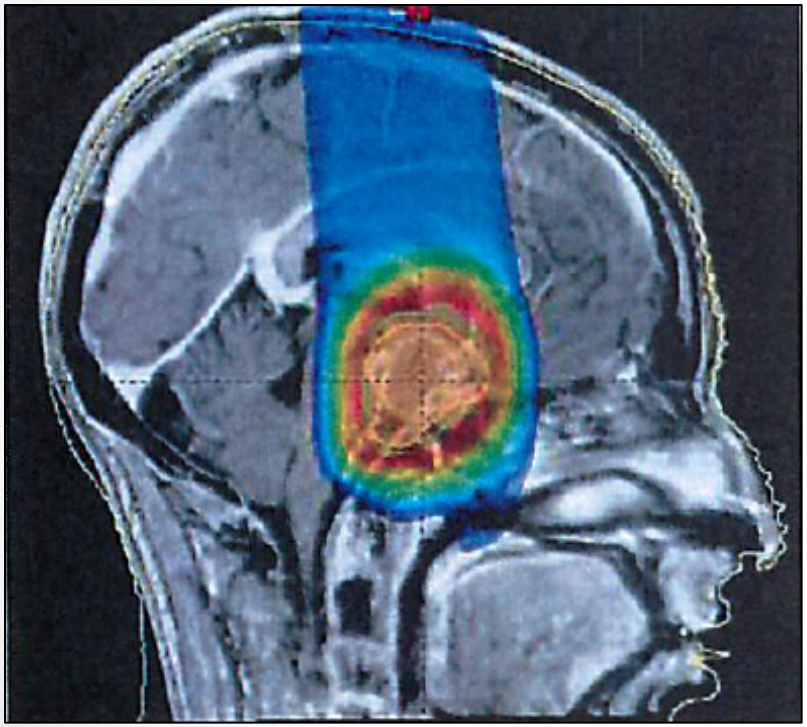
- May 17 2014 – July 9 2014
- 44 days of treatment
  - 54 CGE (Gy) at 1.8 CGE per daily fraction
  - Used a three field 3D conformal proton plan

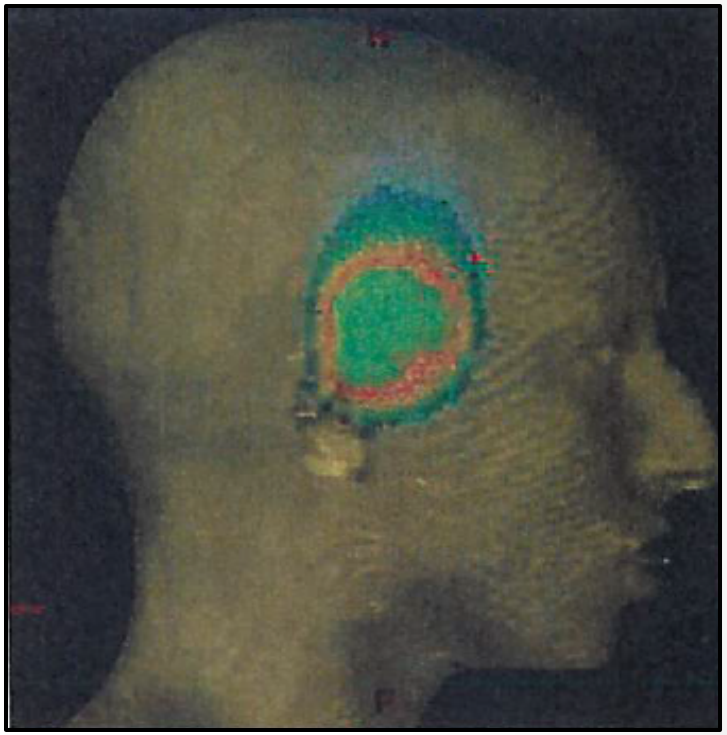
Proton Beams





Proton beams





Post radiation patches (both sides)

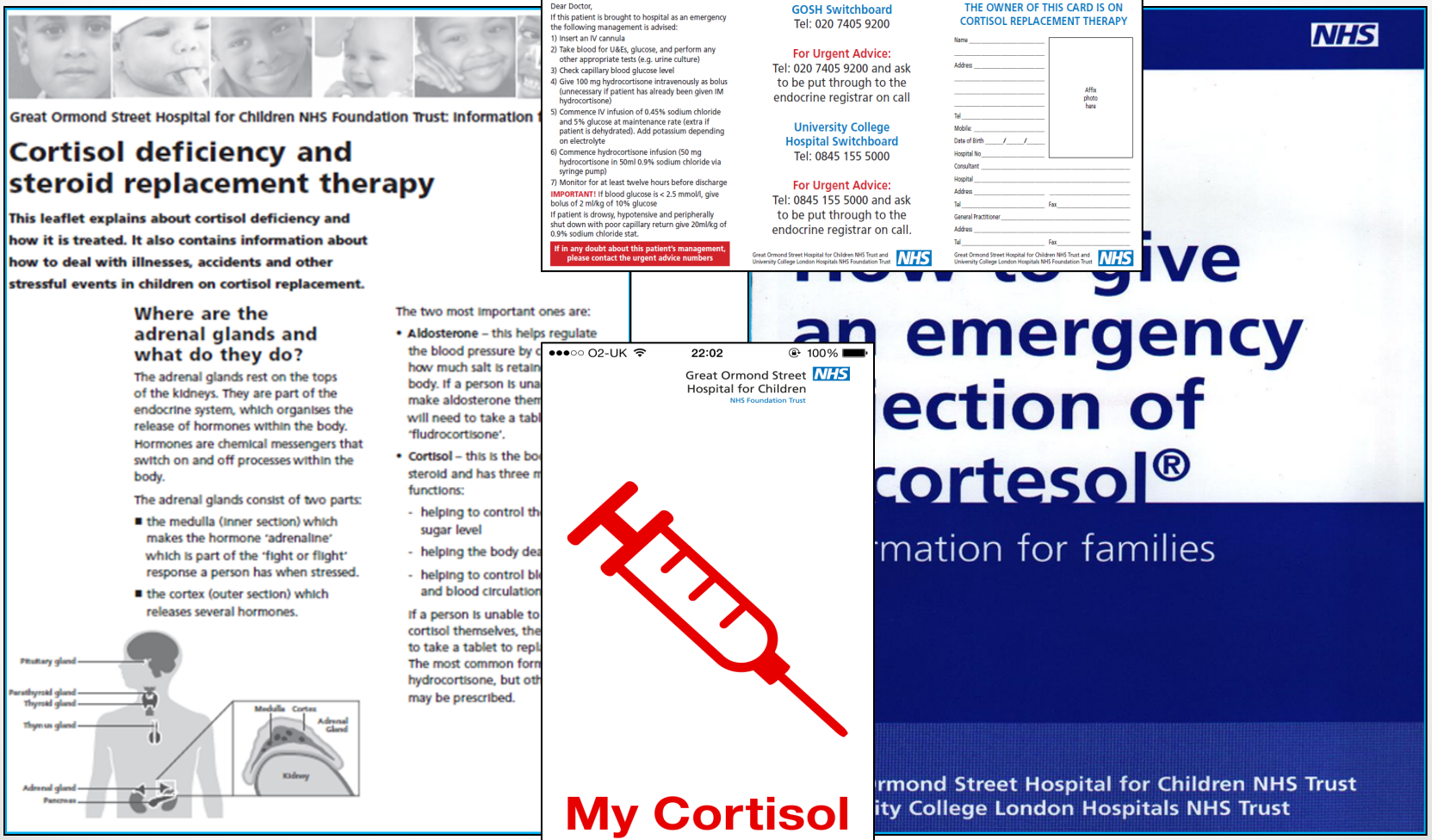
Recommendations after Proton Therapy

- Neurocognitive testing
  - Post treatment baseline
  - Every 2/3 years minimum
- Neuroendocrine testing within 6 months
  - Post treatment baseline
  - Continue every 6/12 at least through puberty
    - Ideally lifelong
      - Pay particular attention to GH
- Ophthalmology and visual acuity

Endocrine follow up

- Back in the UK – July 2014
- Clinical Nurse Specialist review
  - Growth hormone
  - Thyroxine
  - Hydrocortisone
    - Intensive emergency management teaching
      - Medic Alert bracelet
      - Ongoing with school
      - Translations into Spanish

Emergency management



Tom..

- Continue neuropsyschological and ophthalmological assessments
  - Good cognitive assessments
    - A* at GCSEs
    - A Levels in Barcelona
    - University to study mechanical engineering
- GH discontinued February 2015
- No gonadotrophin deficiency, but Testosterone low normal level
  - USA: 320ng/dl (238 – 850)
- Hydrocortisone increased 7.5 / 5 / 5mg
- Family
  - Increased support wanted - Barcelona

Continuing plan

- Stay off growth hormone
  - ? Start adult GH
- Encourage Thyroxine compliance
- Observe for evolving gonadotrophin deficiency
- Continue annual 24 hour cortisol profiles
  - ? Increase hydrocortisone to 10 / 5/ 5
- Transition – now nearly 19years old

Discussion

- What is the adult endocrine nursing approach with a ‘child’ such as Tom coming to your clinic?

Tom today

Conclusion

- Differing reasons why children may be GHD
- Very different patient journeys
- Food for thought at transition