BRAIN TUMOURS AND GROWTH

Dr. Hoong-Wei Gan, MSc, PhD, MRCPCH

Consultant Paediatric Endocrinologist | Lead for Neuroendocrine Effects of Brain Tumour Service

Great Ormond Street Hospital for Children NHS Foundation Trust, UK

Hoong.Gan.11@ucl.Ac.Uk

@Hwganendodoc

NHS Great Ormond Street Hospital for Children NHS Foundation Trust

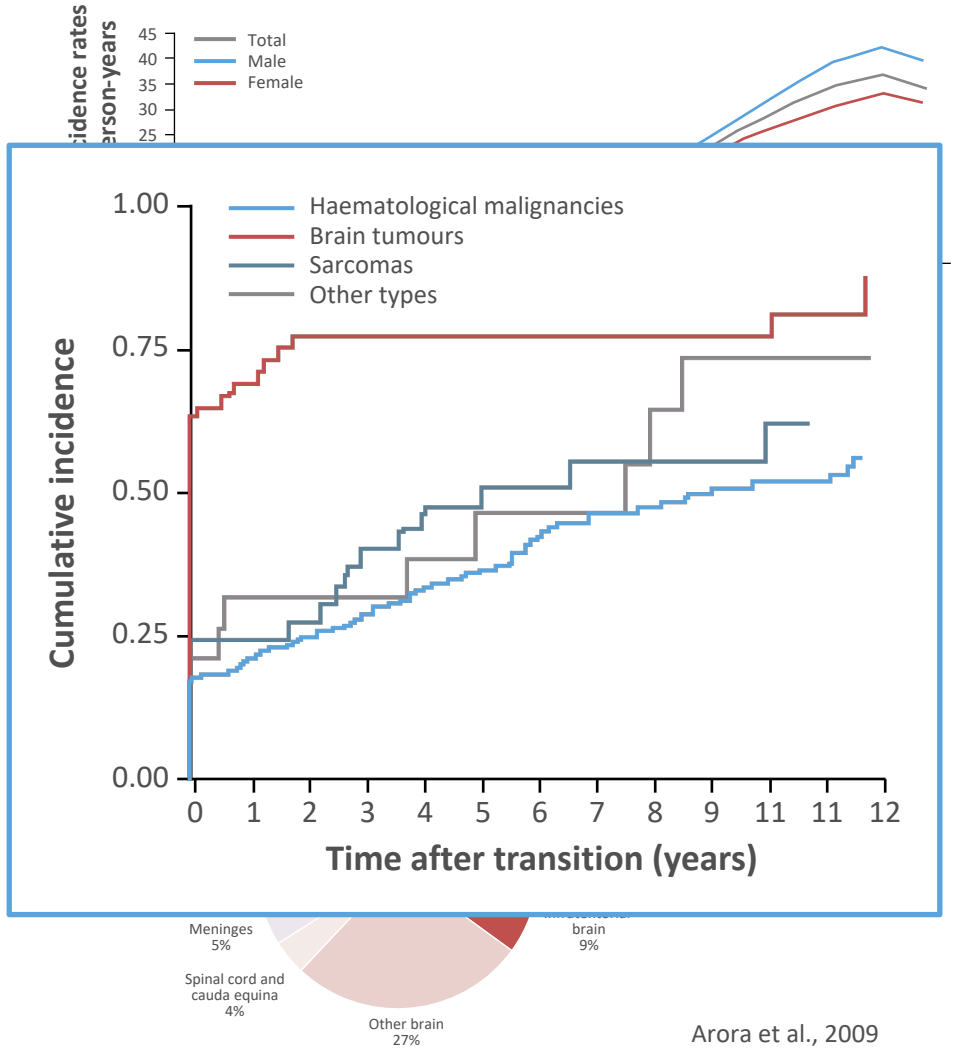
UCL GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

DISCLOSURES

- Deputy Chair of the UK National Paediatric Craniopharyngioma Group
- Speaker fees – Ipsen Ltd. , Novo Nordisk Ltd.
- Travel & hospitality – Novo Nordisk Ltd.

PAEDIATRIC BRAIN TUMOURS

- Commonest solid tumour in childhood[1,2]
  - 25% of all childhood cancer, after leukaemia (30%)
  - 43% astrocytomas
- Commonest (32%) cause of cancer-related death in childhood[1–3]
  - 5-year survival 41% → 75%
- >60% of childhood cancer survivors have 1+ chronic morbidity[4,5]
  - 28% severe/life-threatening
  - >50% with endocrinopathies

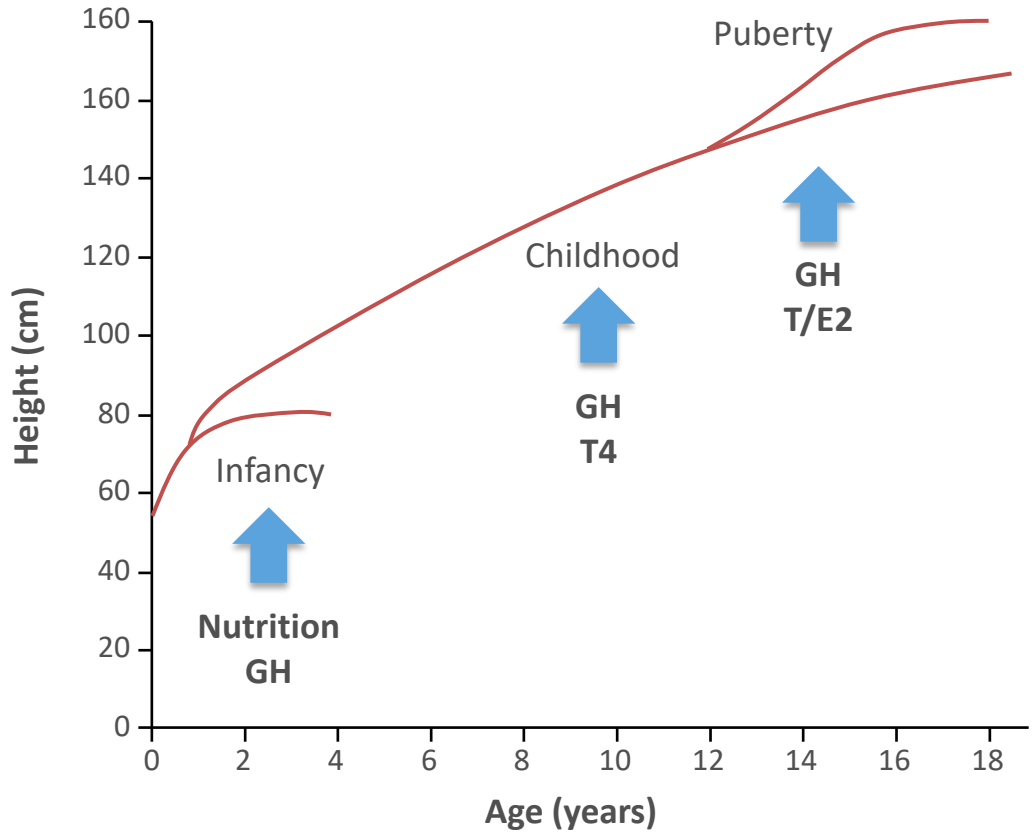


Arora et al., 2009

CNS, central nervous system

1. Wilne S, et al., Eur J Pediatr. 2012;171(1):87-93; 2. NCRAS. http://www.ncin.org.uk; 3. Cancer Research UK, 2010: info.cancerresearchuk.org/cancerstats; 4. Brignardello E, et al. Eur J Endocrinol. 2013;168(3):465-72; 5. Oeffinger K, et al. N Engl J Med. 2006;355(15):1572-82

NORMAL GROWTH IN CHILDHOOD AND ADOLESCENCE – A RECAP



The infancy–childhood–puberty (ICP) model of growth for boys.
Data shown are the mean height values (cm) for age (adapted from Kalberg et al.)

- Karlberg infant-childhood-puberty (ICP) model
  - Infancy 45% of growth
  - Childhood 45% of growth
  - Puberty 10% of growth
- Proportions
  - ~2/3 of spinal growth is in puberty

GH, growth hormone; ICP, infant-childhood-puberty; T4, thyroxine; T/E2, testosterone/oestradiol

Karlberg J, et al. Acta Paediatr Scand Suppl. 1989;350:70-94

CASE 1 – CRANIOPHARYNGIOMA

CASE 1

- 1-2 years of growth failure and visual impairment at age 7 years
- At diagnosis:

	Value	NR
IGF-1 ng/ml	**<25**	**64-345**
LH IU/l	**<0.1**	**0.7-1.3**
FSH IU/l	**<0.1**	**0.2-3.1**
T nmol/l	<0.69	
fT4 pmol/l	**9.6**	**10.8-19.0**
TSH mU/l	**1.3**	**<6.0**
0900-h cortisol nmol/l	236	>200
0900-h ACTH ng/l	16.5	10-50
PRL mU/l	379	47-438

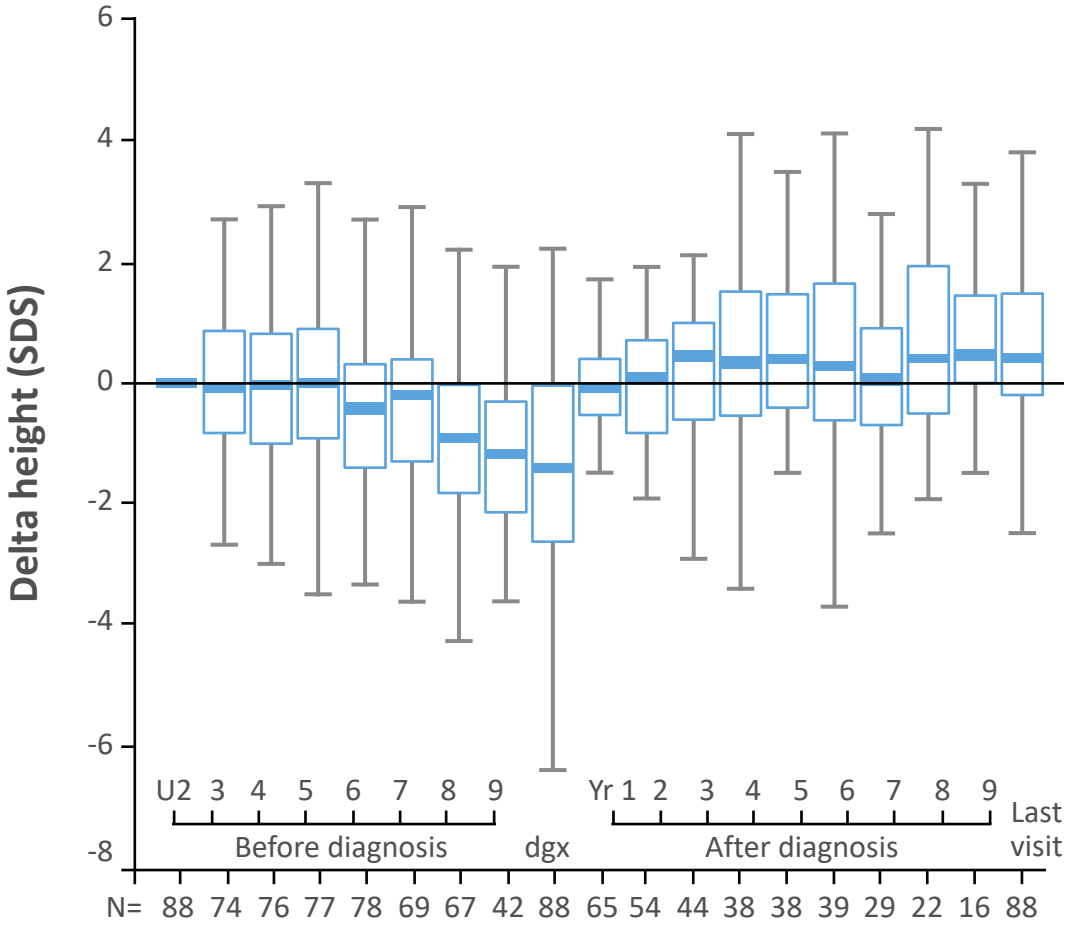
ACTH, adrenocorticotropic hormone; FSH, follicle-stimulating hormone; fT4, free thyroxine; IGF-1, insulin-like growth factor 1; LH, luteinizing hormone; NR, normal range; PRL, prolactin; T, testosterone; TSH, thyroid-stimulating hormone

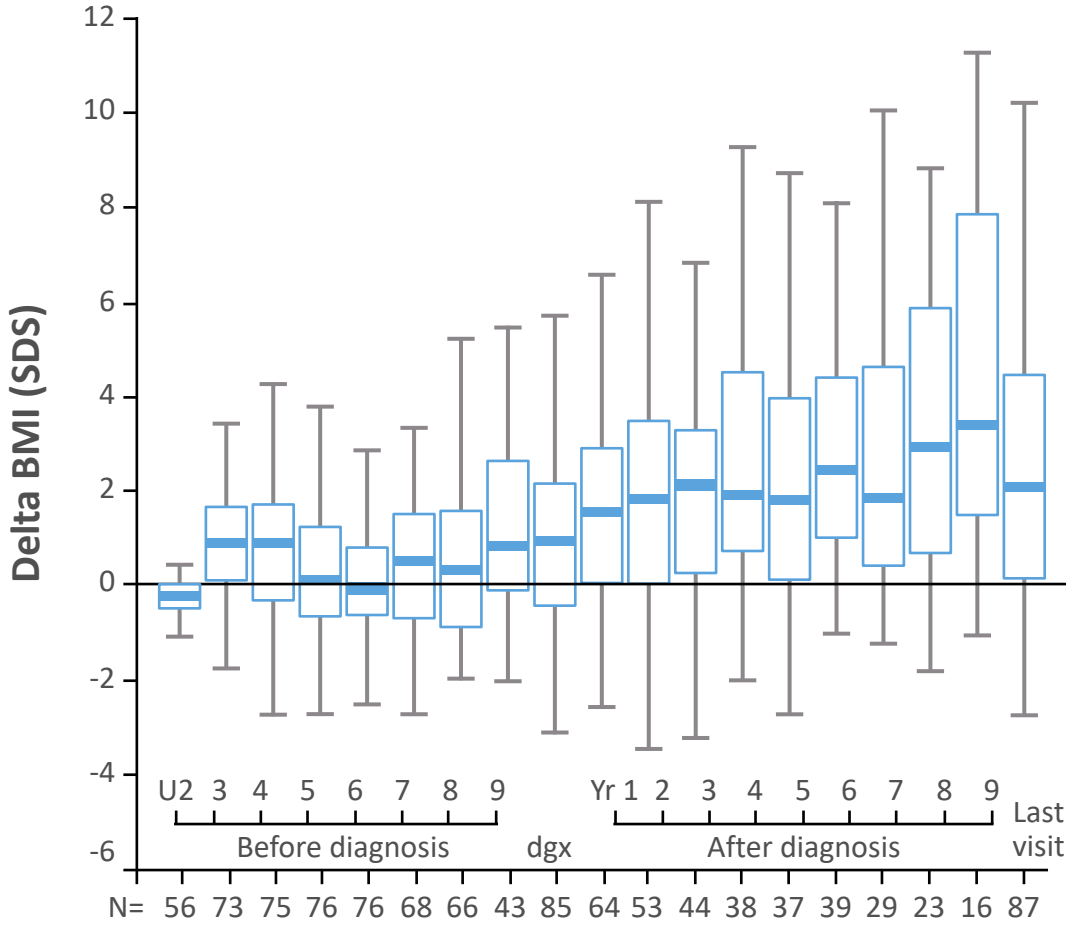
ENDOCRINOPATHIES AT DIAGNOSIS OF CRANIOPHARYNGIOMA

Presenting feature	Median frequency (range)
Headaches (22, 24, 25, 28-30)	64% (51-78)
Reduction in visual acuity (22, 24-26, 28-31)	51% (23-73)
Restriction in visual fields (22, 24-26, 28-30)	46% (17-61)
Nausea/vomiting (22, 24, 25, 28-30)	43% (31-61)
Linear growth failure/short stature (22, 24-26, 28, 29, 32, 37, 38)	33% (14-86)
Papilloedema (29)	29%
Lethargy/somnolence (22, 24, 32)	21% (5-22)
Cranial nerve palsy (22, 24, 29)	20% (11-27)
Weight loss (22, 24, 26, 32)	17% (5-31)
Polyuria/polydipsia (22, 24, 26, 28, 29, 32)	16% (9-28)
Pubertal delay/arrest (22, 24, 28, 29, 32)	10% (5-24)
Cognitive impairment (24)	10%
Blindness (24, 26)	9% (3-15)
Ataxia (4, 22, 29)	8% (7-18)
Hemiparesis (4, 22, 26, 29)	8% (7-12)
Decreased consciousness (24, 29)	8% (5-10)
Hyperphagia/weight gain (22, 24, 26, 32)	6% (5-30)
Seizures (22, 26, 29)	5% (5-6)
Optic atrophy (24)	5%
Behaviour change/psychiatric symptoms (22, 24, 26)	4% (3-10)
Gynaecomastia/galactorrhoea (22)	4%
Cold intolerance (22, 24)	3% (0-5)
Precocious puberty (26, 28, 29, 32)	2% (0-3)
Sleep/wake cycle disturbance (22)	2%

Gan H-W, et al. CCLG 2021. UK National Paediatric Craniopharyngioma Guideline

GROWTH ABNORMALITIES IN CRANIOPHARYNGIOMA





BMI, body mass index; dgx, diagnosis; SDS, standard deviation score; U, standardised age

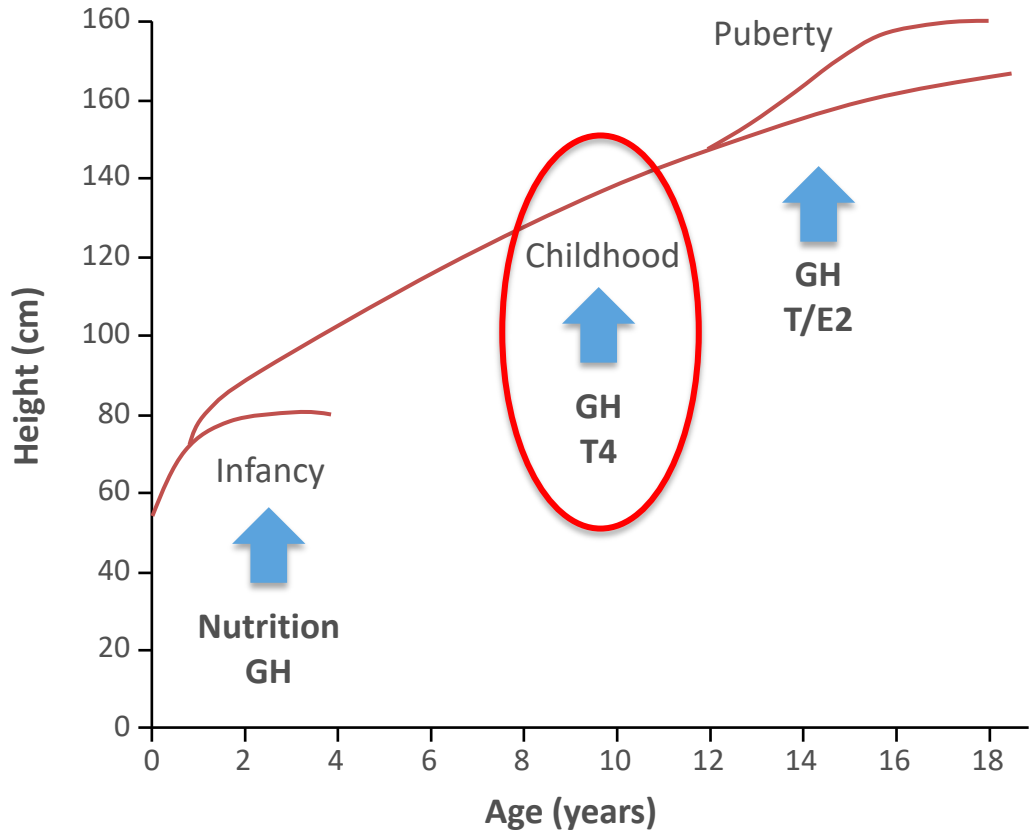
Müller H, et al. J Clin Endocrinol Metab. 2004;89(7):3298-305

CASE 1

Diagnosis	• Cyst aspiration • Reservoir insertion • **GH deficiency confirmed (peak 0.5 ng/ml to glucagon)**
3 months	• Progression
4 months	• Debulking • **Postoperative ACTH deficiency + permanent central DI**
5 months	• Proton beam therapy

ACTH, adrenocorticotropic hormone; DI, diabetes insipidus; GH, growth hormone

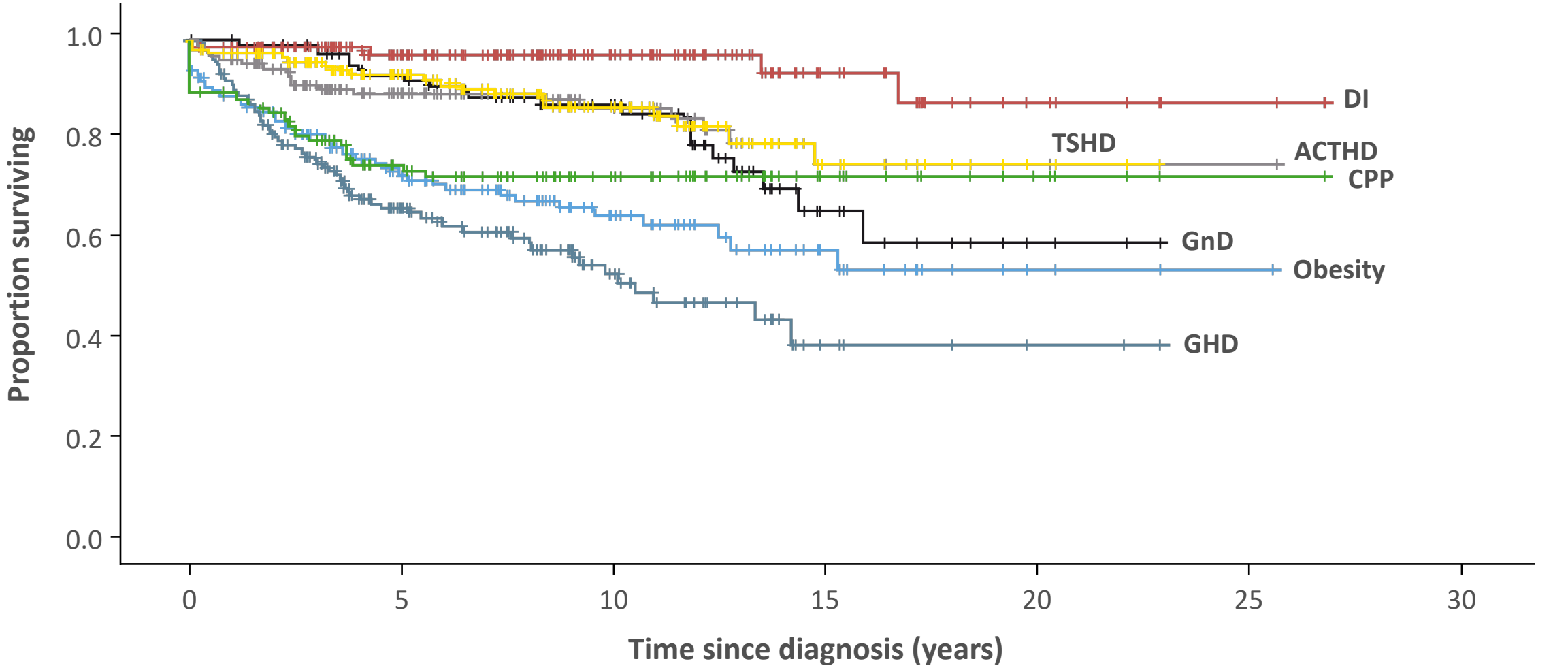
CASE 1



The infancy–childhood–puberty (ICP) model of growth for boys.
Data shown are the mean height values (cm) for age (adapted from Kalberg et al.)

GH, growth hormone; ICP, infant-childhood-puberty; T4, thyroxine; T/E2, testosterone/oestradiol

PROGRESSION OF ENDOCRINE DEFICITS

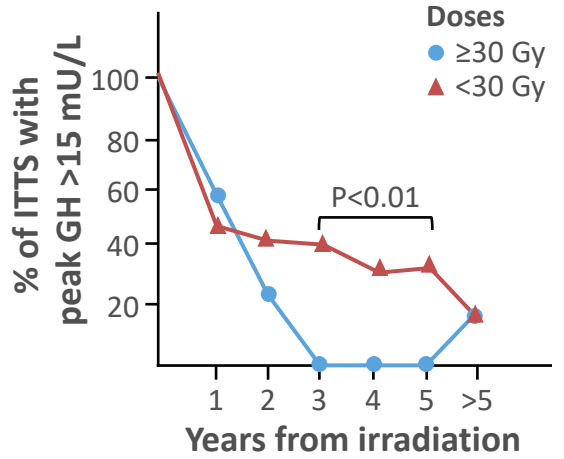


ACTHD, adrenocorticotropic hormone deficiency; CPP, central precocious puberty; DI, diabetes insipidus; GHD, growth hormone deficiency; GnD, gonadotropin deficiency; TSHD, thyroid-stimulating hormone deficiency

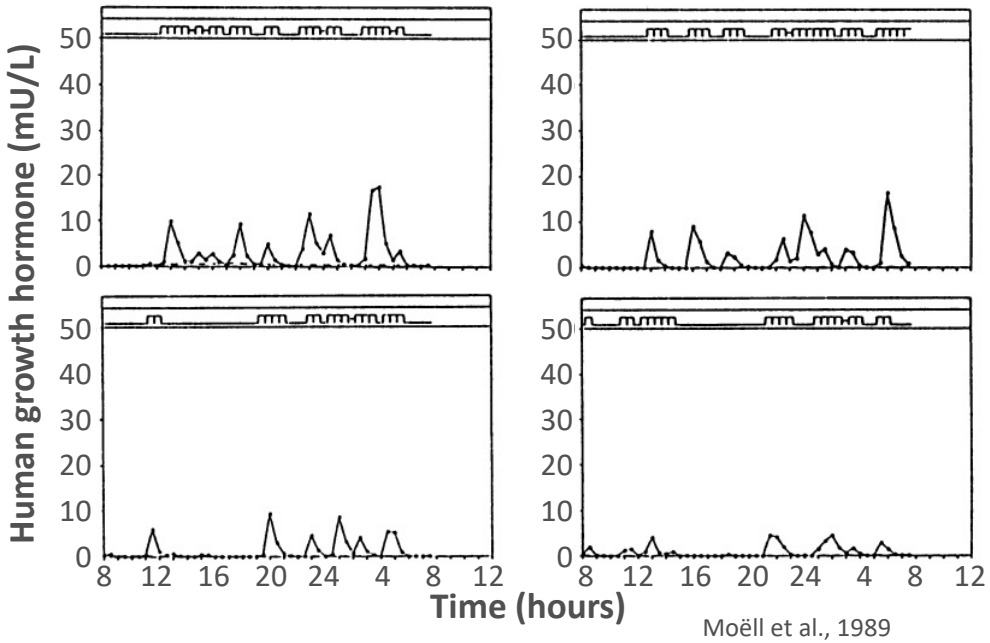
Gan, H-W, et al. J Clin Endocrinol Metab. 2015;100(10):3787-99

GH DEFICIENCY IN BRAIN TUMOURS

- Commonest endocrinopathy[1]
- Tumour (suprasellar) or treatment (surgery, radiotherapy)-related
- **Beware concurrent precocious puberty**
- Post-radiotherapy GHD:
  - **IGF-1/IGFBP-3 NOT a reliable marker**[2–4]
    - IGF-1 sensitivity 31.9-66%, specificity 77-100%
    - IGFBP-3 sensitivity 20%
  - **Speed of onset is dose-dependent**[5]
    - Highest risk with pituitary doses ≥30 Gy[5]
    - BUT any radiation is a risk – lower doses may cause abnormal pulsatility/"neurosecretory dysfunction"[6]
    - More evident in puberty[7]
  - **Do not use GHRH stimulation to diagnose**[78]



Clayton et al., 1991



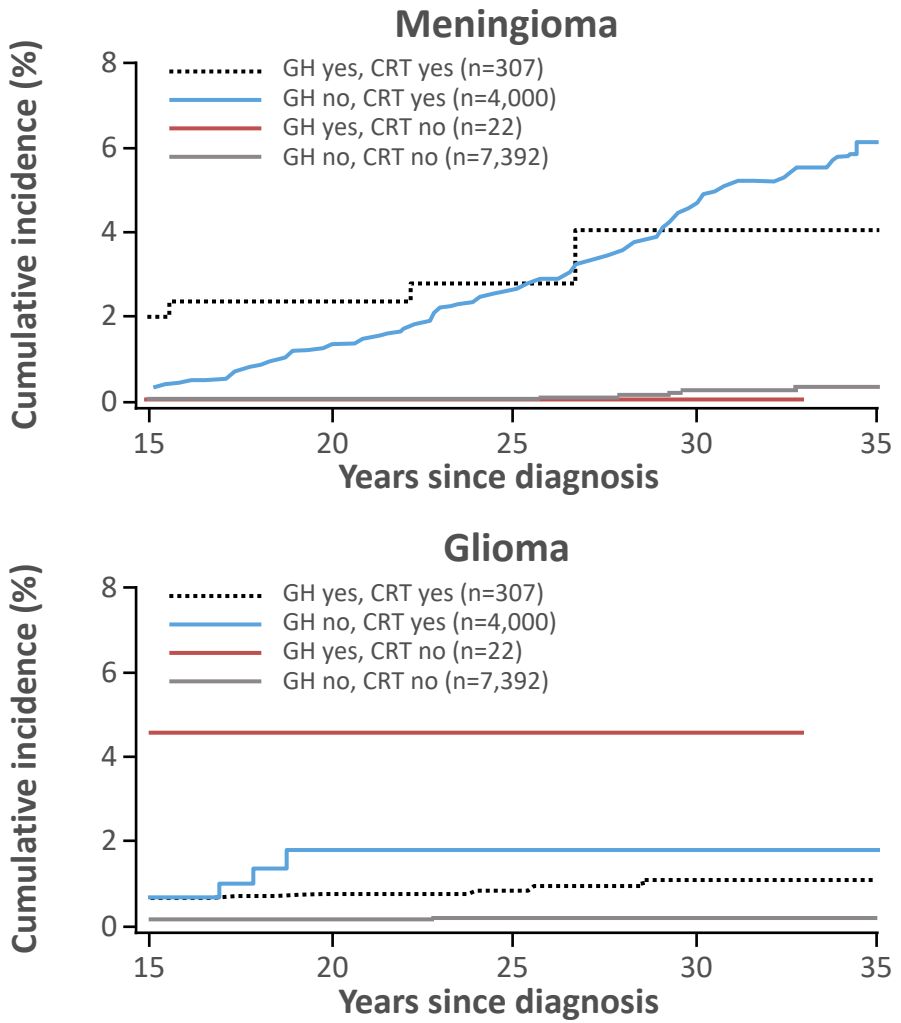
Moëll et al., 1989

GH, growth hormone; GHD, GH deficiency; GHRH, GH-releasing hormone; IGF-1, insulin-like growth factor 1; IGFBP-3, insulin-like growth factor binding protein 3; ITT, insulin tolerance test

1. Vatner R, et al. J Clin Oncol. 2018;36(28):2854-62; 2. Sfeir JG, et al. J Clin Endocrinol Metab. 2018;103(8):2785-93; 3. Cattoni A, et al. Horm Res Paediatr. 2018;90(5):314-25; 4. Sklar C et al. 1993;129(6):511-5; 5. Clayton P, et al. J Pediatr. 1991;118(2):226-8; 6. Ryalls M, et al. J Endocrinol. 1993;136(2):331-8; 7. Moëll C, et al. Arch Dis Child. 1989;64(2):252-8; 8. Sklar C, et al. J Clin Endocrinol Metab. 2018;103(8):2761-84

TREATMENT OF GH DEFICIENCY

- **No evidence that GH in replacement doses causes tumour progression** [1-3]
- **Risk of 2nd tumours?**
  - Acute lymphoblastic leukaemia – no increase risk in IGHD[4]
  - Meningiomas/gliomas – marginal RR 2.34 (0.96-5.70; p=0.06) → subsequently disproven[2,5]
  - Other cancers – SAGhE study – no dose-dependent effect, not in IGHD[6]
- **Timing – controversial**
  - Only one guidelines (LWPES 2018) suggests 1 year from EOT + disease free but NO EVIDENCE[7]
  - Craniopharyngiomas/optic pathway gliomas exceptional[7]



Patterson et al., 2014

CRT, cranial radiation therapy; EOT, end of treatment; GH, growth hormone; IGHD, isolated GH deficiency; LWPES, Lawson Wilkins Pediatric Endocrine Society; RR, relative risk

1. Gan, H-W, et al. J Clin Endocrinol Metab. 2015;100(10):3787-99; 2. Sklar C, et al. J Clin Endocrinol Metab. 2002;87(7):3136-41; 3. Swerdlow A, et al. J Clin Endocrinol Metab. 2000;85(12):4444-9;
4. Fradkin J, et al. JAMA. 1993;270(23):2829-32; 5. Patterson B, et al. J Clin Endocrinol Metab. 2014;99(6):2030-7; 6. Swerdlow A, et al. J Clin Endocrinol Metab. 2017;102(5):1661-72;
7. Sklar C, et al. J Clin Endocrinol Metab. 2018;103(8):2761-84

CASE 2 – ATYPICAL TERATOID RHABDOID TUMOUR (ATRT)

CASE 2

- Presented with spinal cord compression at age 3 years
  - Left arm → leg → neck pain

Diagnosis	• Subtotal resection: anaplastic meningioma?
1 year	• Progression • Debulking: ATRT
2 years	• Completion of chemotherapy • Vincristine/cyclophosphamide/doxorubicin/carboplatin/etoposide/idarubicin/irinotecan • Craniospinal radiotherapy

ATRT, atypical teratoid rhabdoid tumour

CASE 2

3 years

- GH insufficency (peak 4.1 ng/ml to glucagon

4 years

- Compensated primary hypothyroidism (fT4 14.8 pmol/l, TSH 6.58 mU/l)

6 years

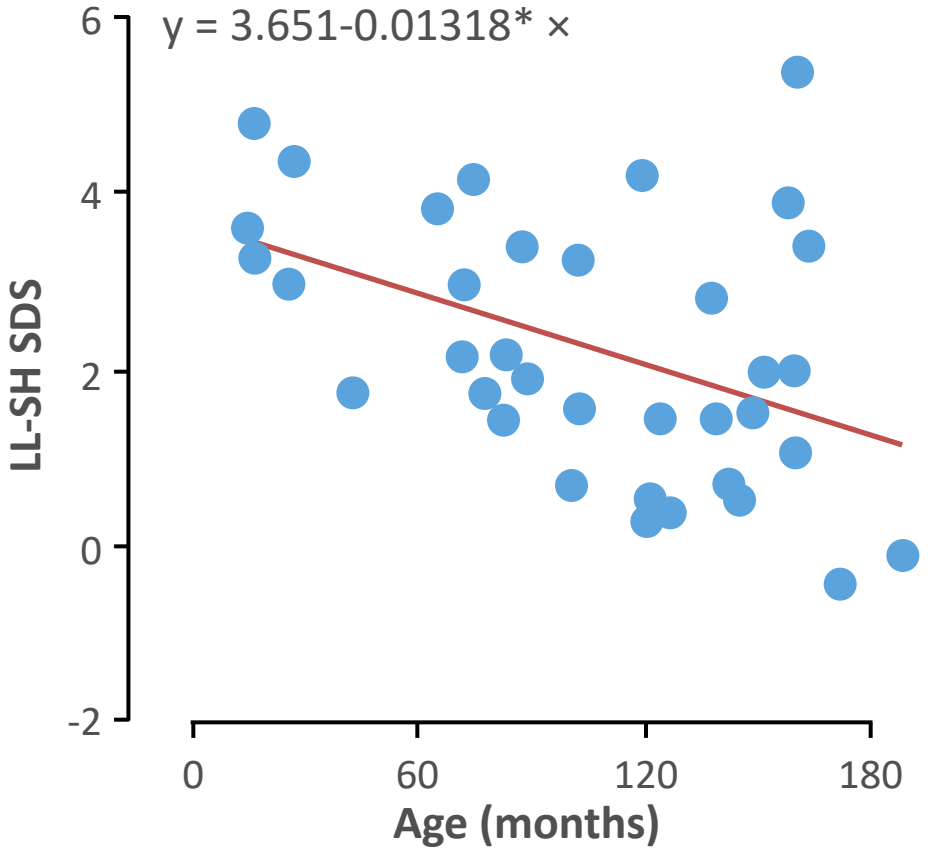
- Hypergonadotrophic hypogonadism/ premature ovarian failure (LH 8.7 IU/l, FSH 55.7 IU/l, E2 <44 pmol/l, AMH <3.0 pmol/l)

- Also doxo/idarubicin-induced cardiomyopathy, oesophageal dysmotility
- **BUT REMEMBER SPINAL IRRADIATION**

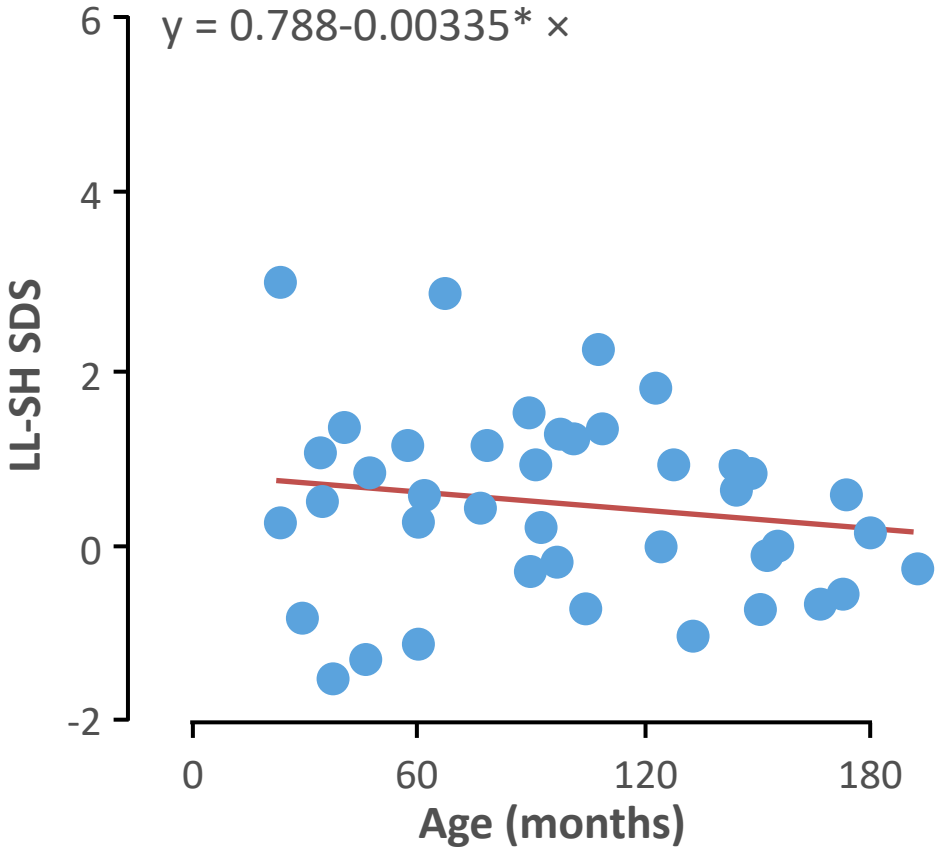
AMH, anti-Müllerian hormone; E2, oestradiol; FSH, follicle-stimulating hormone; fT4, free thyroxine; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone

EFFECT OF SPINAL IRRADIATION ON GROWTH

CRANIOSPINAL RT



CRANIAL RT



LL-SH SDS, leg length-sitting height standard deviation score; RT, radiation therapy

Shalet S, et al. Arch Dis Child. 1987;62(5):461-4

CASE 3 – SUPRASELLAR OPTIC PATHWAY ASTROCYTOMA/ LOW-GRADE GLIOMA

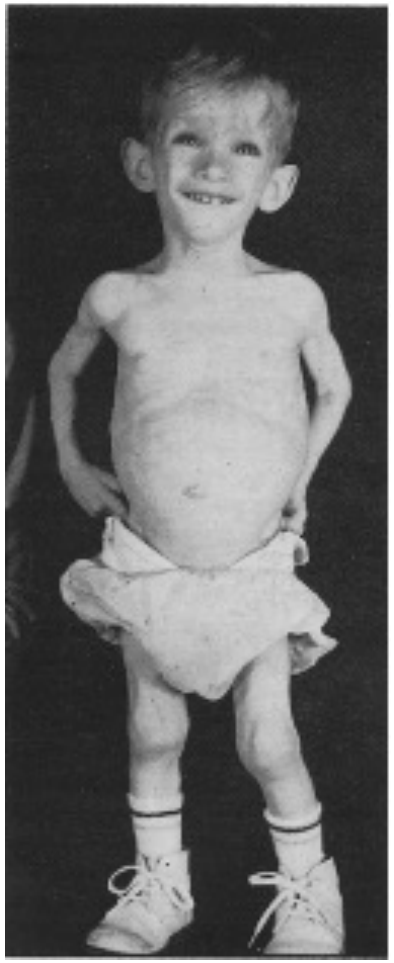
CASE 3

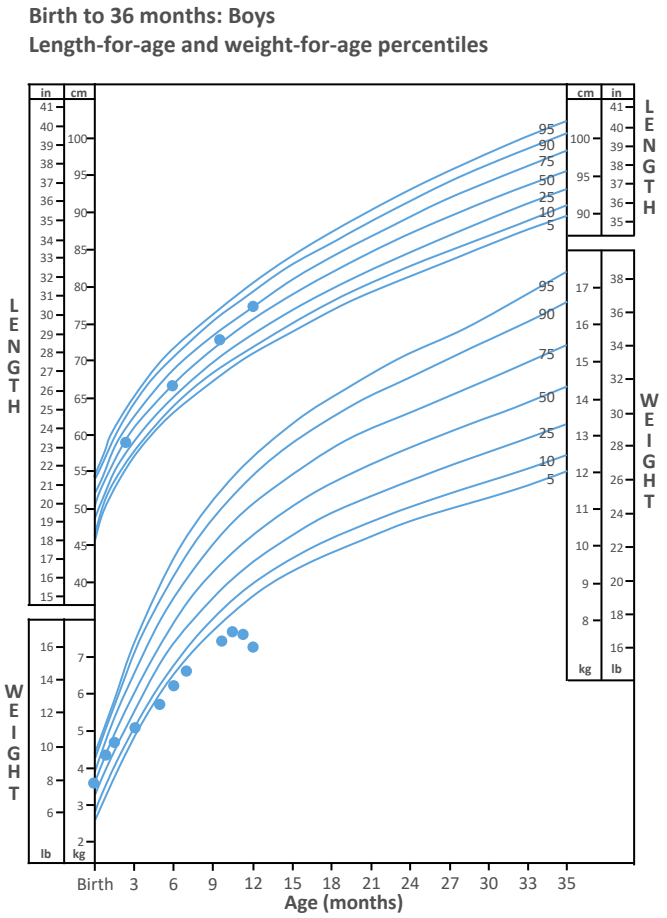
- Presented with diencephalic syndrome + hyponatraemia (SIADH/CSWS) at age 4 months
- Initial treatment carboplatin/ vincristine

CSWS, cerebral salt-wasting syndrome; SIADH, syndrome of inappropriate antidiuretic hormone

DIENCEPHALIC SYNDROME (RUSSELL SYNDROME)[1]

- Severe emaciation associated with infantile (<2 years) anterior hypothalamic tumours
- Major criteria
  - Emaciation, height acceleration, euphoria, hyperactivity
- Minor criteria
  - Pallor, hypoglycaemia, hypotension
- <5% low-grade gliomas
- Endocrinology
  - GH resistance with biochemical acromegaly
  - Precocious puberty
  - ↓leptin ↑ghrelin
  - ↑REE





Smith et al., 1965; Fleischman et al., 2005

Data compiled from multiple case reports. References available on request.

GH, growth hormone; REE, resting energy expenditure

1. Russell A. Arch Dis Child. 1951;26:270-5; 2. Smith K, et al. J Neurosurg. 1965;23(3):348-51; 3. Fleischman A, et al. Pediatrics. 2005;115(6):e742-8

CASE 3

Diagnosis	• Biopsy – hydrocortisone started post-dexamethasone • Carboplatin/vincristine • **2 years central precocious puberty (Tanner stage 2, 4 ml testes)**
3 years	• Progression → temozolomide • Progression → thioguanine/procarbazine/CCNU/vincristine
4 years	• **Central hypothyroidism**
5 years	• **GH deficiency (peak 5.5 ng/ml to glucagon stimulation)**

CCNU, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; GH, growth hormone

CASE 3

8.5 years	• Progression → vinblastine • **9 years leuprorelin stopped**
10.5 years	• Progression → cyst drainage + biopsy • **11 years pubertal arrest (no further progress in puberty)**
13 years	• Progression → radiotherapy
14 years	• Tanner stage 5 testes 4 ml • LH 4.9 IU/l, FSH 22.7 IU/l, testosterone 1.54 nmol/l, low-normal inhibin B

FSH, follicle-stimulating hormone; LH, luteinizing hormone

CASE 3

CENTRAL PRECOCIOUS PUBERTY VS. HYPOGONADOTROPHIC HYPOGONADISM

- Long-term retrospective analysis of 166 children with pediatric optic gliomas
  - 26% CPP at last follow-up
    - Risk factor hypothalamic involvement (HR 4.42, 95% CI: 1.97-9.92; p<0.001)
  - 20% hypogonadotrophic hypogonadism at last follow-up
    - Risk factor hypothalamic involvement (HR 5.09, 95% CI: 1.95-13.31; p=0.001)
    - Risk factor radiotherapy (HR 3.27, 95% CI: 1.35-7.94; p=0.009)
  - HOWEVER
    - 37.5% CPP vs 14.6% non-CPP → hypogonadotrophic hypogonadism (p=0.048)
    - 50.0% hypogonadotrophic hypogonadism vs. 19.6% non-hypogonadotrophic hypogonadism had previous CPP (p=0.02)
- **Therefore beware pubertal arrest following cessation of GnRH analogues**
- **Beware combined hypo/hypergonadotrophic hypogonadism with concurrent chemotherapy**

CI, confidence interval; CPP, central precocious puberty; GnRH, gonadotrophin-releasing hormone; HR, hazard ratio

Gan, H-W, et al. J Clin Endocrinol Metab. 2015;100(10):3787-99

CASE 4 – BIFOCAL GERMINOMA

CASE 4

8 years old

- 2 years polyuria/polydipsia + vomiting
- Panhypopituitarism + central DI + obese at diagnosis

6 months

- Cisplatin/etoposide/ifosfamide chemotherapy
- Whole ventricular radiotherapy

1 year

- Suspected insulin insensitivity (peak insulin 130 mU/l to OGTT)

DI, diabetes insipidus; OGTT, oral glucose tolerance test

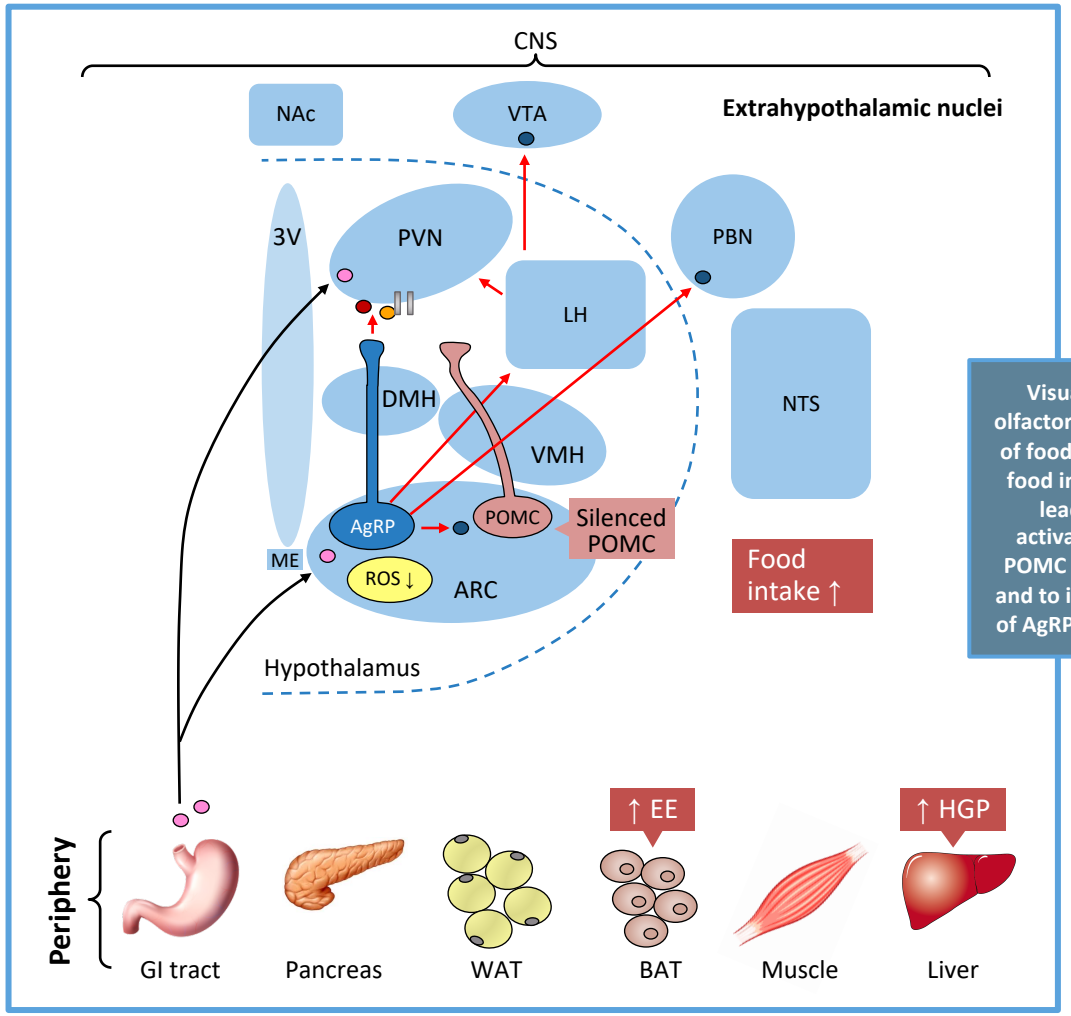
CASE 4

HYPOTHALAMIC OBESITY

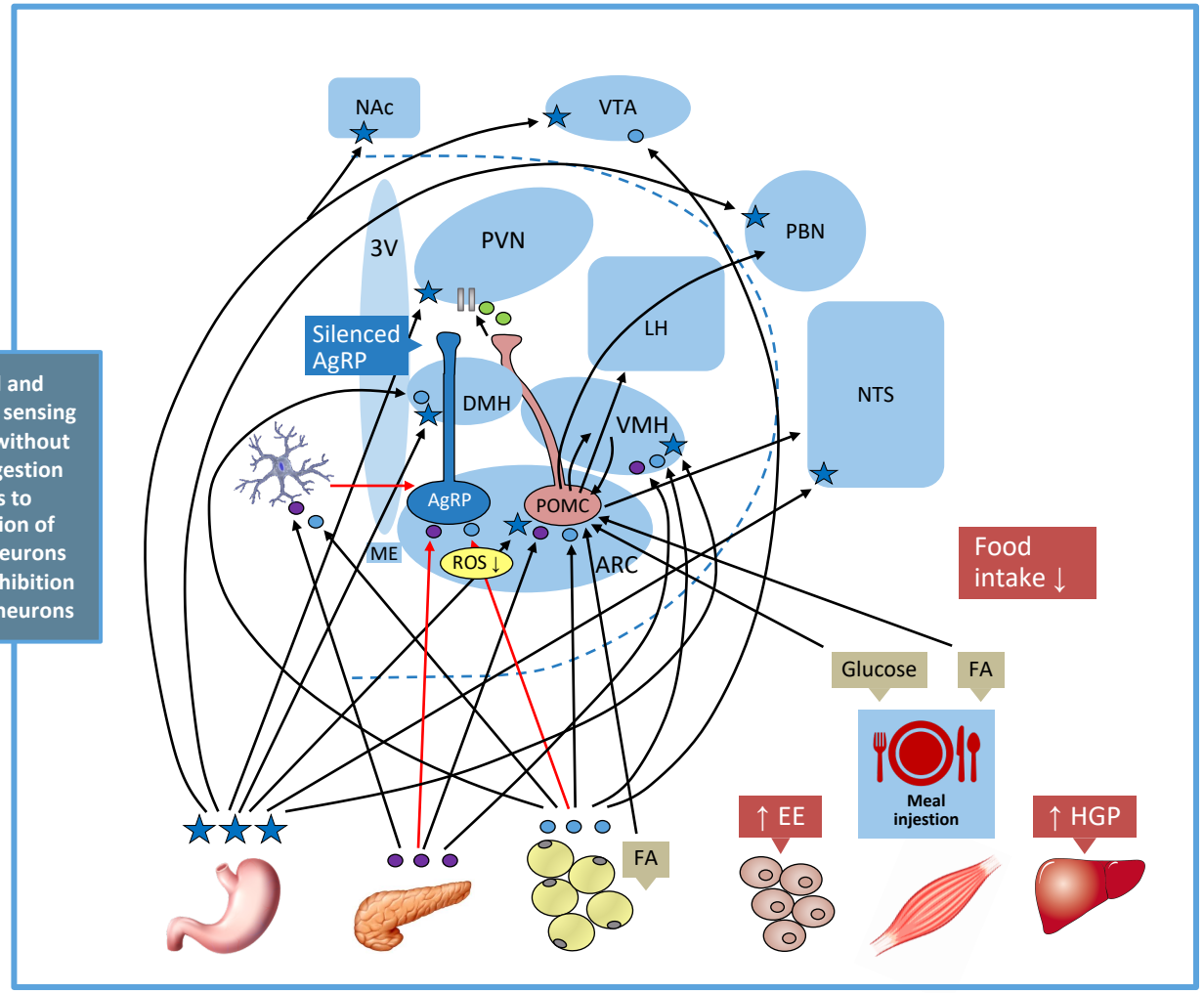
Diagnosis	Incidence (per million)	5-year survival, %	Obese, %	Estimated no. obese (per million)
Low-grade glioma	7.0	95%	53%[1]	3.5
Craniopharyngioma	1.4	97%	77%[2]	1.0
Hypothalamic harmatoma	1.0	~100%?	59% (adults)	0.6
Germinoma	0.5	92%	14%	0.06
Pituitary adenoma	0.1	100%	39%	0.04
Septo-optic dysplasia	100	~100%?	40%	50?

1. Armstrong G, et al. Neuro Oncol. 2011;13(2):223-34; 2. Pinto G, et al. Horm Res. 2000;53(4):163-9; 3. Odagiri K et al., Int J Radiat Oncol Biol Phys. 2012;84(3):632-8; 4. Steele CA et al., Eur J Endocrinol. 2010;163(4):515-22.

HYPOTHALAMIC OBESITY



Visual and olfactory sensing of food without food ingestion leads to activation of POMC neurons and to inhibition of AgRP neurons



3V, third ventricle; AgRP, agouti-related peptide; ARC, arcuate nucleus; BAT, brown adipose tissue; CNS, central nervous system; DMH, dorsomedial hypothalamus; EE, energy expenditure; FA, fatty acids; GI, gastrointestinal; HGP, hepatic glucose production; LH, lateral hypothalamus; ME, median eminence; NAc, nucleus accumbens; NTS, nucleus of the solitary tract; PBN, parabrachial nucleus; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; ROS, reactive oxygen species; VMH, ventromedial hypothalamus; VTA, ventral tegmental area; WAT, white adipose tissue

Timper K, et al. Dis Model Mech. 2017;10(6):679-89

HYPOTHALAMIC OBESITY

Study	Treatment	ΔBMI	Maximum duration of effect
Smith et al. 1983	Pancreatic vagotomy	-26 kg	6 years
Mason et al. 2002	Dextroamphetamine	-0.6 SDS	24 months
Fernandes et al. 2002	Triiodothyronine	-1.2 SDS	27 months
Lustig et al. 2003	Octreotide	-0.2 kg/m^2	6 months
Danielsson et al. 2007	Sibutramine	-0.4 SDS	5 months
Greenway et al. 2008	Caffeine + ephedrine	-9.5%	6 years
Rakshani et al. 2010	Intensive lifestyle	0.0 SDS	41 months
Hamilton et al. 2011	Diazoxide + metformin	-0.04 SDS	6 months
Muller et al. 2011	Gastric banding	+0.4 SDS	9.1 years
Ando et al. 2014	Liraglutide	-8 kg	2 years

Table compiled from a mix of date from case studies and clinical trials. Sources available on request.
BMI, body mass index; SDS, standard deviation score.
Smith D, et al. Lancet. 1983;1(8337):1330-1; Mason P, et al. Arch Pediatr Adolesc Med. 2002;156(9):887-92; Fernandes J, et al. Metabolism. 2002;51(11):1381-3; Lustig R, et al. J Clin Endocrinol Metab. 2003;88(6):2586-92; Danielsson P, et al. J Clin Endocrinol Metab. 2007;92(11):4101-6; Greenway F, et al. Endocr Pract. 2008;14(6):697-703; Rakhshani N et al. Obesity (Silver Spring). 2010;18(9):1768-74; Hamilton J, et al. Int J Pediatr Endocrinol. 2011;2011(1):417949; Muller et al. 2011; Ando T, et al. Intern Med. 2014;53(16):1791-5

SUMMARY

GROWTH FAILURE

- Growth hormone deficiency
- (Central precocious puberty)
- Hypogonadotrophic/hypergonadotrophic hypogonadism
  - Delayed/ arrested puberty
- Central/primary hypothyroidism
- Spinal irradiation
- Glucocorticoid-induced
- Chemotherapy-induced (cytokines, growth plate arrest, vomiting, mucositis)
- Diencephalic syndrome
- Malnutrition

GROWTH EXCESS

- Central precocious puberty
- Biochemical acromegaly (suprasellar low-grade gliomas)
- Growth without growth hormone
- Hypothalamic obesity
- Hypothyroidism