18 yo Man with Learning Difficulty

Sikarin Upala, MD, MS

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Dr. Upala does not have any relevant financial relationships with any commercial interests

Learning Objectives

- Differential diagnosis of sellar/ parasellar masses/CP
- Review craniopharyngioma
  - Presenting symptoms
  - Outcome in childhood vs adult onset
  - Hormone deficits pre vs post op
  - Metabolic consequences

HPI

- VI is a 18 yo hispanic male with no prior PMX
- Good grades at school and no concerns about behavior few months prior to admission (PTA)
- 1-2 months PTA school indicates that VI has decreased attention, increased somnolence. He fails 3 out of 4 subjects. Mother notices difficulty with short term memory (*he could not recall what just happened)*. Reports him more quiet and less conversant. Decreased appetite

HPI

- Always has had soft voice, no facial hair
- Often bullied at school because he looked like a child
- Normal development in the past, no complication at birth
- His older brother had normal puberty at age 16 yrs (normal range 12-16 yrs in boys)

HPI

- 4 days PTA, VI experiences fatigue, drowsiness, nausea, vomiting, severe headaches
- At outside ED initial GCS of 13, then rapidly becomes poorly responsive requiring emergency intubation
- CT head: ventriculomegaly and suprasellar mass
- Refer to U of C for further of treatment

Other History

- Past Medical History
  - None
- Past Surgical history
  - None
- Family History
  - Father: obesity
- Allergy
  - No Known Allergies
- Social History
  - Never smoked
  - No alcohol intake
  - No recreational drugs
  - 12th grade student
- Medication
  - None

Review of Systems

- Constitutional: No fevers, night sweats, **+Decreased appetite appetite change, + weight gain, snore at night**
- HEENT: No photophobia, blurred vision, pain, hearing loss, difficulty swallowing, thirst, hoarseness
- Resp: No cough, dyspnea, increased WOB
- CV: No CP, diaphoretic, palpitation**,** DOE, orthopnea, PND, palpitations, LE edema
- GI: No abdominal pain, nausea, vomiting, diarrhea, constipation
- GU: No dysuria, urgency, polyuria, hematuria
- MSK: No myalgias, joint pain, back pain
- Neuro: No syncope, No numbness, paresthesias, seizures, tremors,
- **+headaches**, **+memory problems**
- Heme: No adenopathy or easy bruising/bleeding
- Endo: No heat or cold intolerance, dry skin, dry hair, hair loss
- Derm: No rashes, ulcers, abdominal striae, hirsutism, acne
- Psych: **+ depressed per mother**

Physical Exam (post op)

- BP: 136/95 | Pulse 64 | Temp 36.6 °C (97.9 °F) | Resp 18 | Ht 170.2 cm (5' 7") | Wt 93.2 kg (205 lb 7.5 oz) | BMI 32.18 kg/m2

- GEN: NAD, obese, female appearance
- Chest: +gynecomastia
- ABD: soft, NT, ND
- EXT: no edema
- GU: testes 7 ml both descended, penis 2 inches, tanner stage 1 (no pubic or axillaryn hair), +acanthosis nigricans
- Skin: no facial or axillary hair
- NEURO: alert, dressing with mild bleeding
- PSYCH: flat affect

Lab

Cortisol: 1.5

Urine free cortisol: 44 (4.5-45)

ACTH: 1 (<52)

IGF-1: 4.7 (10-500)

LH: 0.2

FSH: 0.8

Prolactin: 10.19 (4-15)

TSH: 1.29 (0.3-4)

FT4: 1.1 (0.9-1.7)

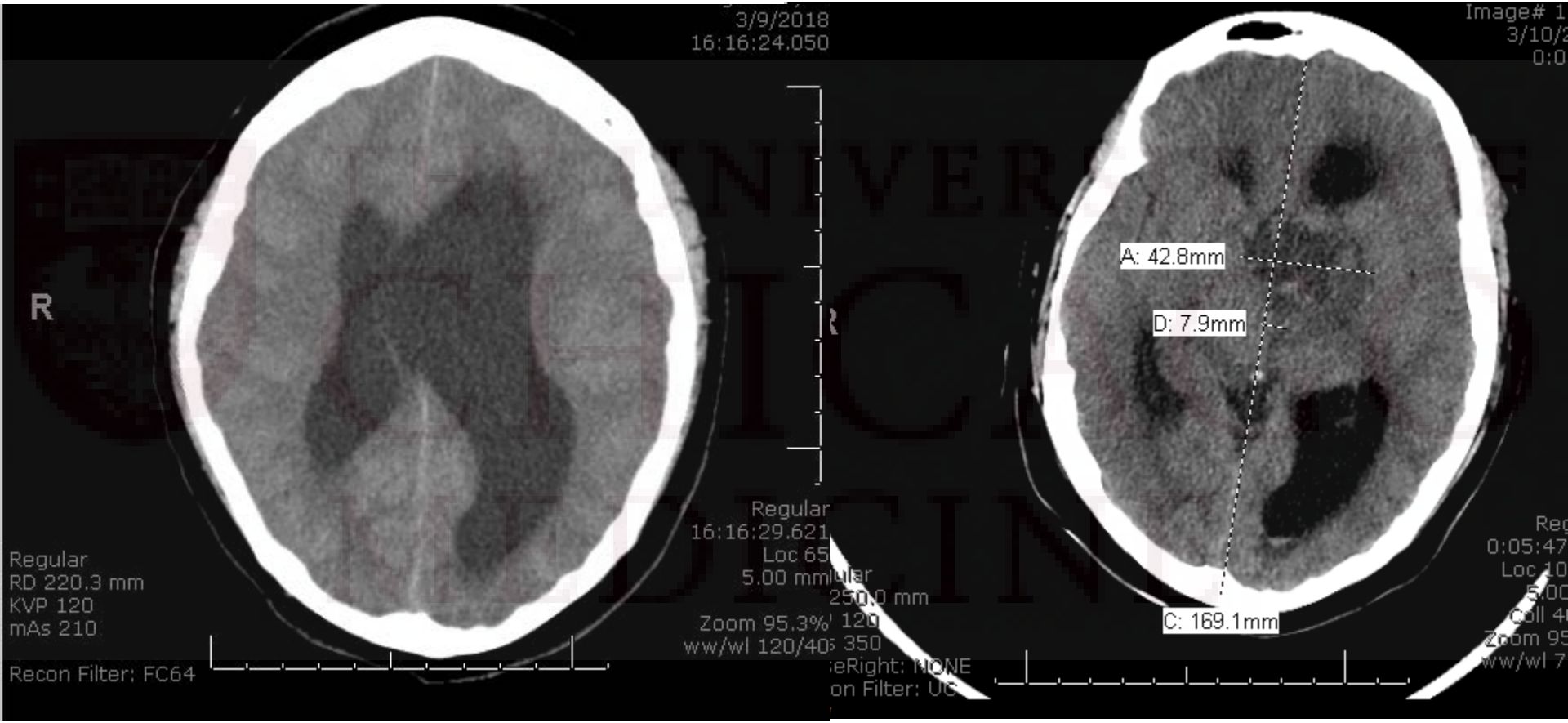
FT3: 220 (230-420)

These labs were not on steroids or levothyroxine

Imaging

- **CT Head wo 3/10/18:**
  - Suprasellar mass with ventriculomegaly, midline shift 6mm, and bilateral uncal herniation. Max diameter is approximately 4x5 cm

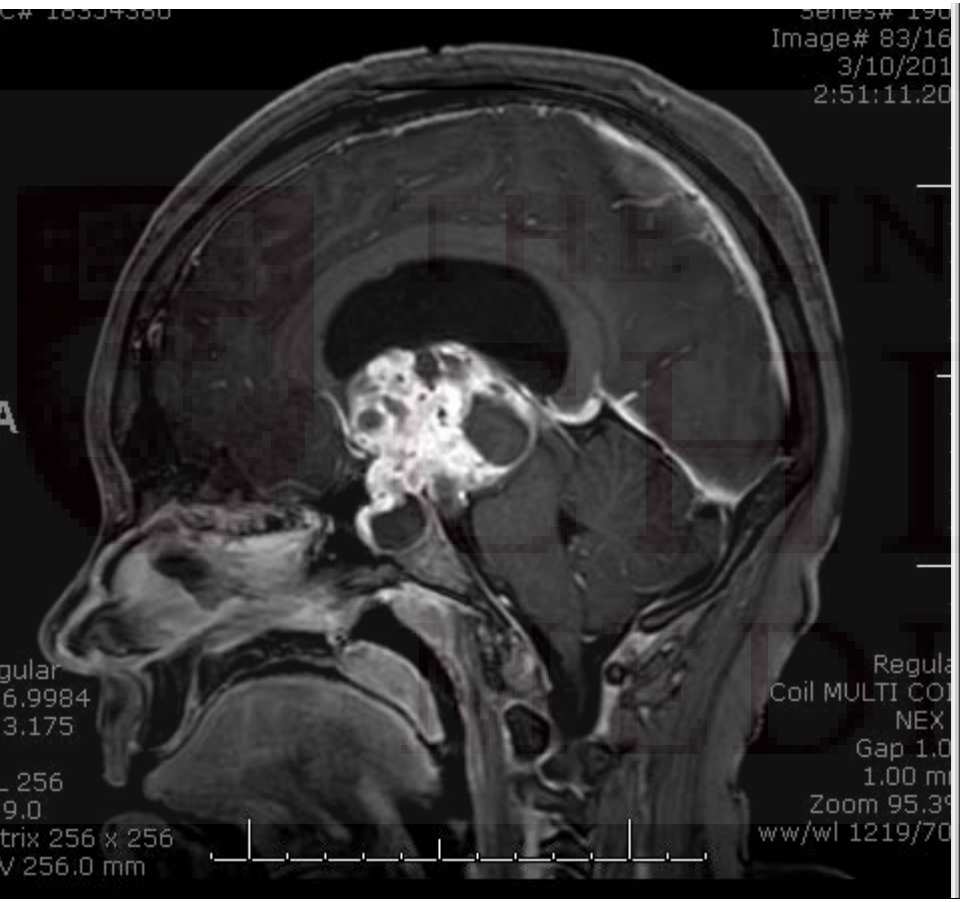
Imaging



Imaging

- **MRI brain w contrast 3/10/18:**
  - The mass overall measures **5.4 x 4.2 cm** in greatest axial dimensions, by 5.5 cm CC. The dominant cystic component along the right posterior lateral aspect of the mass measures 4.2 x 2.2 cm in greatest axial dimensions.
  - **Large predominantly suprasellar mass with sellar component which appears solid and cystic with associated susceptibility which could relate to mineralization an/or blood products, resulting in severe lateral ventricular obstructive hydrocephalus. Significant localized mass effect including upon the midbrain.** Differential diagnosis would include primarily a craniopharyngioma, hypothalamic astrocytoma, germinoma, and less likely pituitary adenoma.
  - Elevation of right greater than left optic nerve heads concerning for increased intracranial pressure.

Imaging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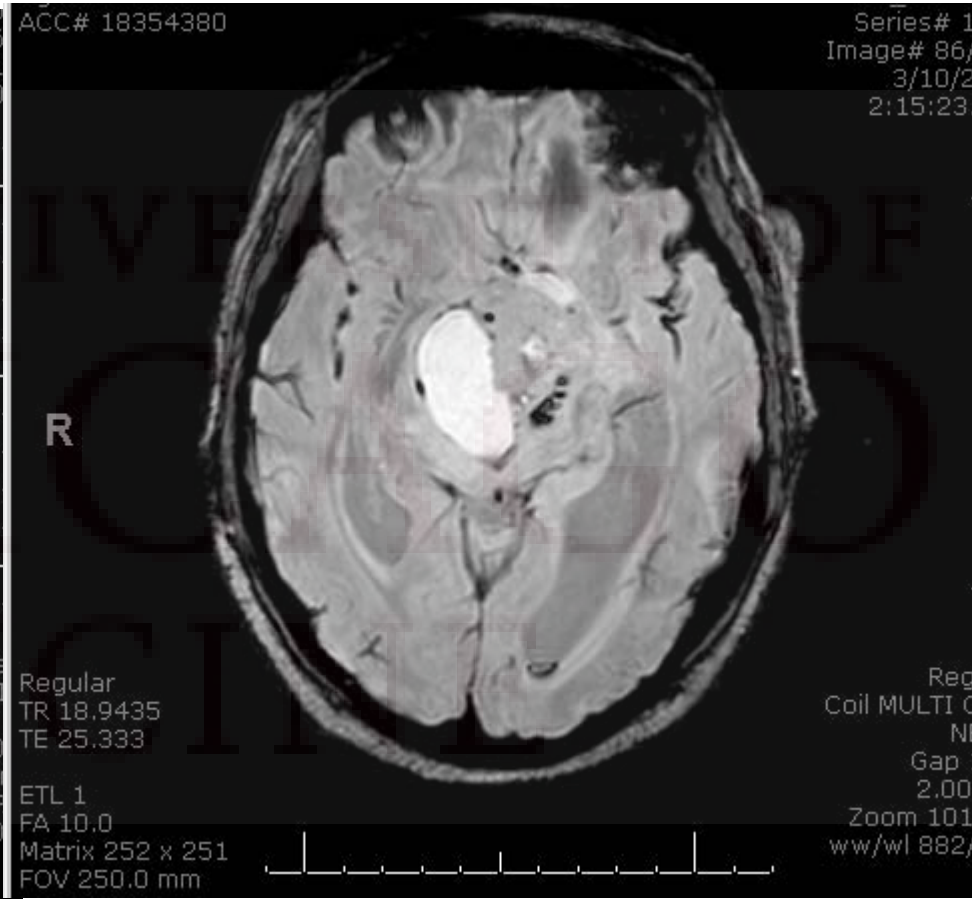
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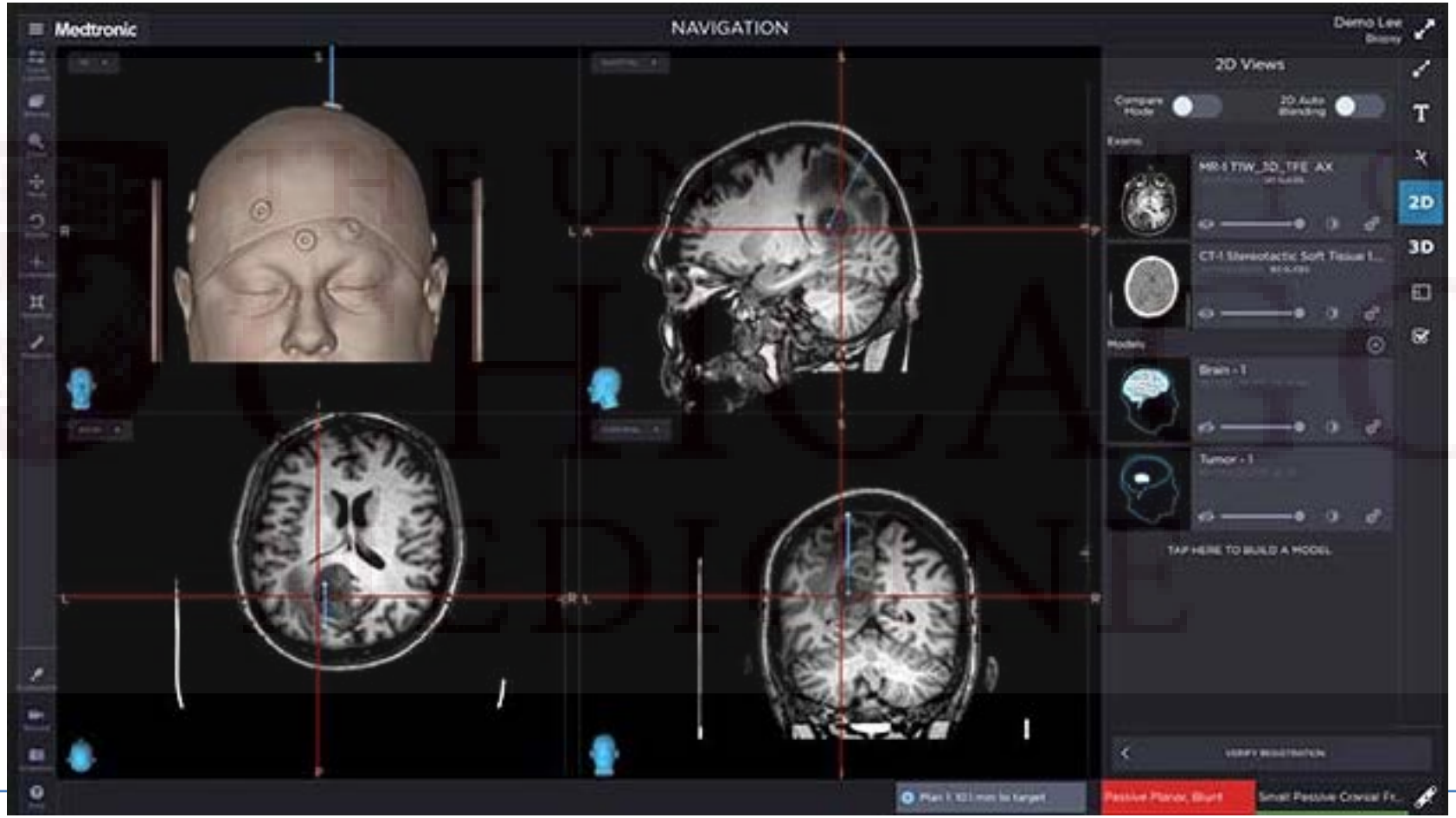
Surgery

- Medtronic STEALTH guided right craniotomy for interhemispheric approach to resection of craniopharyngioma
- Intraoperative ultrasonography
- Microneurosurgery with Leica
- Interventricular septostomy and third ventriculocisternostomy
- Harvest of pericranial graft for duroplasty 2cm

Surgery



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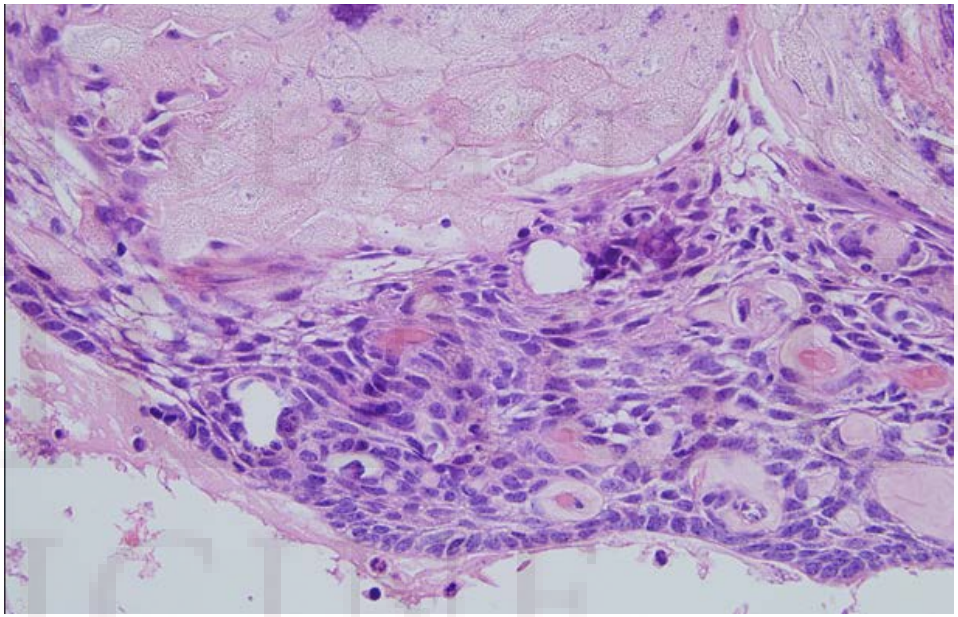
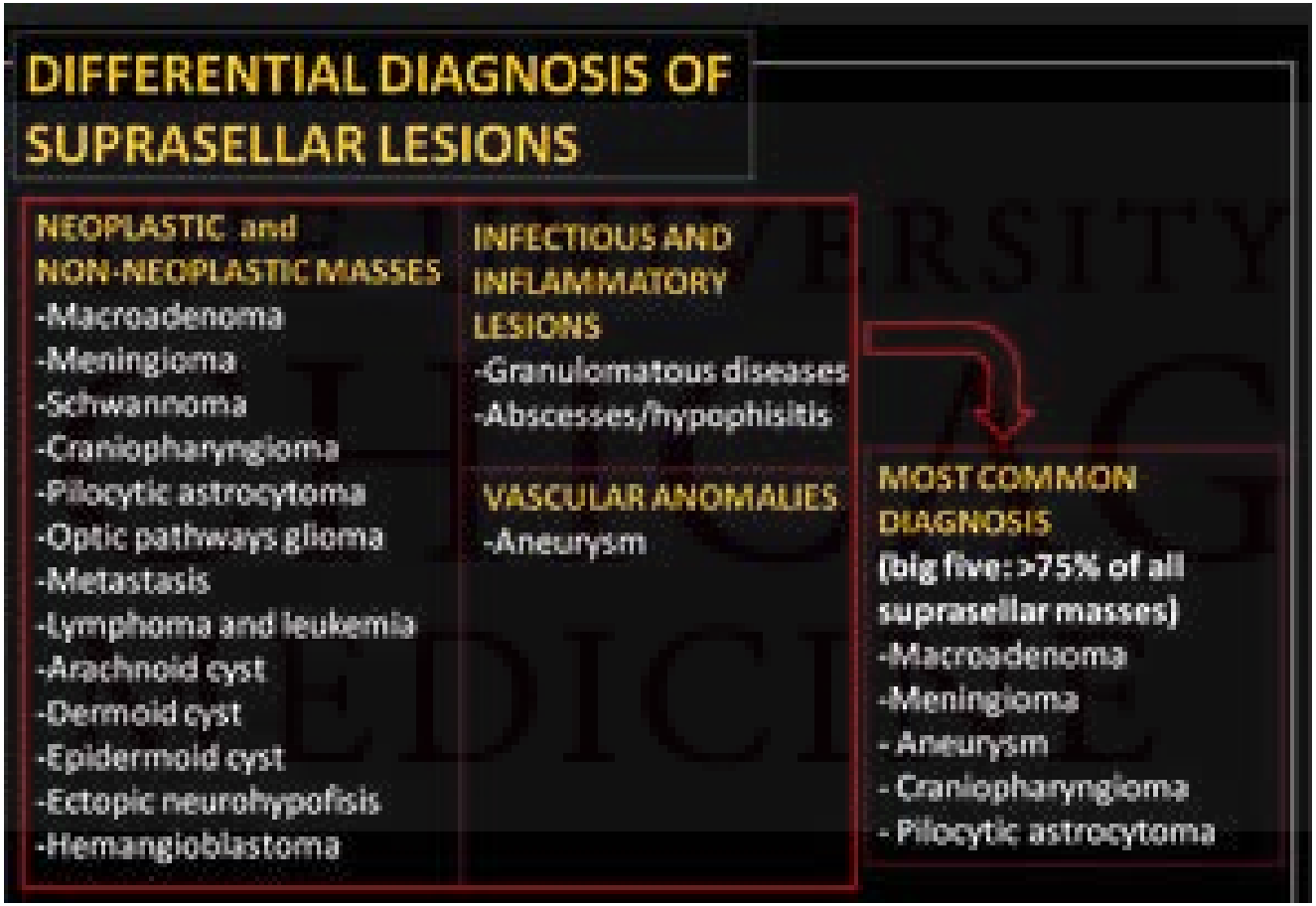
Pathology Report

- Final pathology diagnosis
- Adamantinomatous craniopharyngioma with abundant piloid gliosis
- 5.0 x 4.4 x 0.8 cm aggregate of irregular pink-gray tissue fragments, without obvious hemorrhage or focal heterogeneous areas



DDX Sellar Mass



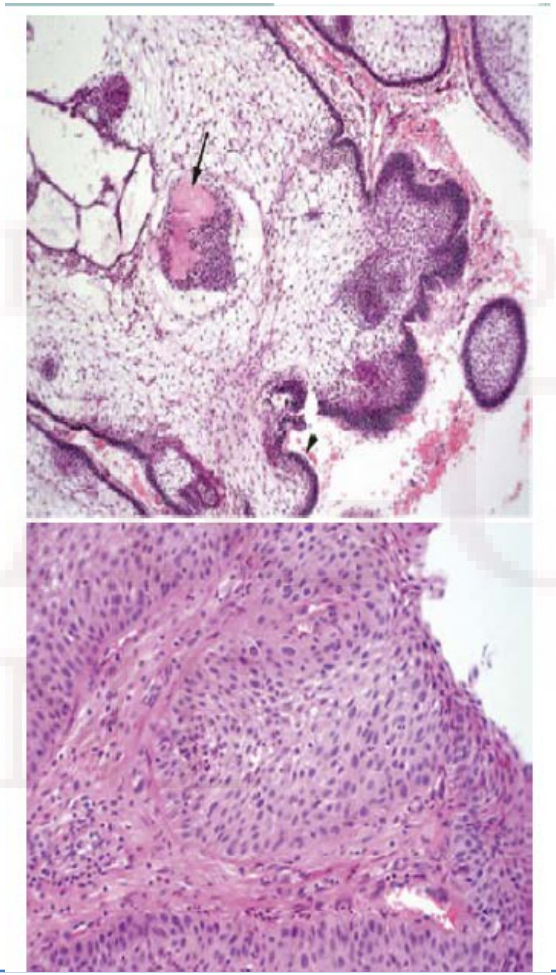
Craniopharyngioma

- Epidemiology
  - 350 new cases each year,
  - 1 to 3% of all brain tumors
  - 5.6 to 15% of intracranial tumors in children
- Bimodal Presentation
  - Children 55% Adults 45% (5-14 years, 55-65 years)
- No differences by gender
- No definite genetic relationship
  - US incidence black > white
- Recurrence reported in 25-70% patients

Merchant et al. 2013

Craniopharyngioma

- Two main histological subtypes:
  - ▫ Adamantinomatous
  - – Predominantly children and adolescents
  - – Cystic or solid components +/- calcifications
  - ▫ Papillary
  - – Adults
  - – Resembles oropharyngeal mucosa
  - – Less infiltration of adjacent brain tissue



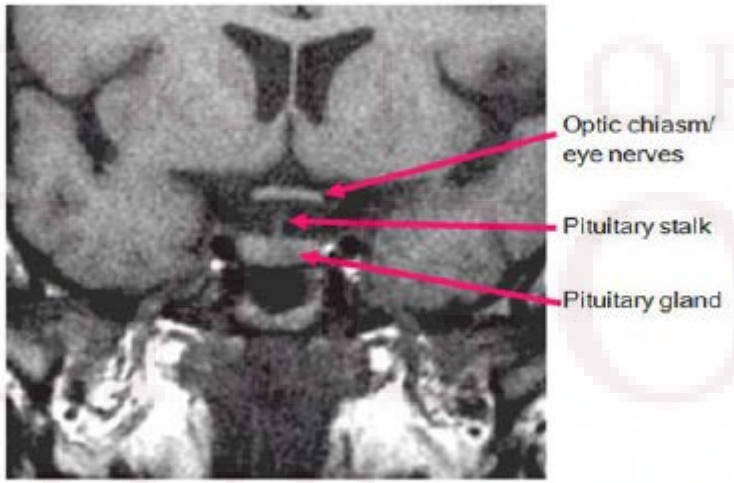
Endocrinol Metab Clin N Am 37 (2008) 173–193

Clinical Questions

- Delay puberty as a presenting symptom of craniopharyngioma?

Clinical Presentation

- Symptoms manifest due to mass effects to various brain structures
- Neurologic
- Brain parenchyma
  - cognitive deficits
- Visual optic pathways
- Visual disturbances
- Ventricular system
  - Headaches, nausea/vomiting, hydrocephalus
- Hypopituitarism/hormonal deficit



Hormone Deficiency: Pre-Op

- Case series
- 1990 and 2008
- 112 patients
- 57 male and 55 female
- mean age:33.3

TABLE 1: Clinical characteristics of 112 patients who underwent operations for craniopharyngioma according to age at surgery*

Variable	Children	Adults	Total
no. of patients	34	78	112
mean age (yrs) at surgery (± SEM)	13.2 ± 0.6	42.0 ± 1.7	33.3 ± 1.8
female sex	15 (44.1)	40 (51.3)	55 (49.1)
adrenal function deficit	16 (47.1)	40 (51.3)	56 (50)
thyroid function deficit	16 (47.1)	37 (48.7)†	53 (48.2)†
gonadal function deficit	NA	59 (75.6)	59 (75.6)
growth deficit	28 (82.3)	NA	28 (82.3)
hyperprolactinemia	7 (20.6)	24 (30.8)	31 (27.7)
diabetes insipidus	12 (35.3)	30 (38.5)	42 (37.5)
obesity	9 (26.5)	12 (15.4)	21 (18.7)
visual deficit	22 (64.7)	63 (80.8)	85 (75.9)
previous surgery	5 (14.7)	14 (17.9)	19 (17.0)
transsphenoidal approach	10 (29.4)	26 (33.3)	36 (32.1)

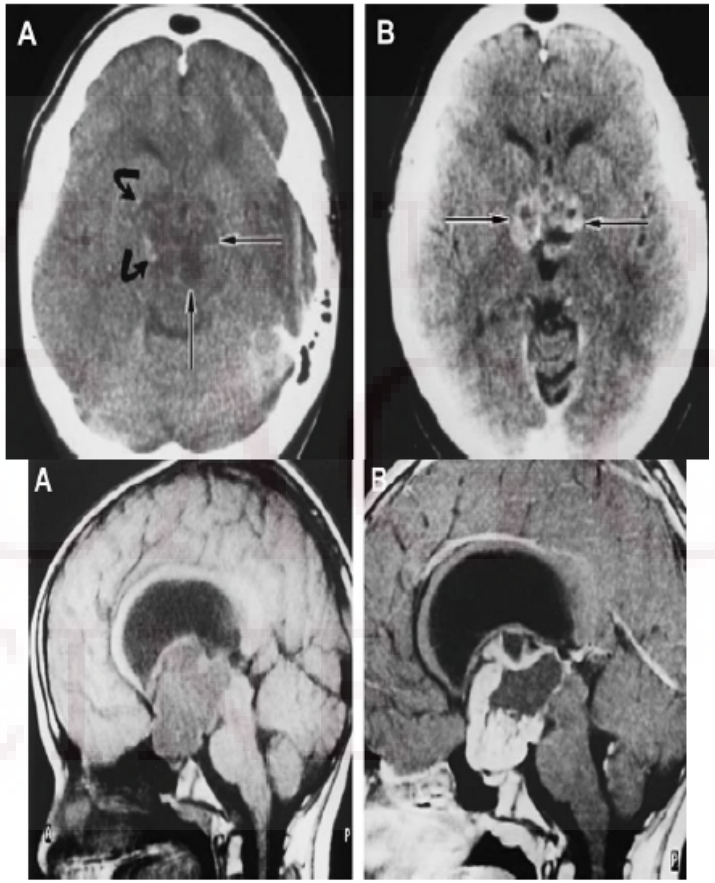
* Values given as number of patients (%) unless otherwise indicated. Childhood is defined as < 18 years old, adulthood as ≥ 18 years old. Abbreviation: NA = not applicable.

Only 1 person had delay puberty

Mortini. J neurosurgery 2011

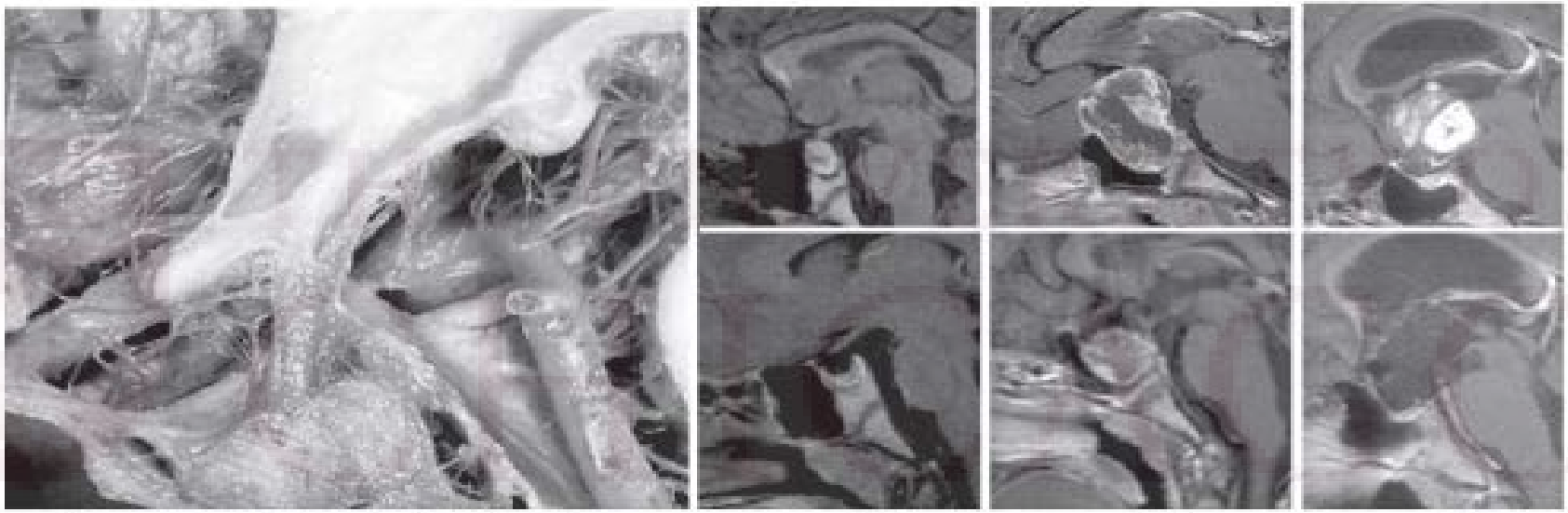
Radiologic Findings

- General
  - Well encapsulated tumor, mixed cystic and solid component
- CT
  - Detect calcifications
- MRI
  - Most important used to plan surgical approach
  - Show relationship between tumor, vasculature, and optic apparatus



Grading System

FIGURE 1



Grading system hypothalamic lesions: grade 0 grade 1 grade 2

Based on degree of hypothalamic displacement:

- Grade 0 = None
- Grade 1 = Abutting/displacing
- Grade 2 = Involving/Infiltrating – marked by absence of hypothalamus on imaging

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Puget et al.

Clinical Questions

- Treatment option (surgery, chemical therapy, monitor)

Treatment Overview

- Surgical resection +/- EBRT
  - Mainstay Tx
- Intracystic RT
- Chemotherapy
  - Bleomycin – reduce tumor size
- Aspiration
  - Purely cyst mass with goal of delaying treatment

Julow, J.V. (2013). Pituitary

Surgical Treatment

- Craniotomy
  - Pterional
  - Bifrontal and interhemispheric
- Transsphenoidal route – 1990's
  - Originally only dedicated to intrasellar masses due initial difficulty w/ CSF leaks, and difficulty visualizing w/ microscope

Stam 2010. Craniopharyngioma

Surgical Treatment

- Complete resection
  - Potentially curative
  - Post-op imaging indicates residual calcifications or obvious tumor in 15-50% of “totally resected” cases
  - Rate of recurrence after imaging confirmed total resection 15-30%
- Partial resection/cyst aspiration
  - Rapid symptom relief
  - Progression in 70% within 3 years
  - Second surgery

Stam 2010. Craniopharyngioma

Surgical Treatment

TABLE 7. Comparison of Baseline Characteristics and Outcomes Following Resection of Pediatric Craniopharyngiomas via Transcranial and Transsphenoidal Approaches[a]

Variable	Transcranial Series, % (no.)	Transsphenoidal Series, % (no.)	*P* value
Preoperative vision deficits	53.5 (1051 of 1966)	68.5 (124 of 181)	<.001
Preoperative hydrocephalus	41.7 (678 of 1625)	5.1 (5 of 99)	<.001
Preoperative increased ICP	42.6 (729 of 1713)	0 (0 of 138)	<.001
GTR	60.9 (1693 of 2780)	72.1 (199 of 276)	.0003
Recurrence after GTR	17.6 (261 of 1518)	8.0 (16 of 201)	.001
Operative mortality	2.6 (68 of 2622)	1.3 (5 of 373)	.21
Neurological morbidity	9.4 (200 of 2140)	3.1 (10 of 325)	<.001
Diabetes insipidus	69.1 (1437 of 2076)	23.9 (76 of 318)	<.001
Vision improvement	47.7 (454 of 1051)	85.5 (106 of 124)	<.001
Vision deterioration	13 (263 of 2029)	2.3 (8 of 352)	<.001
Obesity or hyperphagia	32.2 (439 of 1363)	32.1 (35 of 109)	1.00
Overall survival	90.3 (2039 of 2258)	93.9 (216 of 230)	.075

[a]GTR, gross total resection; ICP, intracranial pressure.

Eliott. Neurosurgery 2011

Clinical Questions

- Outcomes in childhood onset vs adult onset craniopharyngioma
- Hormonal deficit post op
- Metabolic consequences of craniopharyngioma

Outcomes in Childhood vs Adult Onset

- Large international database (KIMS) for adult patients with GH deficiency (GHD)
- 393 (184 female, 209 male) patients
- 241 AO and 152 CO
- Peak age at onset:15-20 years
- 90% had been treated surgically
- CO patients were shorter than AO patients and had much lower IGF-I

Kendall-taylor, Eur,J Endocrinol.2005

Outcomes in Childhood vs Adult Onset

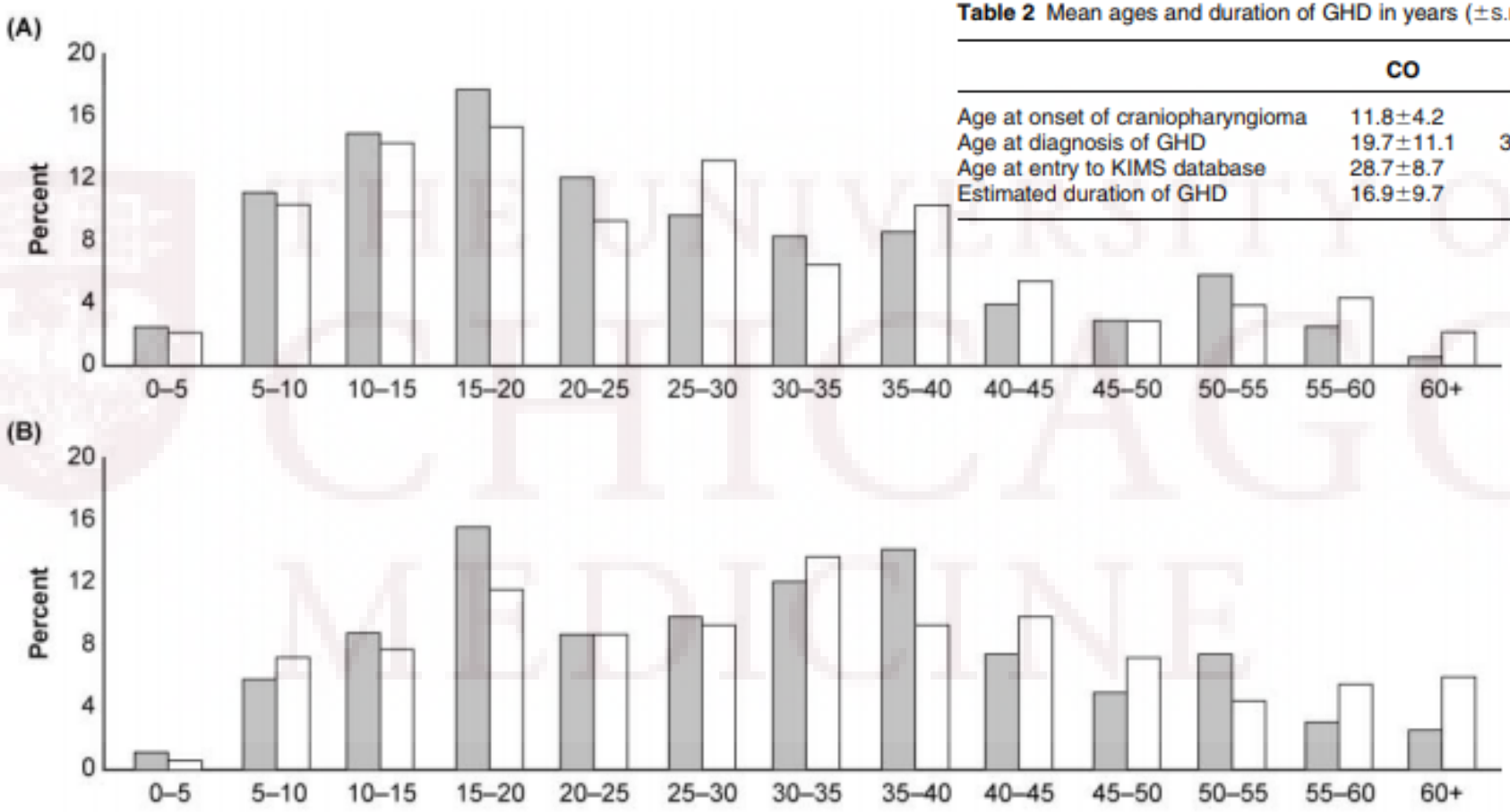


Table 2 Mean ages and duration of GHD in years (±S.D.).

	CO	AO
Age at onset of craniopharyngioma	11.8±4.2	34.3±12.0
Age at diagnosis of GHD	19.7±11.1	39.08±12.8
Age at entry to KIMS database	28.7±8.7	42.0±12.3
Estimated duration of GHD	16.9±9.7	7.8±7.4

Figure 1 (A) Distribution of ages at onset of the craniopharyngioma. (B) Age at the time of diagnosis of GHD. ▒, Male; □, female.

Kendall-taylor, Eur,J Endocrinol.2005

Outcomes in Childhood vs Adult Onset

Table 3 Data relating to GH and other hormone deficiencies (mean±S.D.).

	CO	AO	*P*
Height (cm)	165.5±10.7	168.9±9.6	0.0018
Height SDS	−0.54±1.4	−0.05±1.2	0.0001
IGF-I SDS	−4.42±2.03	−2.05±1.83	0.0001
LH/FSH deficit %	95.3	94.2	ns
ACTH deficit %	86.8	89.6	ns
TSH deficit %	94.1	92.2	ns
AVP deficit %	60.5	63.5	ns
Panhypopituitary %	57.9	59.8	ns

AVP, arginine vasopressin; ns, not significant.

Kendall-taylor, Eur,J Endocrinol.2005

Outcomes in Childhood vs Adult Onset

Table 4 Metabolic data comparing CO and AO males (M) and CO and AO females (F). Results are expressed as (means±S.D.).

	CO (M)	AO (M)	*P*	CO (F)	AO (F)	*P*
Weight (kg)	84.6±27.3	92.5±20.1	0.0014	75.4±20.4	80.2±18.9	0.0358
BMI	28.5±7.5	30.2±5.5	0.0194	29.8±7.9	30.0±6.9	ns
BMI SDS	1.4±1.6	1.9±1.1	0.0306	1.8±1.4	1.8±1.4	ns
Waist circumference (cm)	96.8±16.0	103.1±12.0	0.0027	93.8±16.1	95.8±15.8	ns
Waist/hip ratio	0.99±0.16	1.01±0.18	ns	0.89±0.08	0.88±0.08	ns
Lean tissue (BIA) (kg)	59.7±13.8	64.2±9.1	ns	47.7±10.5	49.5±11.9	ns
Fat tissue (BIA) (kg)	25.6±14.5	26.0±10.1	ns	32.6±13.9	32.9±15.1	ns
Cholesterol (mmol/l)	5.74±1.54	6.12±1.39	ns	5.82±1.22	6.19±1.21	ns
HDL (mmol/l)	1.08±0.36	1.04±0.32	ns	1.35±0.34	1.30±0.43	ns
LDL (mmol/l)	3.52±1.20	3.84±1.19	ns	3.63±1.08	3.79±1.09	ns
Triglycerides (mmol/l)	2.71±2.68	3.39±3.21	ns	1.85±0.83	2.53±1.45	0.0044

ns, not significant.

Obesity was more common in AO patients

Quality of life was reduced in all group, no sig differences

Kendall-taylor, Eur,J Endocrinol.2005

Hormone Deficiency: Post-Op

- Case series
- 1990 and 2008
- 112 patients
- 57 male and 55 female
- mean age:33.3

TABLE 4: New cases of pituitary deficiency according to the type of surgical approach*

Pituitary Hormone	Transsphenoidal	Transcranial	Total	p Value
GH	5/5 (100)	9/12 (75)	14/17 (82.3)	NS
gonadotropin	4/7 (57.1)	8/11 (72.7)	12/18 (66.7)	NS
thyrotropin	9/18 (50)	31/37 (83.8)	40/55 (72.7)	<0.03
adrenocorticotropin	10/17 (58.8)	31/37 (83.8)	41/54 (75.9)	<0.09
antidiuretic hormone	7/25 (28.0)	41/44 (93.2)	48/69 (69.6)	<0.01

* Only patients for whom the relevant information is available are included. Abbreviation: NS = not significant.

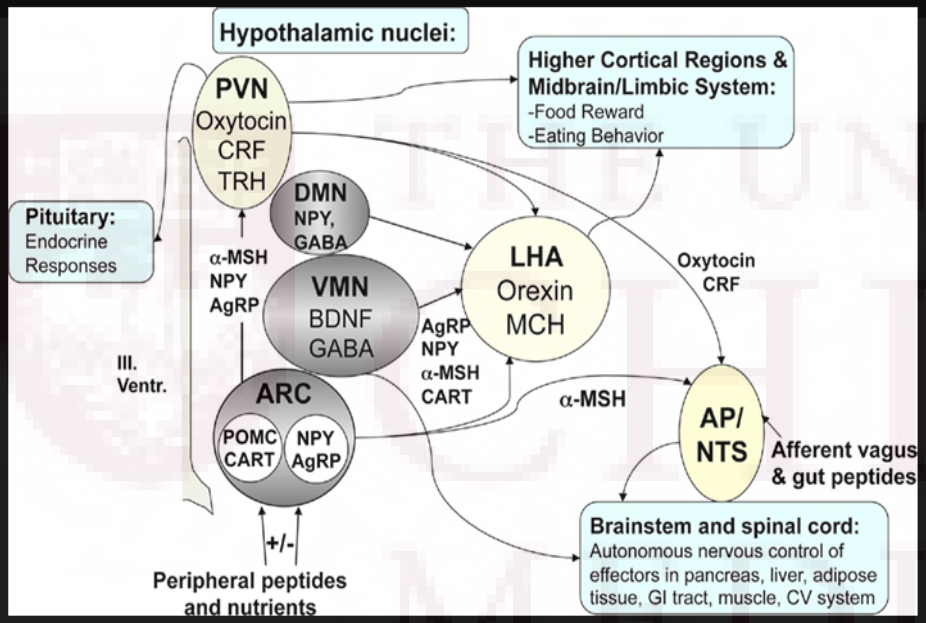
Mortini. J neurosurgery 2011

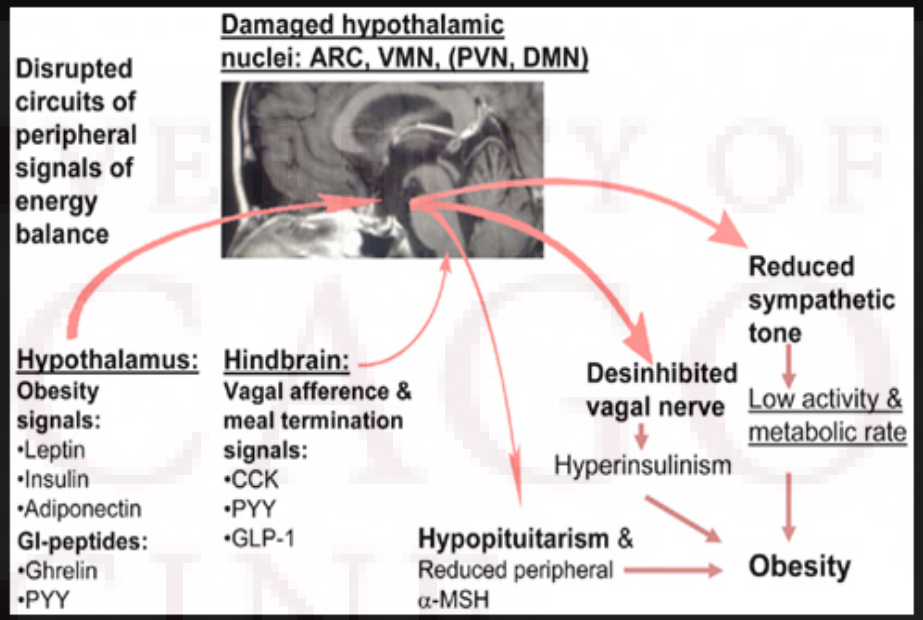
Complications

- 90% will have at least one hormone deficiency
- Panhypopituitarism: hypogonadism, hypothyroidism, adrenal insufficiency, GH deficiency
  - Hypothalamic dysfunction: obesity, temperature regulation, sleep disorders, DI
- Post-treatment visual acuity highly dependent on pre-treatment status
  - Some patients might have improved vision
  - Majority will remain the same
- Secondary malignancies: glioma
- Vascular injury (1-2%): temporal cavernomas, aneurysms, moyamoya syndrome
- Cognitive dysfunction
  - Cognitive delay 20% of patients (IQ <80)

Gunderson; Neuro 2011

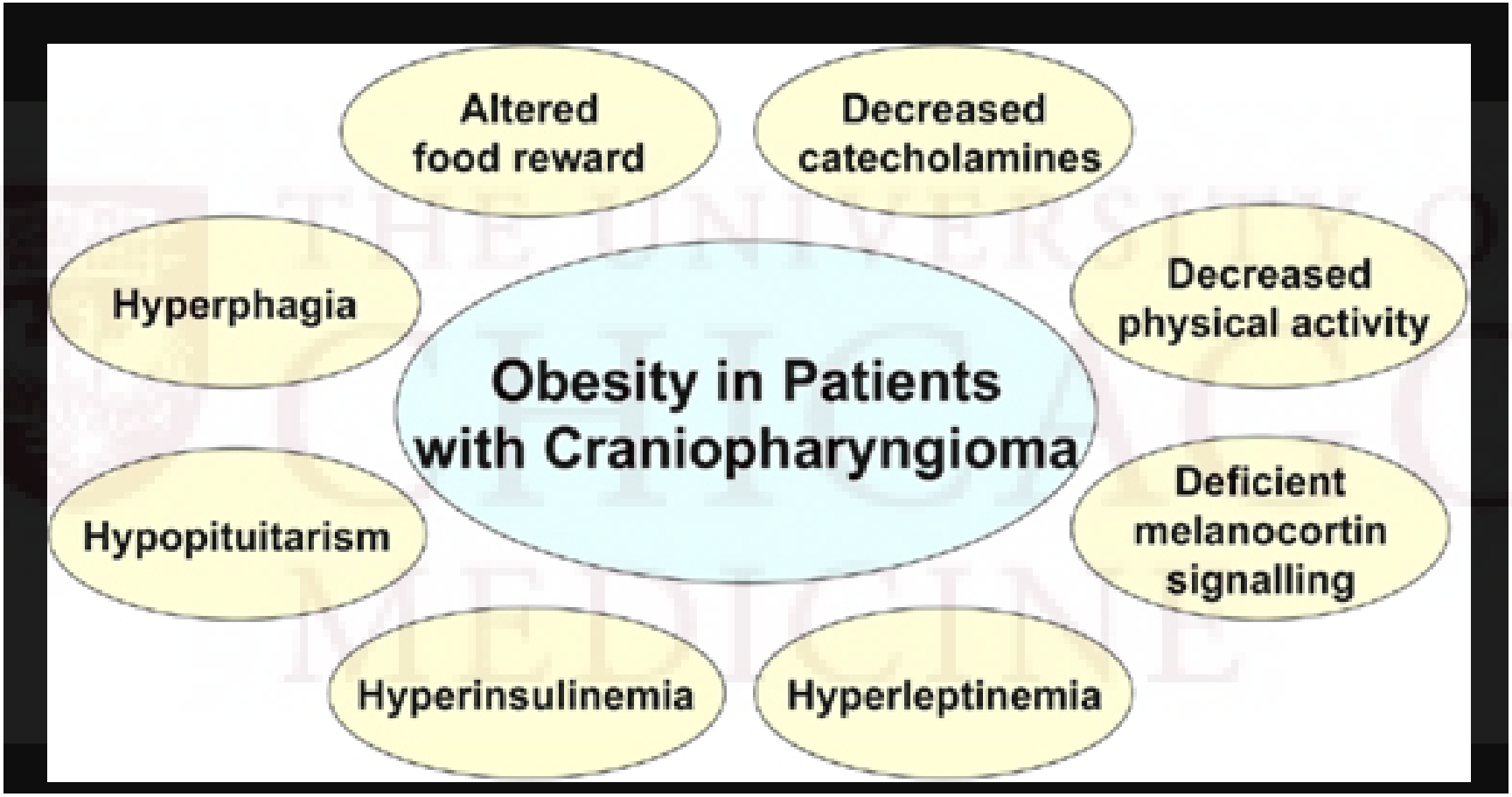
Hypothalamic Obesity





Roth.Front. Endocrinol.2011

Hypothalamic Obesity



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Clinical Questions

- Prognosis?

Prognostic Factors

- Favorable:
  - Lack of calcifications (esp in adults)
  - Extent of surgical resection
  - Caucasian race
- Unfavorable:
  - Age younger than 5 years old
  - Size > 5 cm
  - Hydrocephalus
    - Need for CSF shunting

Merchant et al., 2013

Recurrence-Free Survival

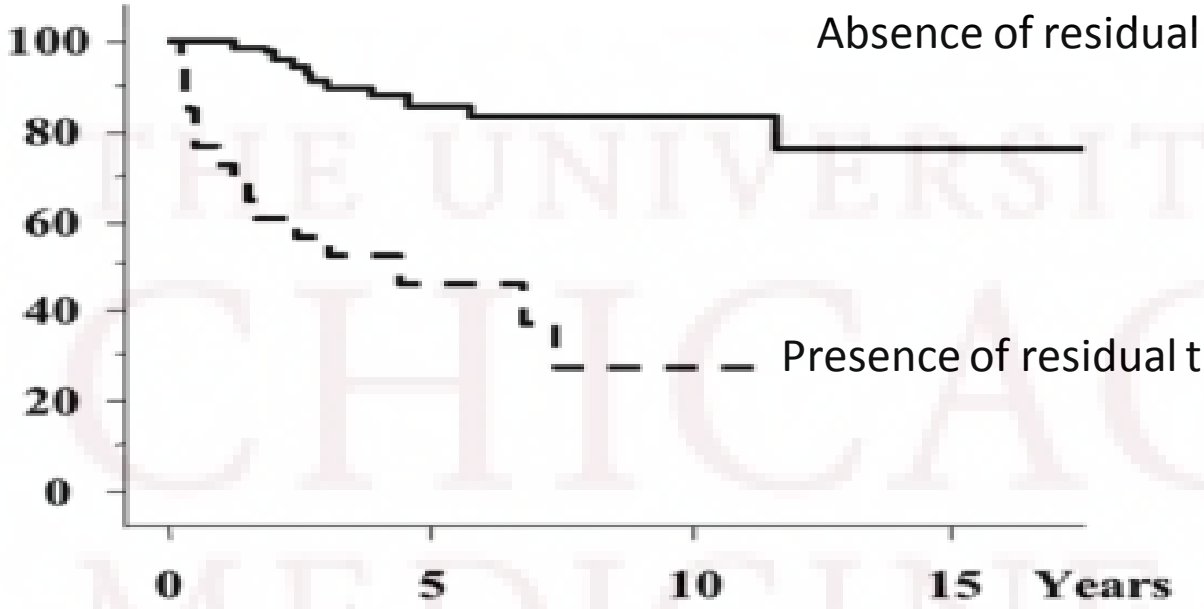
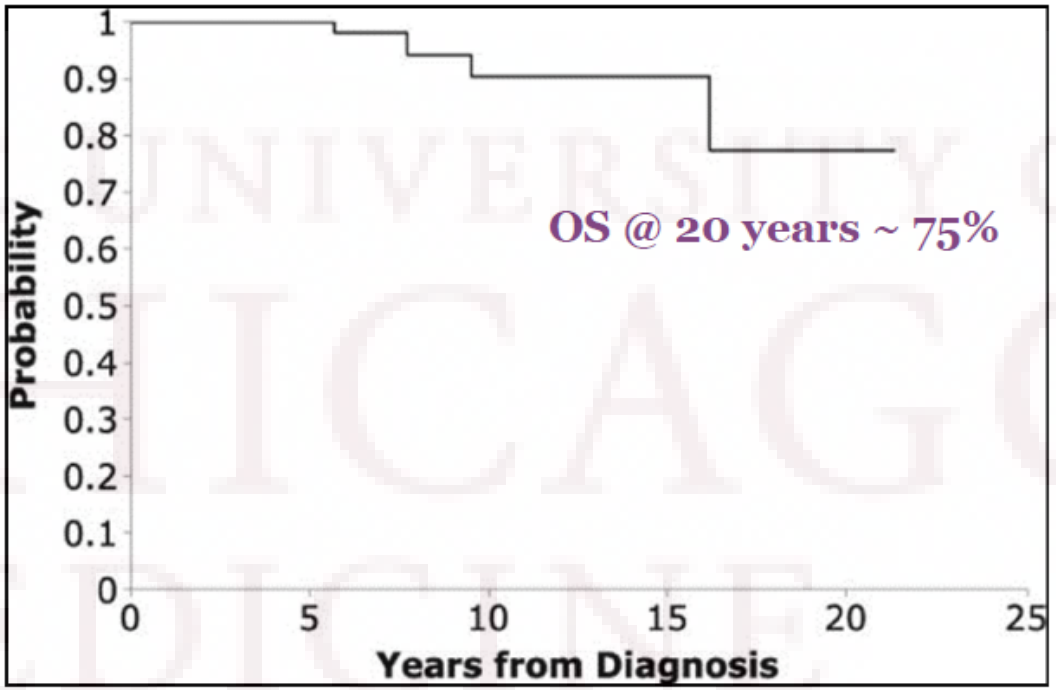


FIG. 3. Kaplan-Meier analysis of recurrence-free survival according to the absence *(solid line)* or presence *(dashed line)* of residual tumor after surgery. The recurrence-free survival rate at 5 years was 85.6% (95% CI 76.8%–94.4%) in 80 patients with no residual tumor after surgery, compared with 46.3% (95% CI 25.7%–66.8%; $p < 0.001$, log-rank test) in 26 patients with residual tumor after surgery.

Mortini. J neurosurgery 2011

Health Status in Long-Term Survivors of Craniopharyngioma

Variable	Total
Sex, *n* (%)	
Male	22 (43.1)
Female	29 (56.9)
Race, *n* (%)	
White	40 (78.4)
Black	11 (21.6)
Age at diagnosis (years), median (min–max)	7.1 (1.2–17.6)
Years from diagnosis to long-term follow-up, median (min–max)	7.6 (5.0–21.3)
Treatment, *n*(%)	
Surgery alone	5 (9.8)
Surgery + radiation therapy only	44 (86.3)
Surgery + radiation therapy + chemotherapy	1 (2.0)
History of shunt placement, *n* (%)	
Yes	21 (41.2)
No	30 (58.8)



Overall Survival

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Clark et al. J Neurosurg 2012

Health Status in Long-Term Survivors of Craniopharyngioma

Patient	Sex/Race	Age at diagnosis (years)	Date of diagnosis	Initially metastatic	Date of death	Survival (years)	Cause of death
1	F/B	12.9	10/13/1986	No	12/8/2002	26.2	Diabetes, myocardial infarction
2	F/W	1.1	1/17/1994	No	7/19/2003	9.5	Metabolic complications, radionecrosis
3	F/B	13.8	9/15/1997	No	5/30/2003	5.7	Metabolic complications
4	M/B	6.0	3/07/2000	No	11/18/2007	5.7	Recurrent craniopharyngioma

Variables	Total (%)
Headache	20 (39.2)
History of seizures	14 (27.5)
Abnormal cerebral vessel	19 (37.3)
Cerebrovascular disease	8 (15.7)
Hearing loss	
Unilateral	3 (5.9)
Bilateral	5 (9.8)
Oculomotor dysfunction	6 (11.8)
Vision < 20/100	
Unilateral	6 (11.8)
Bilateral	18 (35.3)

Variable	Total (%)
Neurocognitive delay	10 (19.6)
Individual educational plan for academic assistance	10 (19.6)
Educational attainment	
Special education certificate of attendance	2 (3.9)
High school diploma	13 (25.4)
College graduate	2 (3.9)
Postgraduate degree	1 (1.9)
Psychological problems	15 (29.4)
Communication disorder	5 (9.8)

Clark et al. J Neurosurg 2012

Hospital Course

- Dx: ventriculomegaly and craniopharyngioma s/p EVD placement on 3/9 and s/p interhemispheric craniotomy for resection on 3/12.
- Postop MRI shows residual tumor along inferior margin. Failed EVD wean. OR for shunt placement on 3/29
- Complicated with DI, upper GI bleeding, inability to pass swallow evaluation
- S/p Peg tube for enteral feeding, still in neuro ICU

Lab

	Ref. Range and Units	6 3/9/2018 2324	5 3/9/2018 2329	4 3/10/2018 1733	3 3/11/2018 0718	2 3/20/2018 0337
ENDOCRINOLOGY						
BHCG, Plasma, Quant.	Latest Range: <2.6 u[iU]/mL	<1.0	<1.0 *			
Cortisol	Latest Units: ug/dL	1.5 *		1.4 *		
GASTRIN	No range found					
INSULIN-LIKE GROWT...	No range found					
Luteinizing Hormone	Latest Units: u[iU]/mL	0.2 *				
Prolactin	Latest Range: 4.0 - 15.2 ng/mL	10.19				
Te Binding Globulin	Latest Range: 10 - 80 nmol/L					19
Calculated Free Te...	Latest Range: 90 - 300 pg/mL					<3 *
Total Testosterone	Latest Range: 300 - 1200 ng/dL					<7
Test Information	No range found					The Total Test... *
CORTISOL, FREE, UR	No range found					
FSH	Latest Units: u[iU]/mL	0.8 *				
IGF BINDING PROTEIN-1	No range found					
ACTH	Latest Range: <52 pg/mL	1.0				

Lab

	Ref. Range and Units	4 3/9/2018 2324	3 3/15/2018 0407	2 3/20/2018 0337	1 3/23/2018 0355
THYROID FUNCTION					
Triiodothyronine, ...	Latest Range: 230 - 420 pg/dL	220 ▼			
Thyroxine, Free	Latest Range: 0.9 - 1.7 ng/dL	1.10	0.99	0.51 * ▼	
Reverse Triiodothy...	Latest Range: 137 - 424 pg/mL		457 * ▲		
Thyrotropin	Latest Range: 0.30 - 4.00 mcU/mL	1.29	0.13 ▼	1.17	1.17
Triiodothyronine	Latest Range: 80 - 195 ng/dL		40 ▼	46 ▼	
Thyroxine	Latest Range: 5.0 - 11.6 ug/dL		5.6		

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Sikarin Upala, MD, MS

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Dr. Upala does not have any relevant financial relationships with any commercial interests