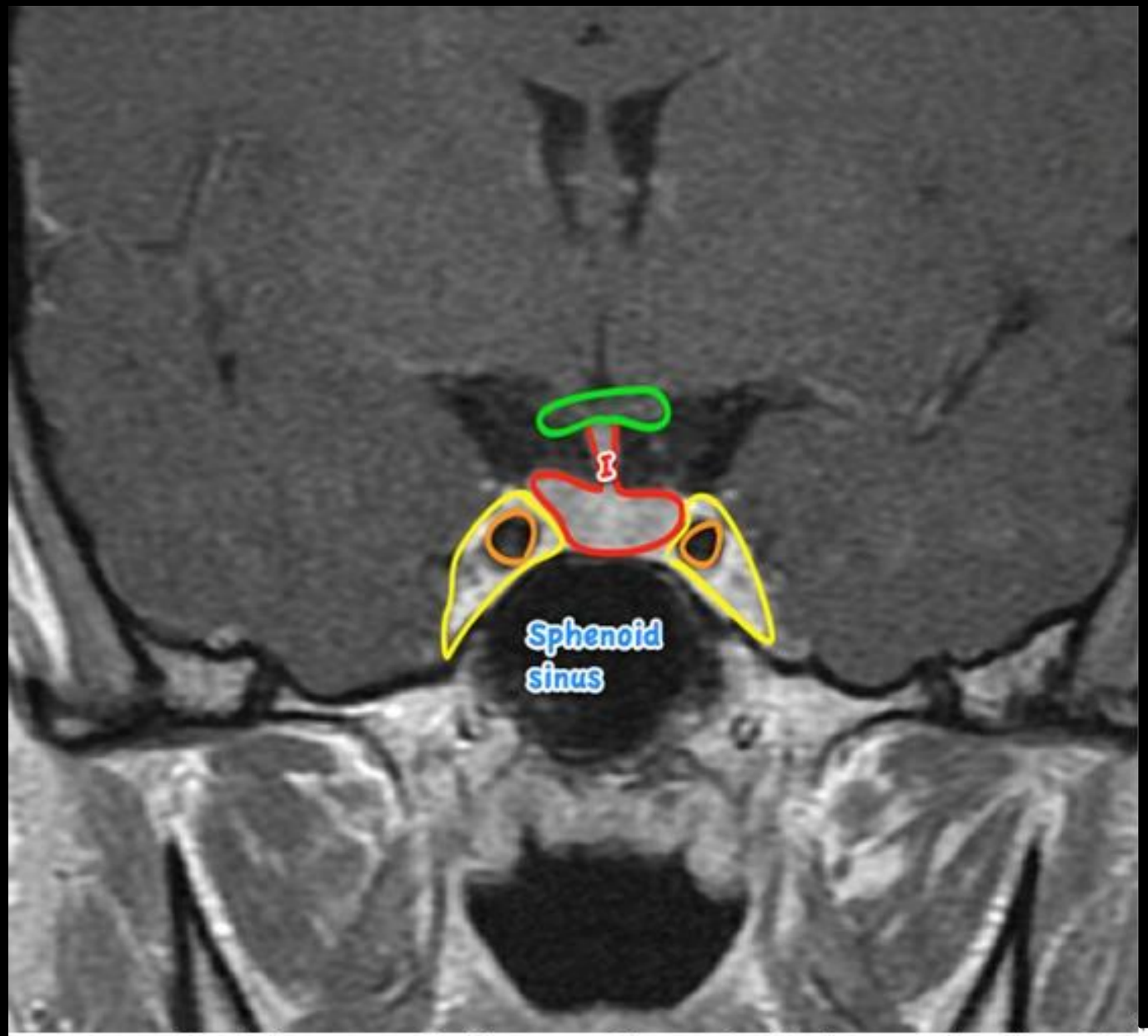
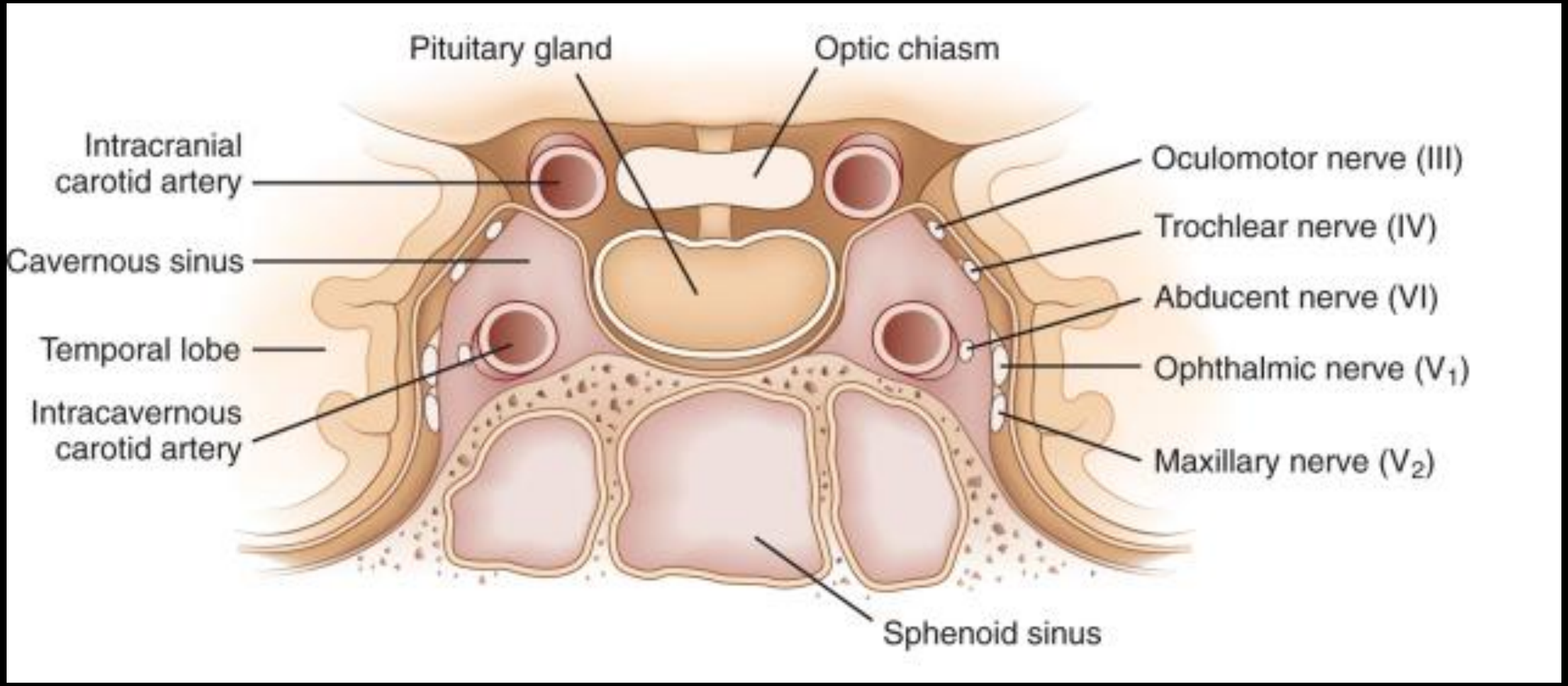
Pituitary apoplexy

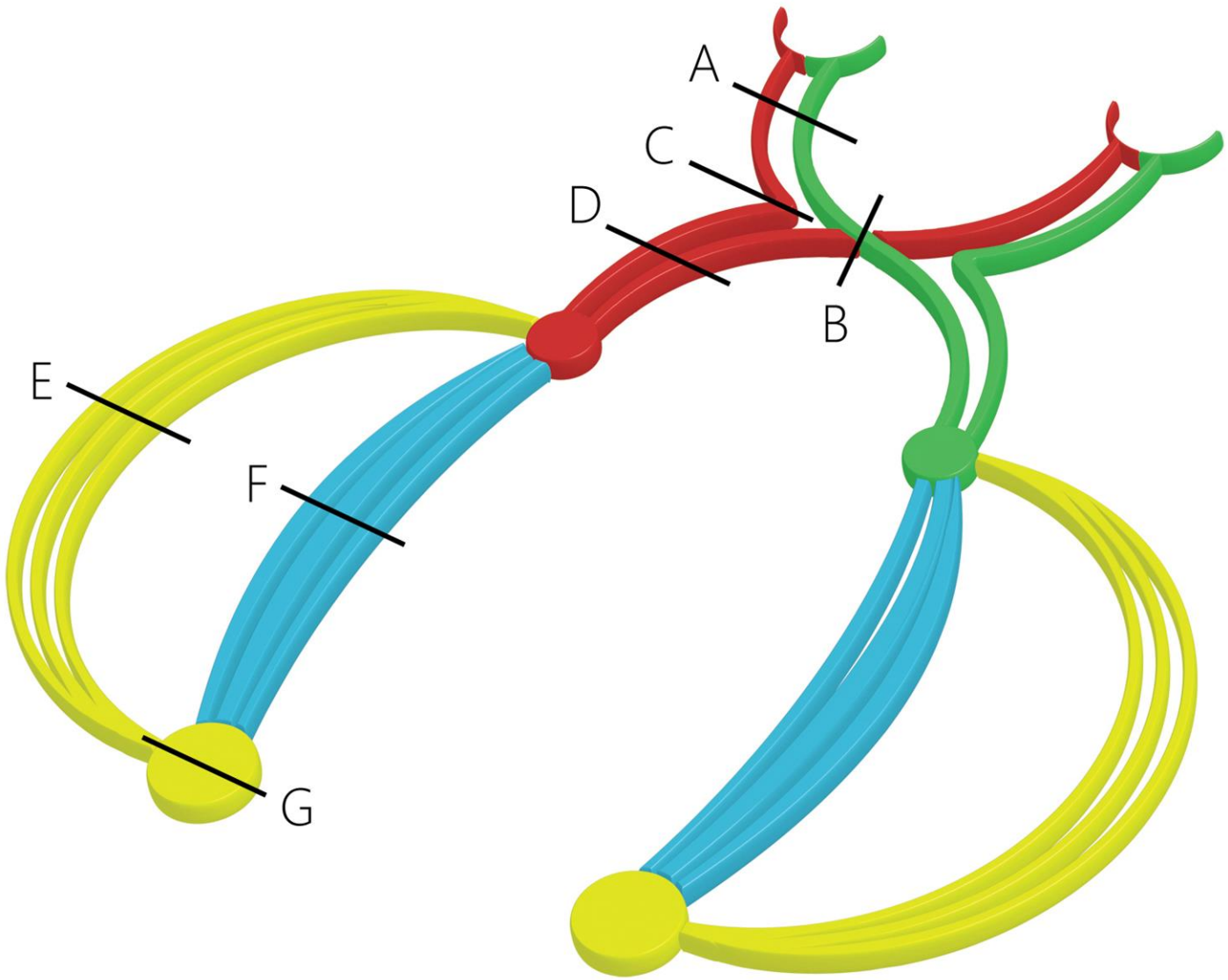
台北榮總 內分泌新陳代謝科 主治醫師 林怡君



green:optic chiasm, I:pituitary stalk, red: pituitary gland, yellow: cavernous sinus
(Case courtesy of Dr Frank Gaillard, Radiopaedia.org)



Williams text book of endocrinology 11th e



A. Left Hemianopia
Left optic nerve lesion

B. Bitemporal Hemianopia
Optic chiasm lesion
Pituitary tumor

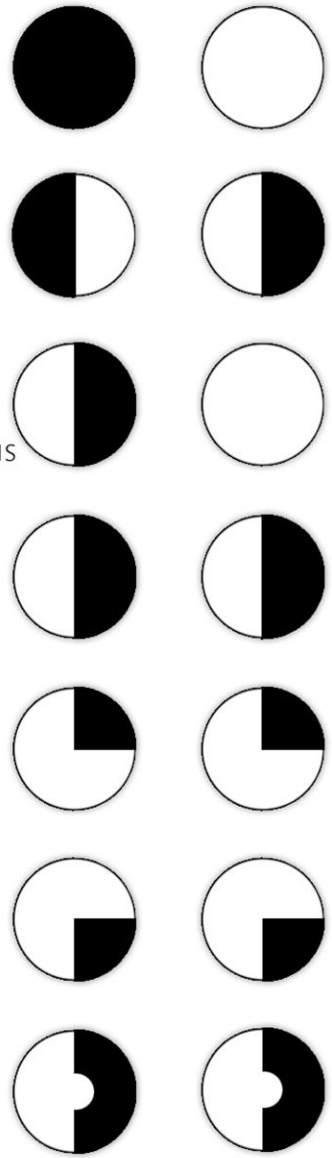
C. Right Nasal Hemianopia
Outer optic tract lesion
Internal carotid artery thrombus

D. Right Homonymous Hemianopia
Optic tract lesion

E. Right Superior Quadrantanopia
Meyer's Loop lesion
Left temporal lesion

F. Right Inferior Quadrantanopia
Dorsal optic radiation lesion
Left parietal lesion

G. Right Hemianopia with Macular Sparing
PCA infarct



Anterior pituitary hormone

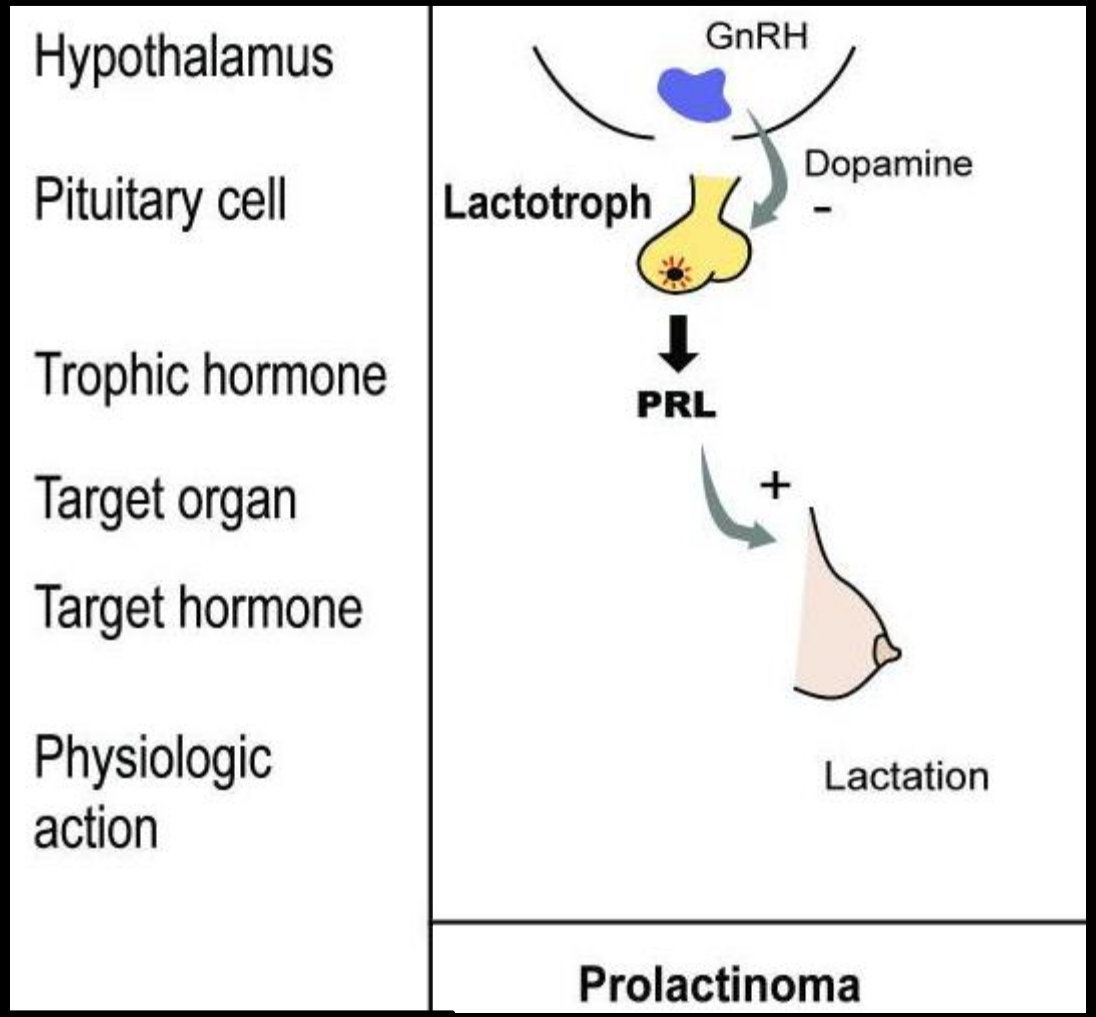
TABLE 401e-1 ANTERIOR PITUITARY HORMONE EXPRESSION AND REGULATION

Cell	Corticotrope	Somatotrope	Lactotrope	Thyrotrope	Gonadotrope
Tissue-specific transcription factor	T-Pit	Prop-1, Pit-1	Prop-1, Pit-1	Prop-1, Pit-1, TEF	SF-1, DAX-1
Fetal appearance	6 weeks	8 weeks	12 weeks	12 weeks	12 weeks
Hormone	POMC	GH	PRL	TSH	FSH, LH
Protein	Polypeptide	Polypeptide	Polypeptide	Glycoprotein α, β subunits	Glycoprotein α, β subunits
Amino acids	266 (ACTH 1–39)	191	199	211	210, 204
Stimulators	CRH, AVP, gp-130 cytokines	GHRH, ghrelin	Estrogen, TRH, VIP	TRH	GnRH, activins, estrogen
Inhibitors	Glucocorticoids	Somatostatin, IGF-I	Dopamine	T_3, T_4, dopamine, somatostatin, glucocorticoids	Sex steroids, inhibin
Target gland	Adrenal	Liver, bone, other tissues	Breast, other tissues	Thyroid	Ovary, testis
Trophic effect	Steroid production	IGF-I production, growth induction, insulin antagonism	Milk production	T_4 synthesis and secretion	Sex steroid production, follicle growth, germ cell maturation
Normal range	ACTH, 4–22 pg/L	<0.5 μg/L[a]	M <15 μg/L; F <20 μg/L	0.1–5 mU/L	M, 5–20 IU/L, F (basal), 5–20 IU/L

[a]Hormone secretion integrated over 24 h.

Abbreviations: M, male; F, female. For other abbreviations, see text.

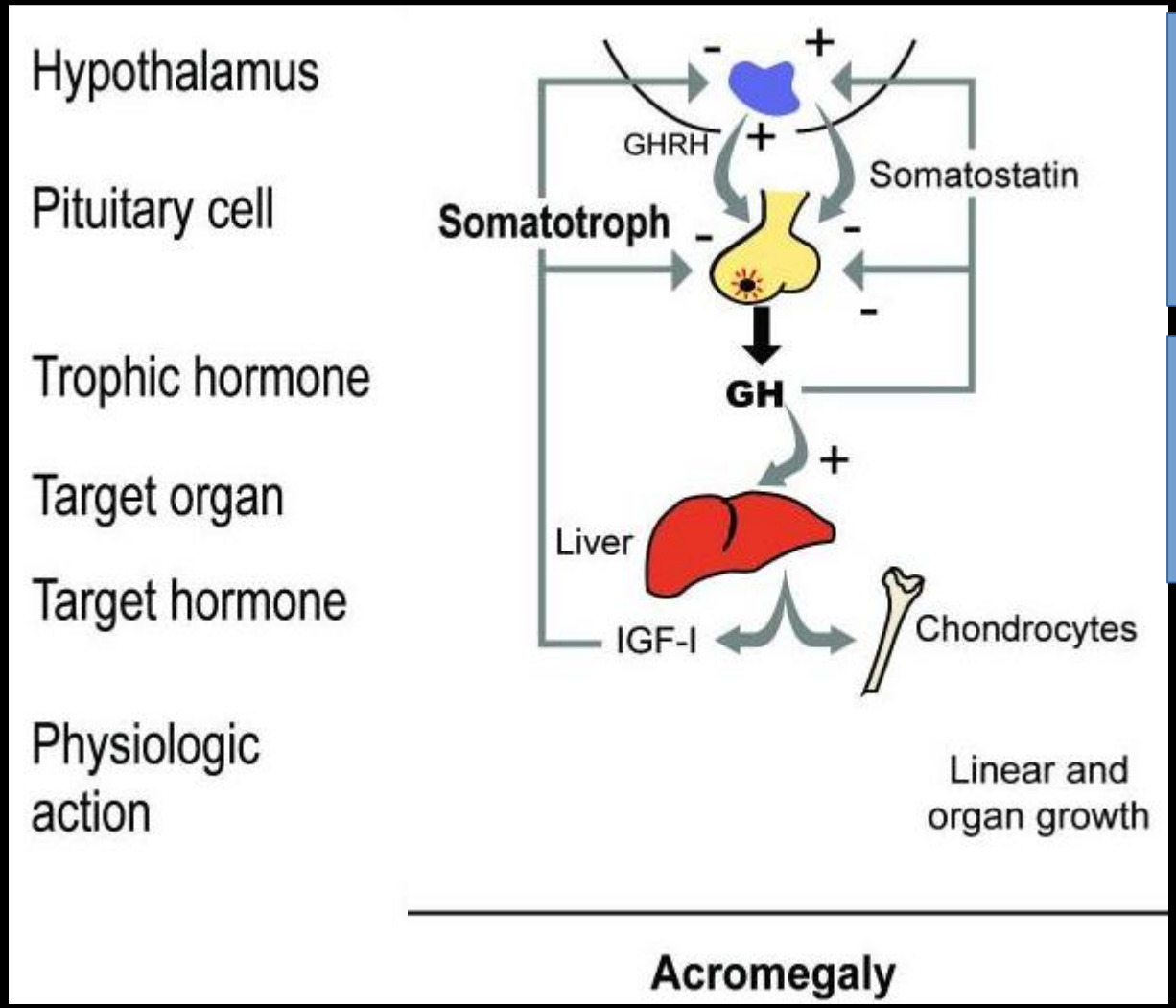
Source: Adapted from I Shimon, S Melmed, in S Melmed, P Conn (eds): *Endocrinology: Basic and Clinical Principles*. Totowa, NJ, Humana, 2005.



10-20% of pituitary cells, increase to 40% during AP
PRL releasing factors: TRH, oxytocin, GH, estrogen
Physiological stimulator: nipple stimulation, sleep

Galactorrhea, amenorrhea, infertility, hypogonadism

J Clin Investigation 2003 112:1603-1618



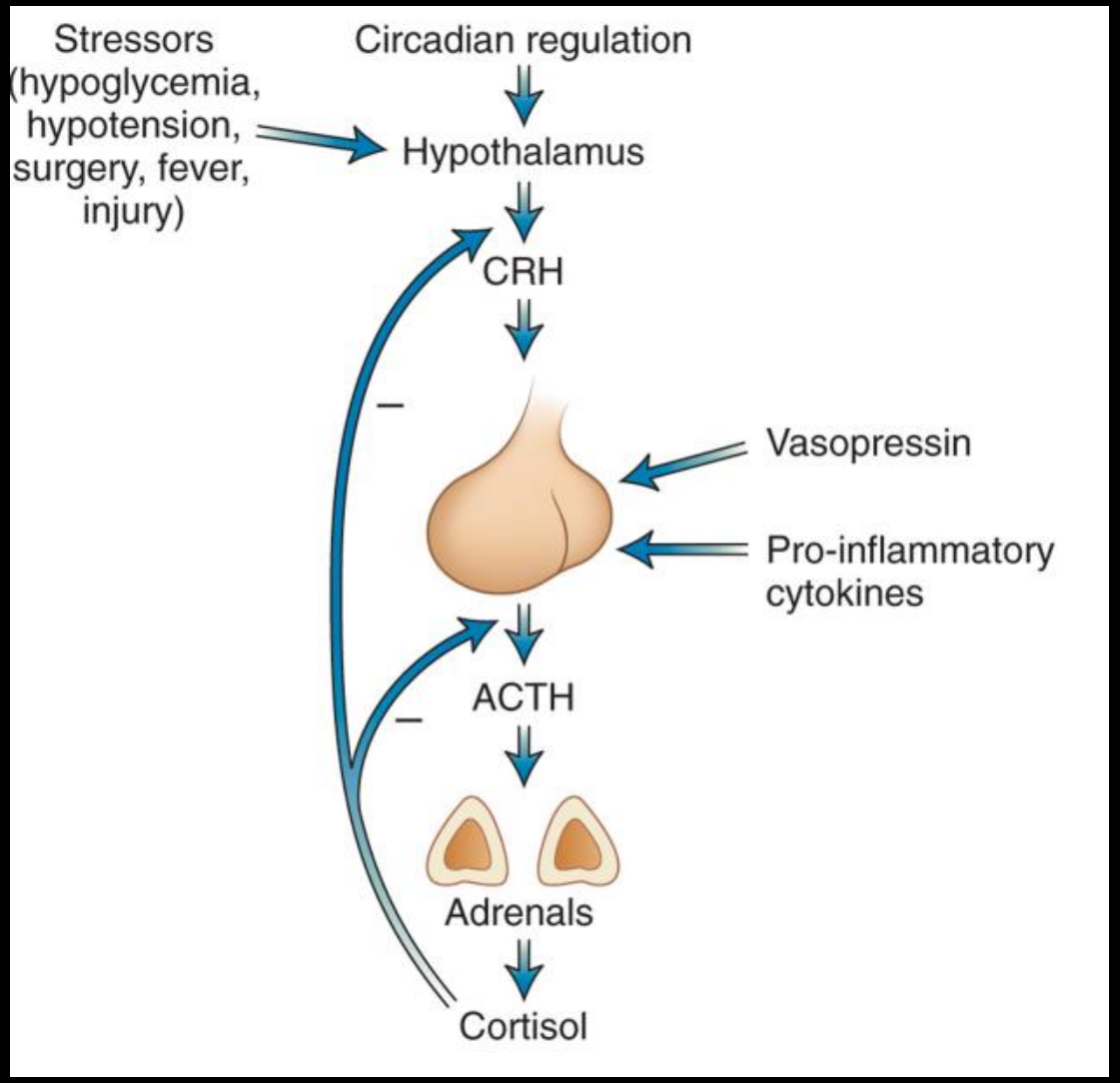
8-12 pulses/day
70% in deep sleep
The most numerous cell type
Somatostatin inhibits GHRH
GHRH stimulate somatostatin release

Obesity, hyperglycemia, FFA: decrease GH
Fasting, hypoglycemia, arginine, ghrelin, dopamine: increase GH
GH secretion: maximal during puberty

Acral enlarge, soft tissue swelling, hypertension, hyperglycemia, cardiac hypertrophy, sleep apnea

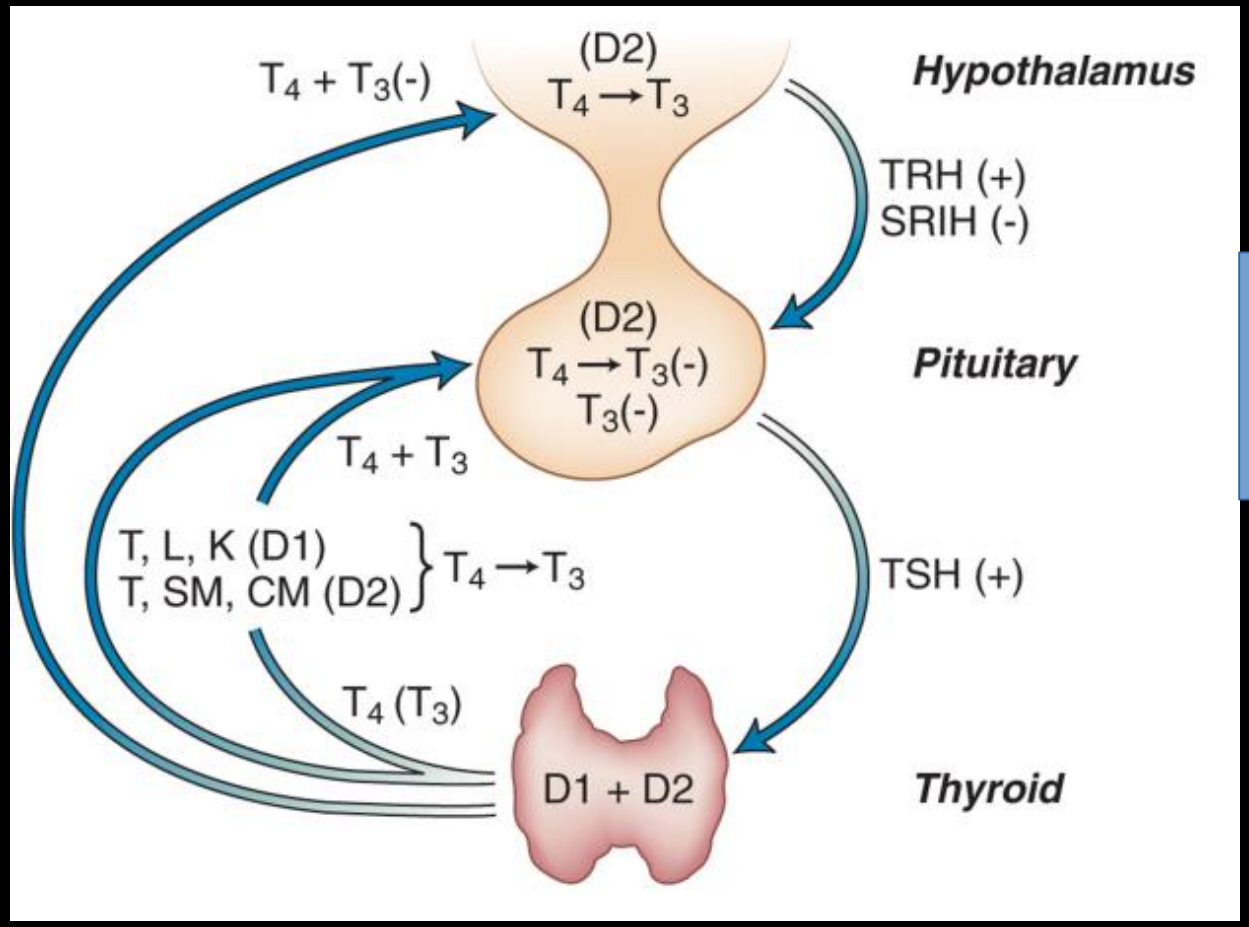
J Clin Investigation 2003 112:1603-1618

HPA axis



Williams test book of endocrinology 11e

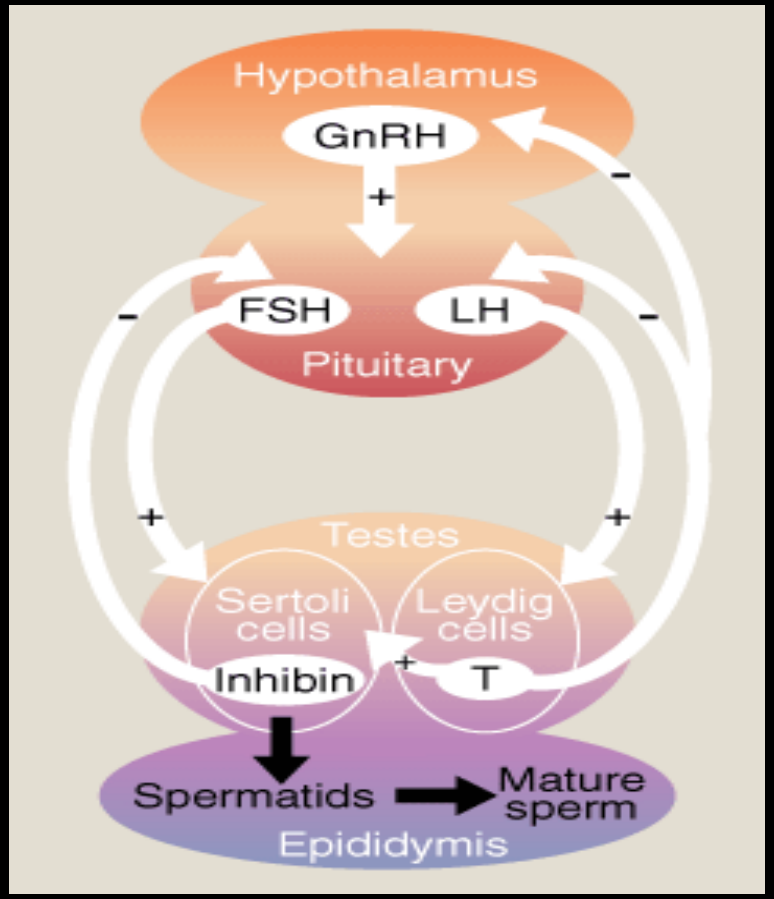
HPT axis

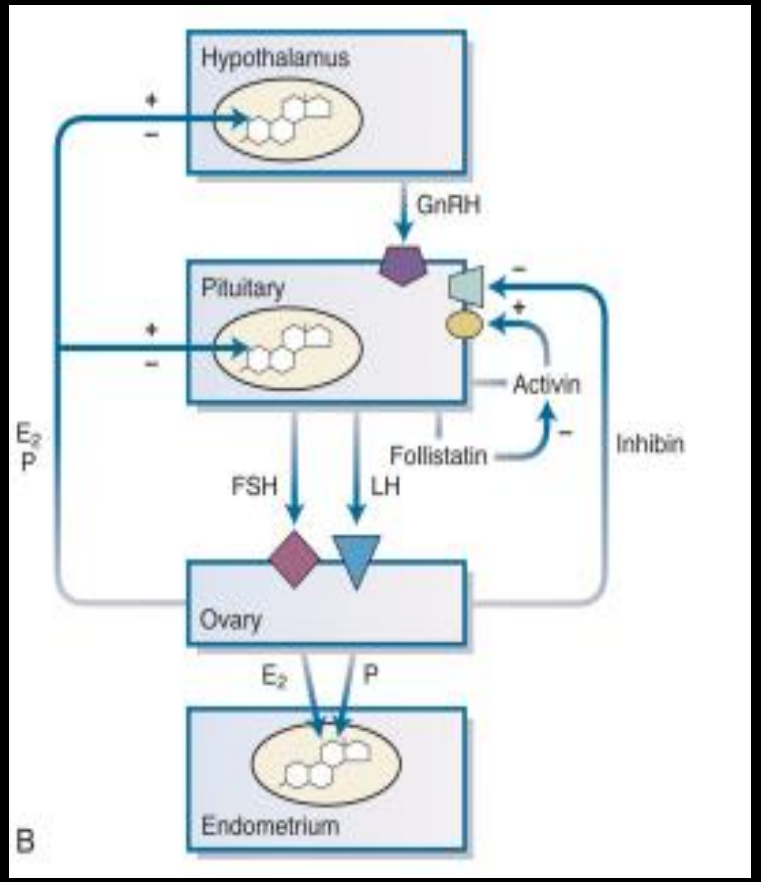


Inhibit TSH: somatostatin, dopamine, fasting, steroid, stress
Stimulate TSH: activity, leptin (by TRH)

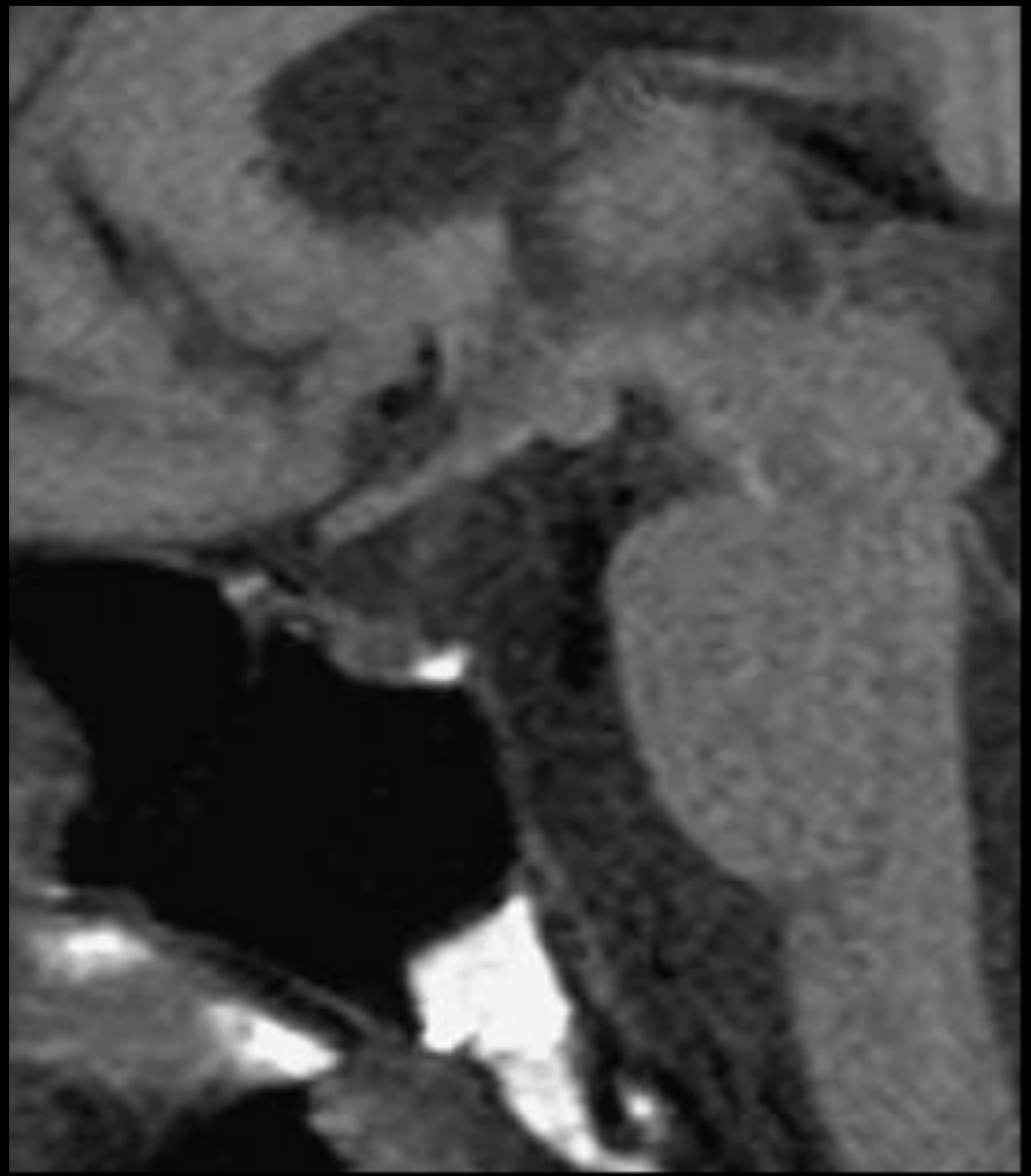
Williams test book of endocrinology 11e

HPG axis





Williams test book of endocrinology 11e



MRI of sella: The high signal in T1W image indicated ADH

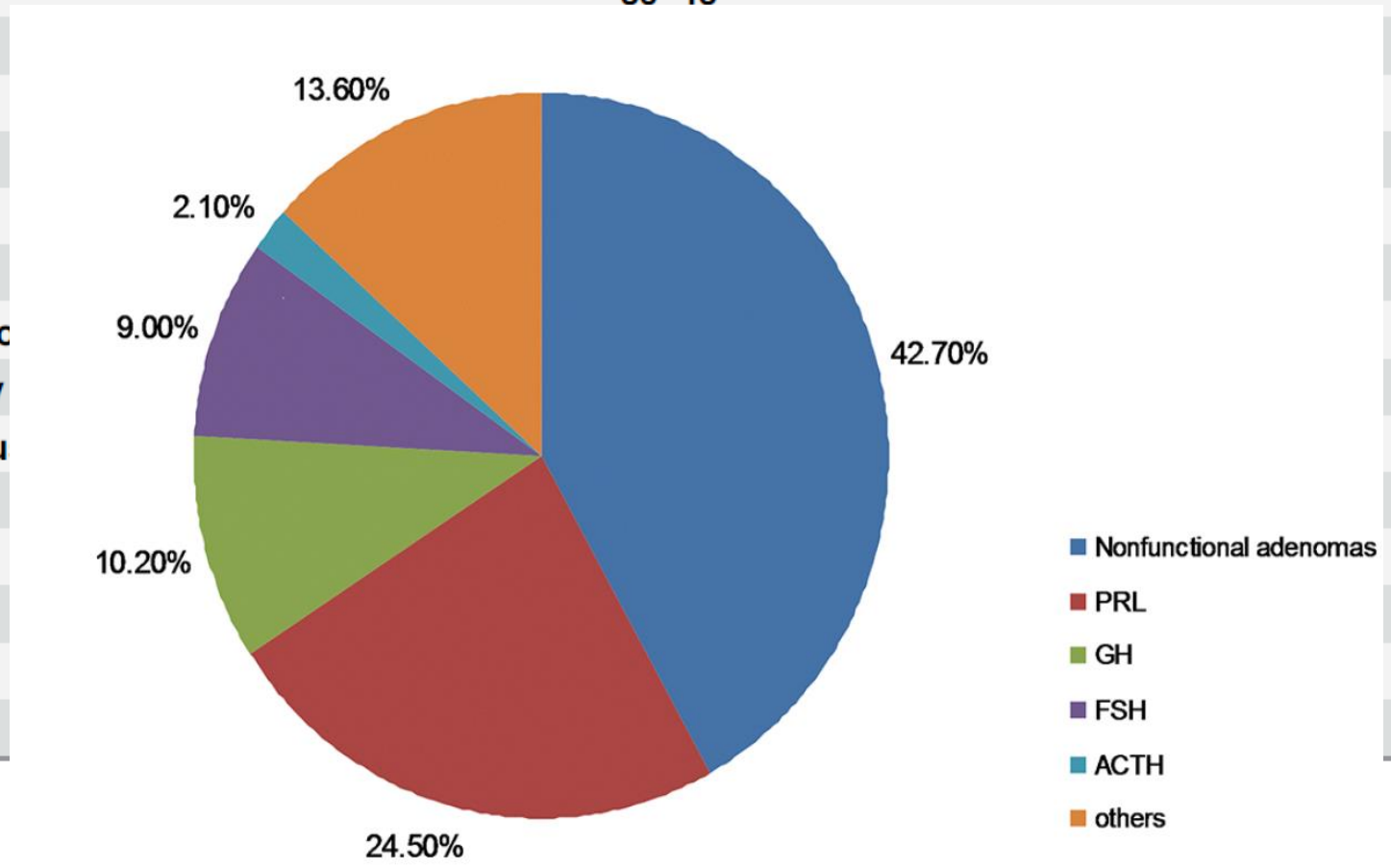
Pituitary apoplexy

Pituitary apoplexy

- Prevalence: approximately 6.2 cases per 100000 individuals
- Sudden hemorrhage of pituitary gland
- Most case (more than 80%) had preexisting pituitary adenoma: nonfunctioning adenoma, followed by prolactinoma
- Can also occur in other lesions: hypophysitis, craniopharyngioma, Rathke’s cleft cyst…

Table 1. Characteristics of all 2021 patients with pituitary tumors, 2005–2007.

Characteristics		n	%
Age			
	≤35	586	29.0
	36~45	519	25.7
		422	20.9
		494	24.4
Gender			
		1076	53.2
		945	46.8
Incidental adenc		92	4.6
Second surgery		168	8.3
Diabetes mellitu		45	2.2
Hypertension		139	6.9
PA		97	4.8
Tumor size			
		1101	54.5
		920	45.5



China, database from Huashan hospital, n=2021

PLoS ONE 10(9): e0139088. Sep 2015

Risk factors

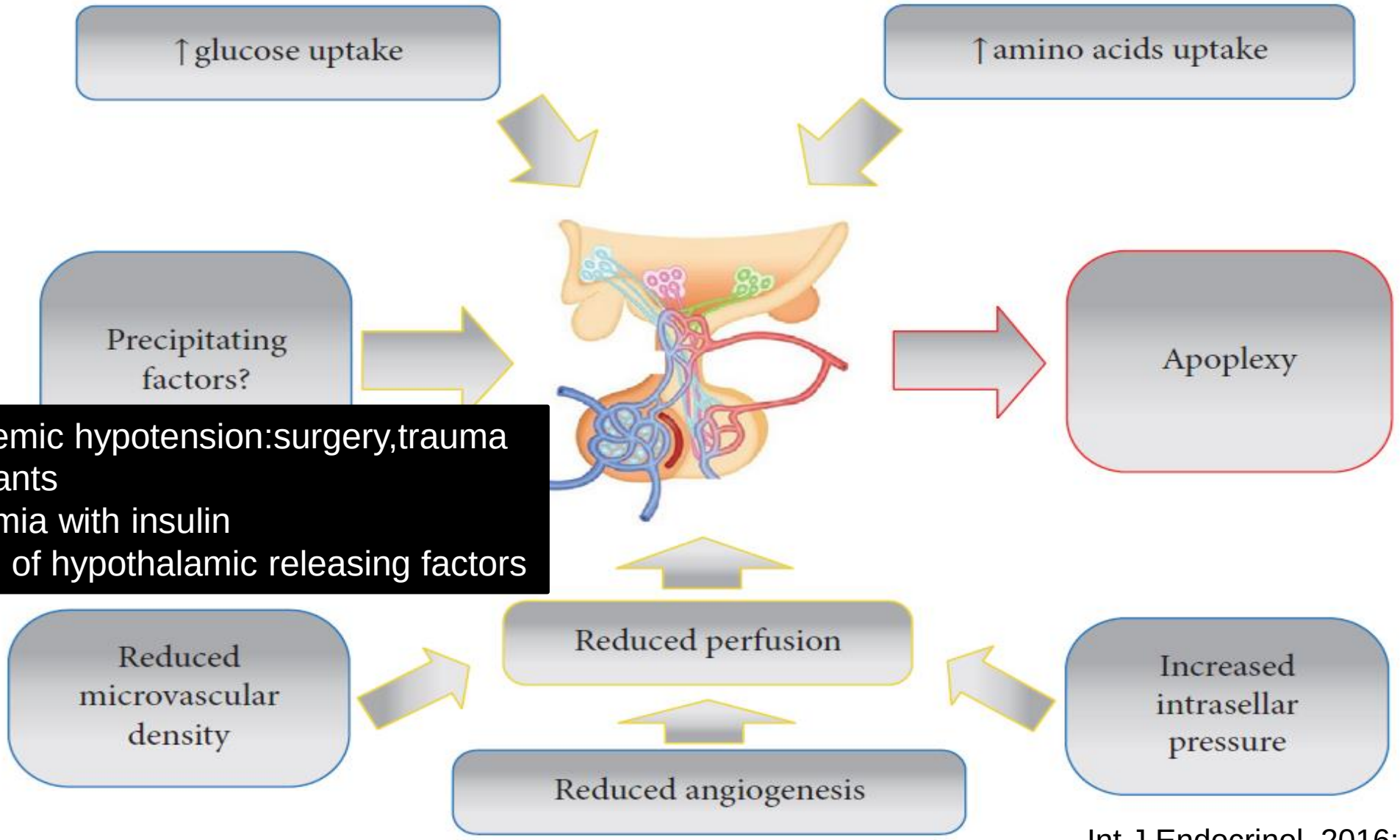
- Hypotension
- Acute hypertension
- Stimulation of pituitary gland
- Anticoagulation

Table 4. Predictors of clinical PA in pituitary adenoma patients.

Factors		Univariate		Adjusted	
		OR (95% CI)	P	OR (95% CI)	P
Age (years)					
	≤35 *	1		1	
	36~45	1.28(0.65~2.54)	0.479	0.92(0.45~1.88)	0.827
	46~55	2.53(1.35~4.74)	0.004	1.50(0.77~2.92)	0.234
	≥56	2.71(1.48~4.97)	0.001	1.52(0.78~2.93)	0.217
Gender					
	Female *	1		1	
	Male	3.11(1.98~4.90)	0.000	2.54(1.59~4.07)	0.000
Diabetes mellitus		1.41(0.69~2.87)	0.341	0.55(0.12~2.52)	0.443
Hypertension		0.92(0.22~3.86)	0.910	0.92(0.42~1.99)	0.828
Tumor recurrence		0.34(0.10~1.09)	0.074	0.34(0.10~1.11)	0.074
Types of pathological staining					
	Positive staining *†	1		1	
	Negative staining ¶	2.61(1.73~3.99)	0.000	2.04(1.29~3.23)	0.002
Adenoma size					
	Microadenoma *	1		1	
	Macroadenoma	30.84(11.29~84.25)	0.000	26.46(9.66~72.46)	0.000

PLoS ONE 10(9): e0139088. Sep 2015

Pathophysiology of pituitary apoplexy



1.Acute systemic hypotension:surgery,trauma
2.Anticoagulants
3.Hypoglycemia with insulin
3.Stimulation of hypothalamic releasing factors

Int J Endocrinol. 2016;2016:7951536.
J Neurosurg 2015;22:1444-1449

Symptoms and signs

- Headache
- Visual loss
- Diplopia
- Cranial nerve palsies due to acute increase in intracranial pressure
- Hypopituitarism

Table 2 Signs and symptoms in patients presenting with pituitary apoplexy.

Symptoms and signs at presentation	
Headache (A=43, NA=9)	40/43
Signs and symptoms of endocrinopathy (A=45, NA=7)	16/45
Fatigue (m=3, f=2)	5/45
Reduced libido (m=3, f=0)	3/45
Oligomenorrhoea/amenorrhoea (m=n/a, f=4)	4/25
Others (e.g. altered hand size/weight gain) (m=1, f=2)	4/45
Vomiting (A=43, NA=9)	22/43
Systolic blood pressure at presentation (A=30, NA=22) (mmHg)	
<90	1/30
91–120	11/30
121–140	7/30
141–180	10/30
>180	1/30
Visual abnormalities (A=35, NA=17)	22/35
Abnormal pupils	7/35
CN3 palsy only	12/35
CN6 palsy only	8/35
CN3 and CN6 palsy	3/35
Visual acuity affected	14/35
Visual fields affected	13/35

UK, Imperial College Healthcare NHS 1991-2015
N=52

Endrocrone connections 2018;7:1058-1066

Hormone deficiency

- Varies
- Adrenal insufficiency and hypogonadotropic hypogonadism are the most common situation

Clinical features of hypopituitarism

Adrenal insufficiency

Clinical manifestations of chronic adrenal insufficiency

Symptom	Frequency, percent
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	6-13
Sign	
Weight loss	100
Hyperpigmentation	94
Hypotension (systolic BP <110 mmHg)	88-94
Vitiligo	10-20
Auricular calcification	5
Laboratory abnormality	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

H:hypotension, hypoglycemia, hypothermia, hyponatremia
A:anorexia
W:weight loss
W:weakness

TABLE 14-19 -- CLINICAL AND LABORATORY FEATURES OF AN ADRENAL CRISIS

Dehydration, hypotension, or shock out of proportion to severity of current illness

Nausea and vomiting with a history of weight lost and anorexia

Abdominal pain, so-called acute abdomen

Unexplained hypoglycemia

Unexplained fever

Hyponatremia, hyperkalemia, azotemia, hypercalcemia, or eosinophilia

Hyperpigmentation or vitiligo

Other autoimmune endocrine deficiencies, such as hypothyroidism or gonadal failure

Assessment of ant. Pituitary function

Present illness - Lab data during OPD

	201701	2017/02	2017/04	07/11	07/28
Cortisol (3.7-19.4)	4.4	7.2	6.0	8.7	6.6
ACTH (<46.0 pg/mL)	18	27.8	18.4	22.2	33.2
TSH (0.40 ~ 4.0)	1.736	1.736	1.221	1.159	1.112
fT4 (0.80 ~ 1.90)	0.57L	0.57L	0.62L	0.68L	0.75L
FSH (3.03-8.08)	1.7				
LH (1.80-11.78)	0.57				
E2 (21-251)	<10				
HGH (<8)	<0.1				<0.1
IGF-1 (109-284)	82.2				58.1L
PRL (1.20-29.93)	5.00				

- Eltroxin tab 50 mcg 1 TAB QD

Less useful in elderly

Image diagnosis

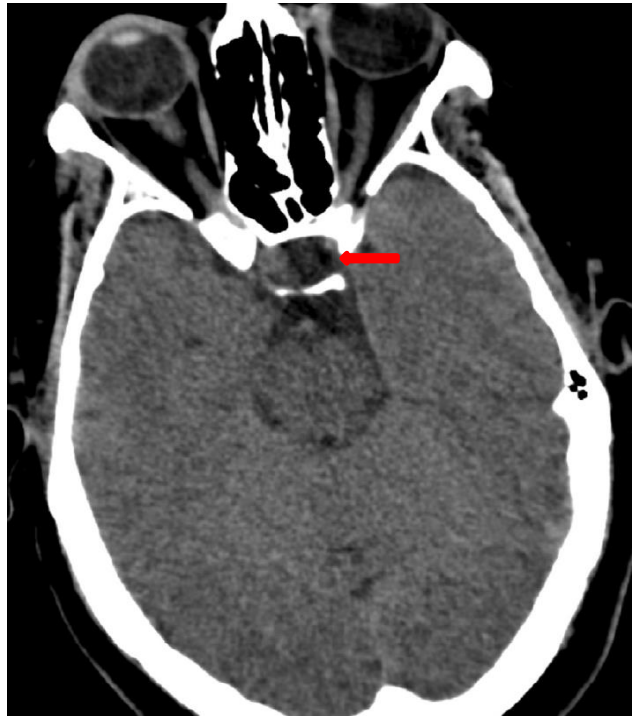
- non-contrast brain CT
- MRI is more sensitive in the subacute phase

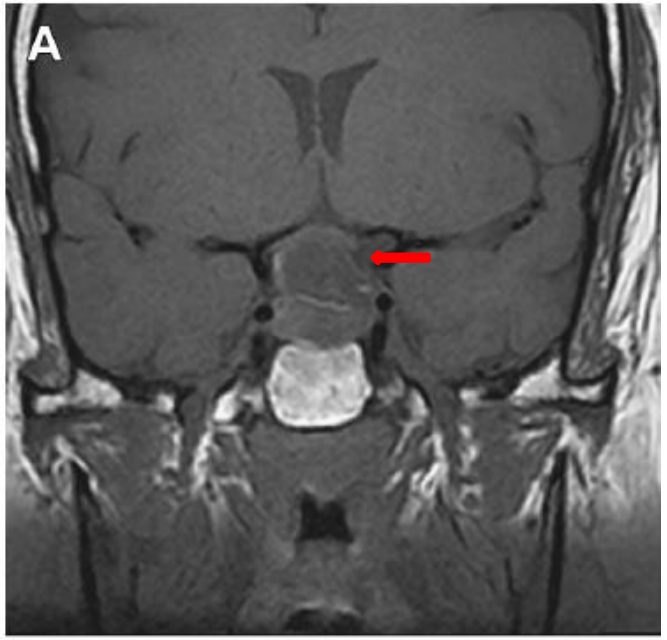
Table 1
Blood component density changes with time on CT and MRI

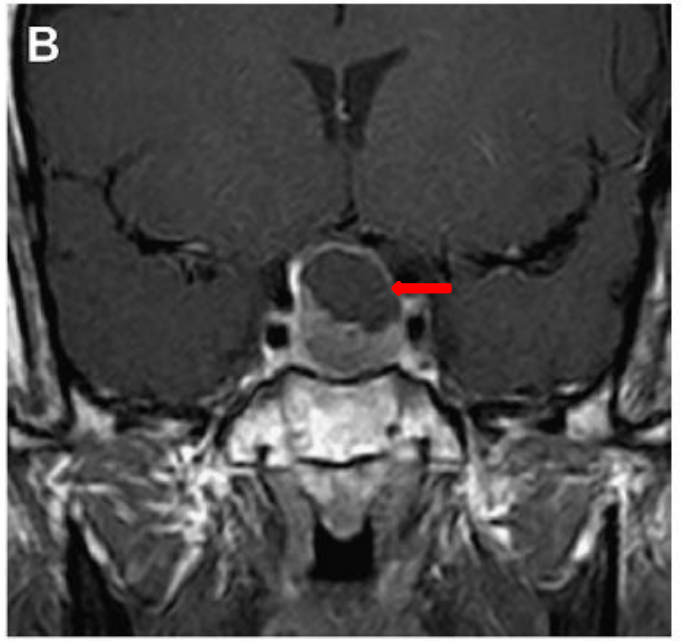
	Hemorrhage	Necrosis
A: CT		
Acute (0–10 d)	Hyperdensity (60–80 HU)	Hypodensity
Subacute (10–20 d)	Isodensity (40 HU)	
Chronic (>20 d)	Hypodensity (10 HU)	
B: MRI		
Acute		Hypo T1, Hyper T2
Oxyhemoglobin (<24 h)	Iso T1, Iso T2	
Deoxyhemoglobin (24–48 h)	Iso T1, Hypo T2	
Subacute		
Intracellular methemoglobin (3–5 d)	Hyper T1, Hypo T2	
Extracellular methemoglobin (>5 d)	Hyper T1, Hyper T2	
Chronic		
Hemosiderin (>3 wk)	Hypo T1, Hypo T2	

Endocrinol Metab Clin N Am 2015;44:199-209

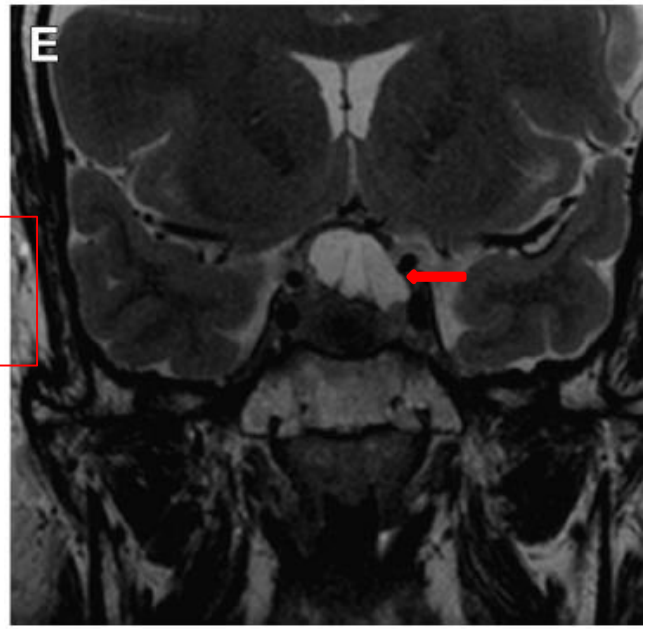
CT: necrosis, hypodense

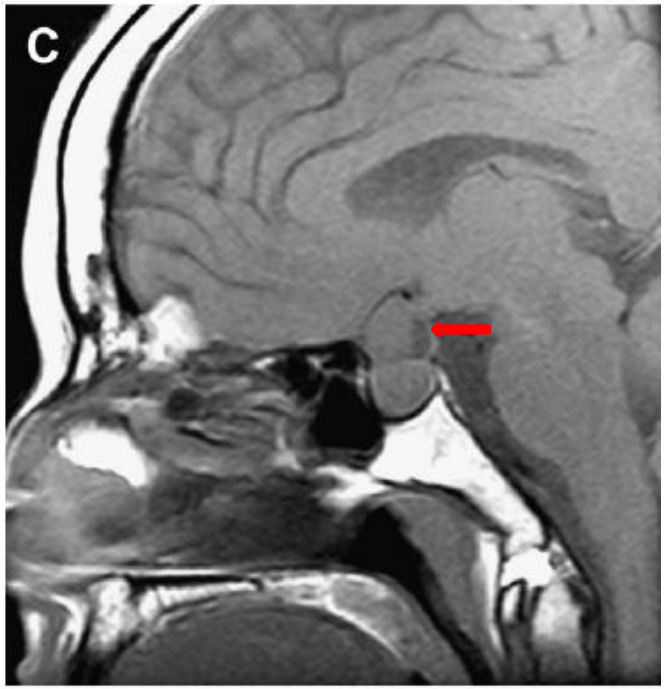


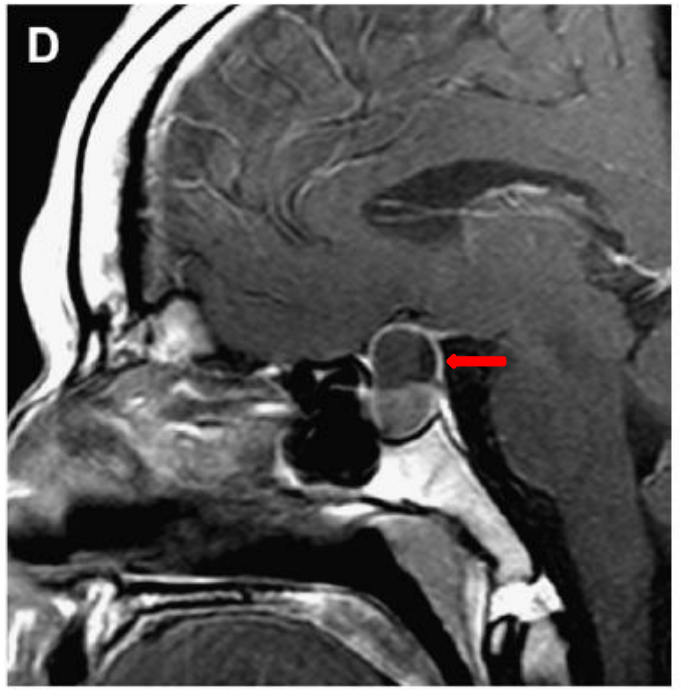




T2: necrosis, hyperintense



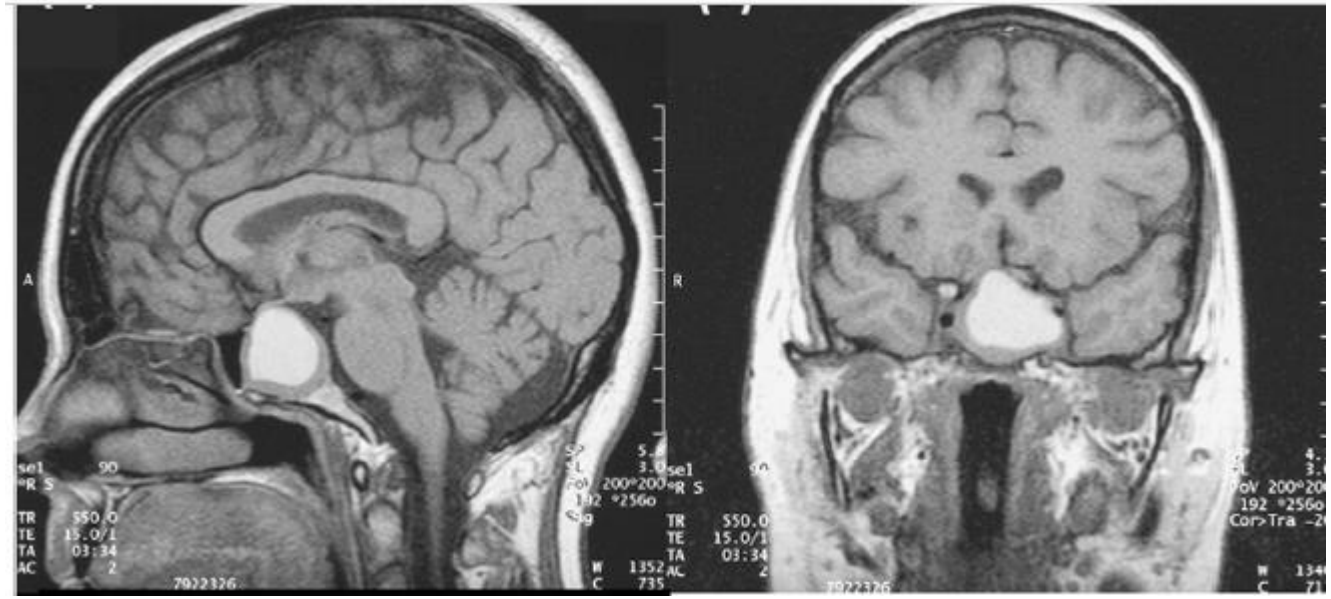




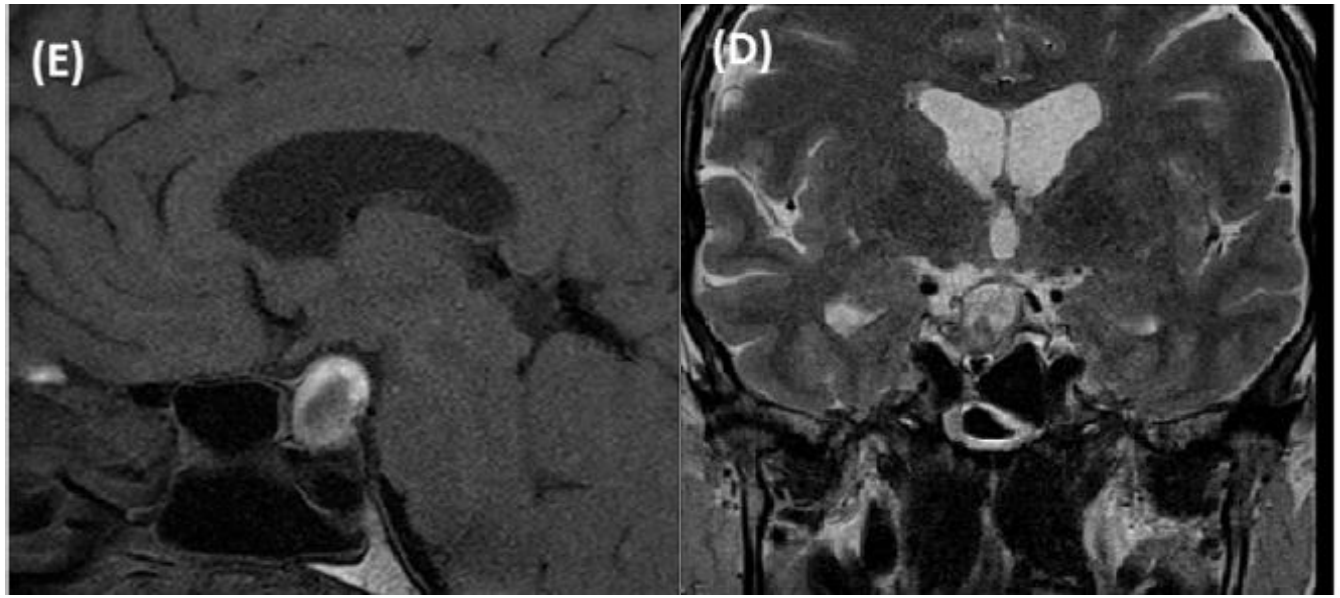
T1:hypointense

T1+C: hypointense

Endocrinol Metab Clin N Am 2015;44:199-209



T1:hyperintense, hemorrhage



T1 and T2: peripheral hyperintense, subacute hemorrhage

J of clinical neuroscience 2015;12:939-944

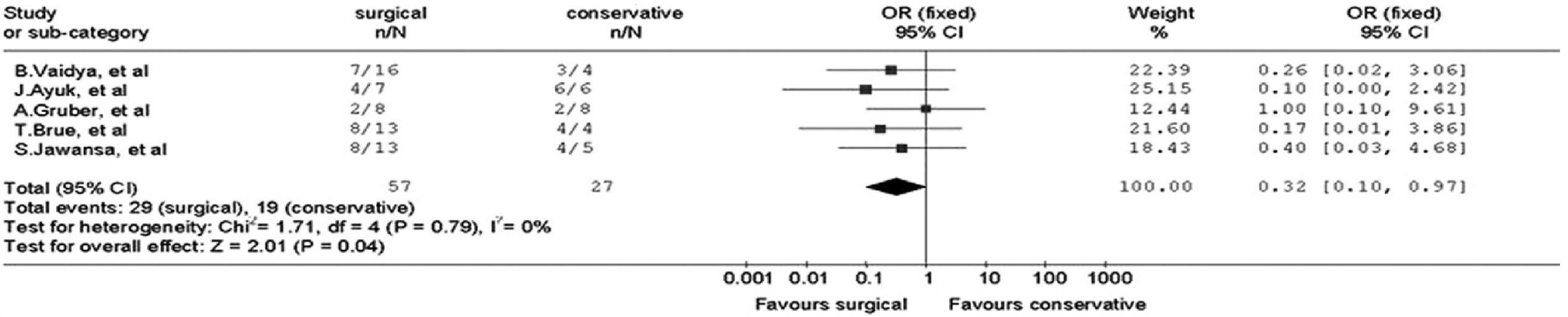
Treatement

- Surgery
- Conservative treatment with high doses of steroids are reserved for selected individuals
- Glucocorticoid treatment should always be started immediately as it maybe life-saving

A

Review: Surgical intervention or conservative treatment for pituitary apoplexy: a meta-analysis
Comparison: 01 Surgical and conservative treatment in the outcome of visual field
Outcome: 01 Surgical and conservative treatment in the outcome of visual field

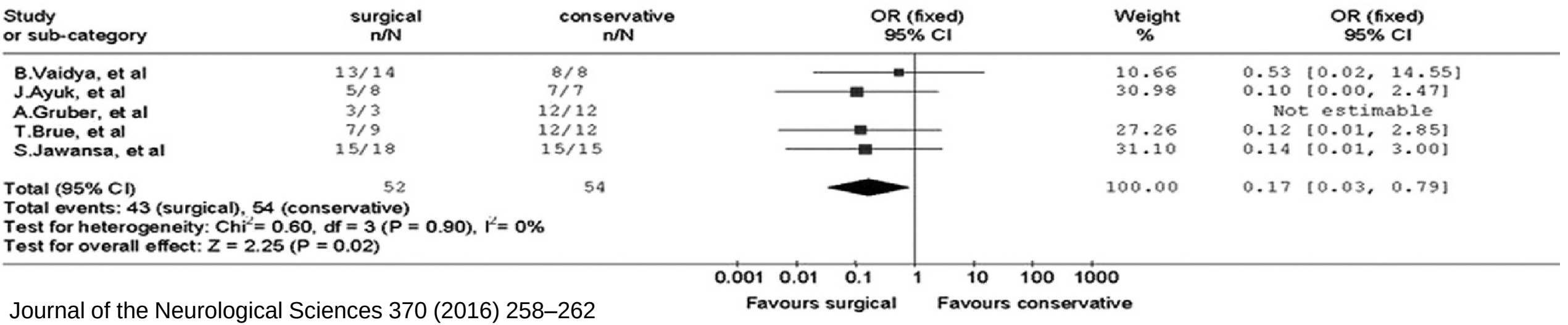
Visual field



B

Review: Surgical intervention or conservative treatment for pituitary apoplexy: a meta-analysis
Comparison: 02 Surgical and conservative treatment in the outcome of ocular plasy
Outcome: 01 Surgical and conservative treatment in the outcome of ocular plasy

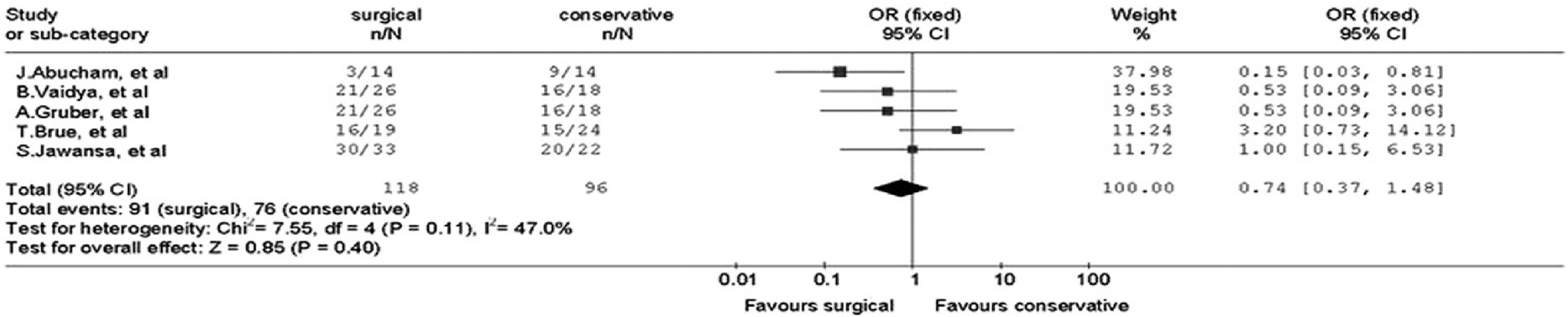
Ocular palsy



A

Review: Surgical intervention or conservative treatment for pituitary apoplexy: a meta-analysis
Comparison: 04 Surgical and conservative treatment in the outcome of pituitary function
Outcome: 01 Surgical and conservative treatment in the outcome of pituitary function

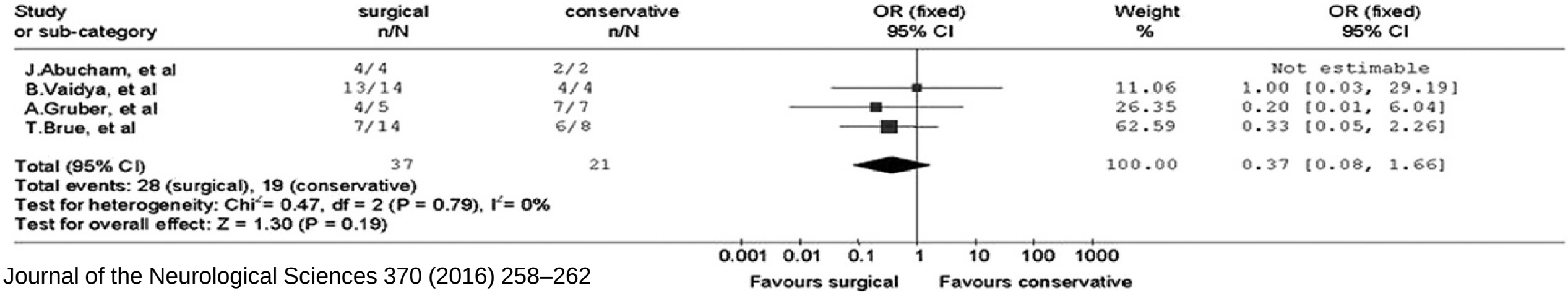
Pituitary function



B

Review: Surgical intervention or conservative treatment for pituitary apoplexy: a meta-analysis
Comparison: 03 Surgical and conservative treatment in the outcome of visual acuity
Outcome: 01 Surgical and conservative treatment in the outcome of visual acuity

Visual acuity



UK, single center, median of f/u:7 years

Table 3. Comparison between all three groups

Within 7 days

Outcome	Conservative management (n = 22) (%)	Emergency surgery (n = 23) (%)	Delayed elective surgery (n = 10) (%)	P-value
Complete/near-complete resolution of visual field defects	80	80	60	NS
Complete/near-complete resolution of cranial nerve palsies	100	92	100	NS
Pituitary hormone replacement	90	96	80	NS

Surgical indication: deteriorating of visual acuity and persistent field defect

Clinical Endocrinology (2014), 80, 419–424

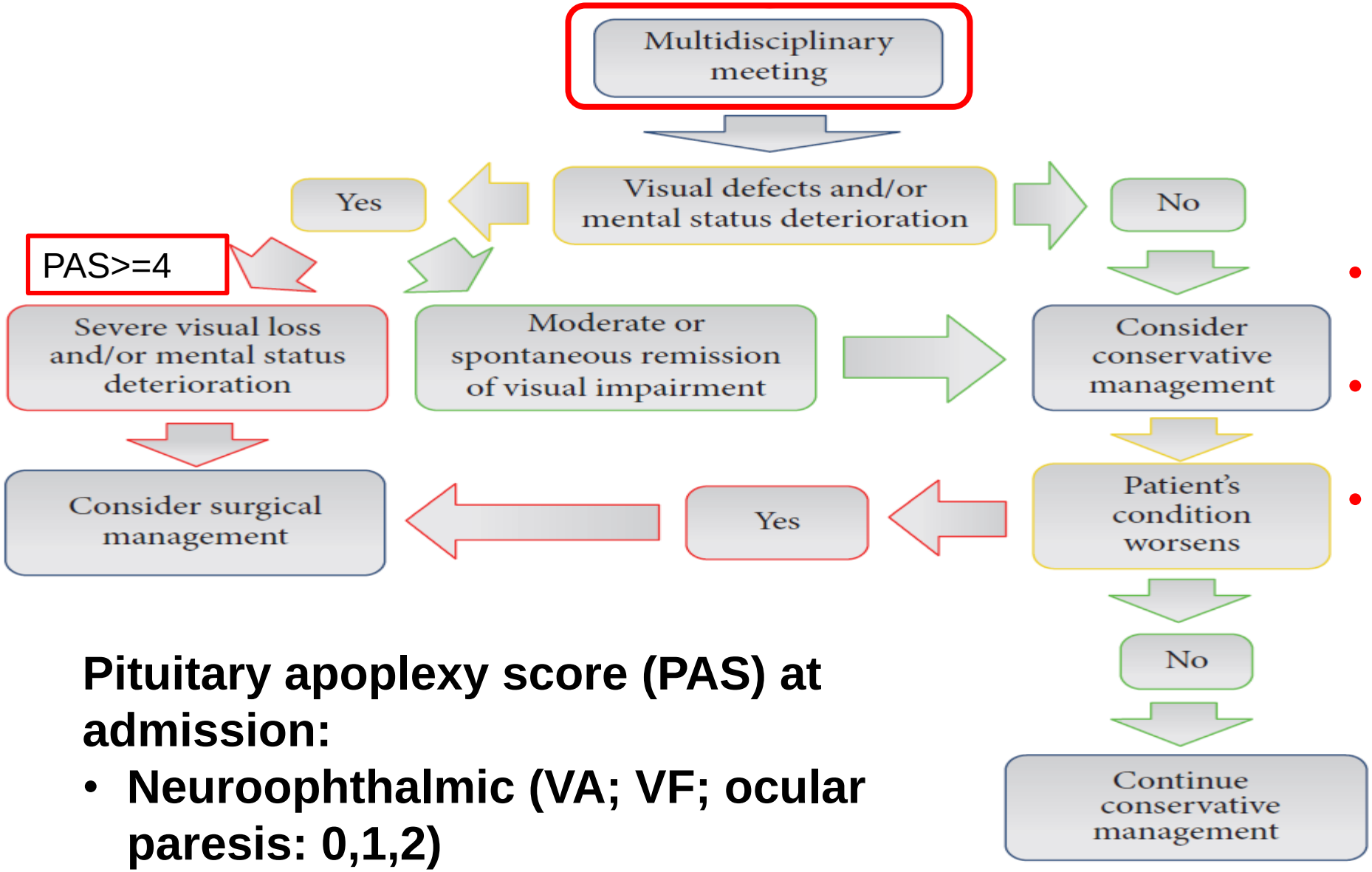
- Mayo Clinic: 1992-2013, n=87
- Similar conclusion
- Severe neuro-ophthalmological deficits recovered excellent with early surgery
- May need long-term hormone replacement

J Neurosurg 2015;122:1450-1457

Pituitary apoplexy grading system

- Grade 1: asymptomatic, incidental found, subclinical apoplexy
- Grade 2: endocrine dysfunction
- Grade 3: c/o headache
- Grade 4: ocular paresis
- Grade 5: acute visual deficits or altered mental status
- Early surgery suggested in higher grade

World neurosurgery 2014;82:781-790



- **Hydrocortisone 100-200mg bolus**
- **Continued and tapered**
- **Eltroxin if needed**

Pituitary apoplexy score (PAS) at admission:

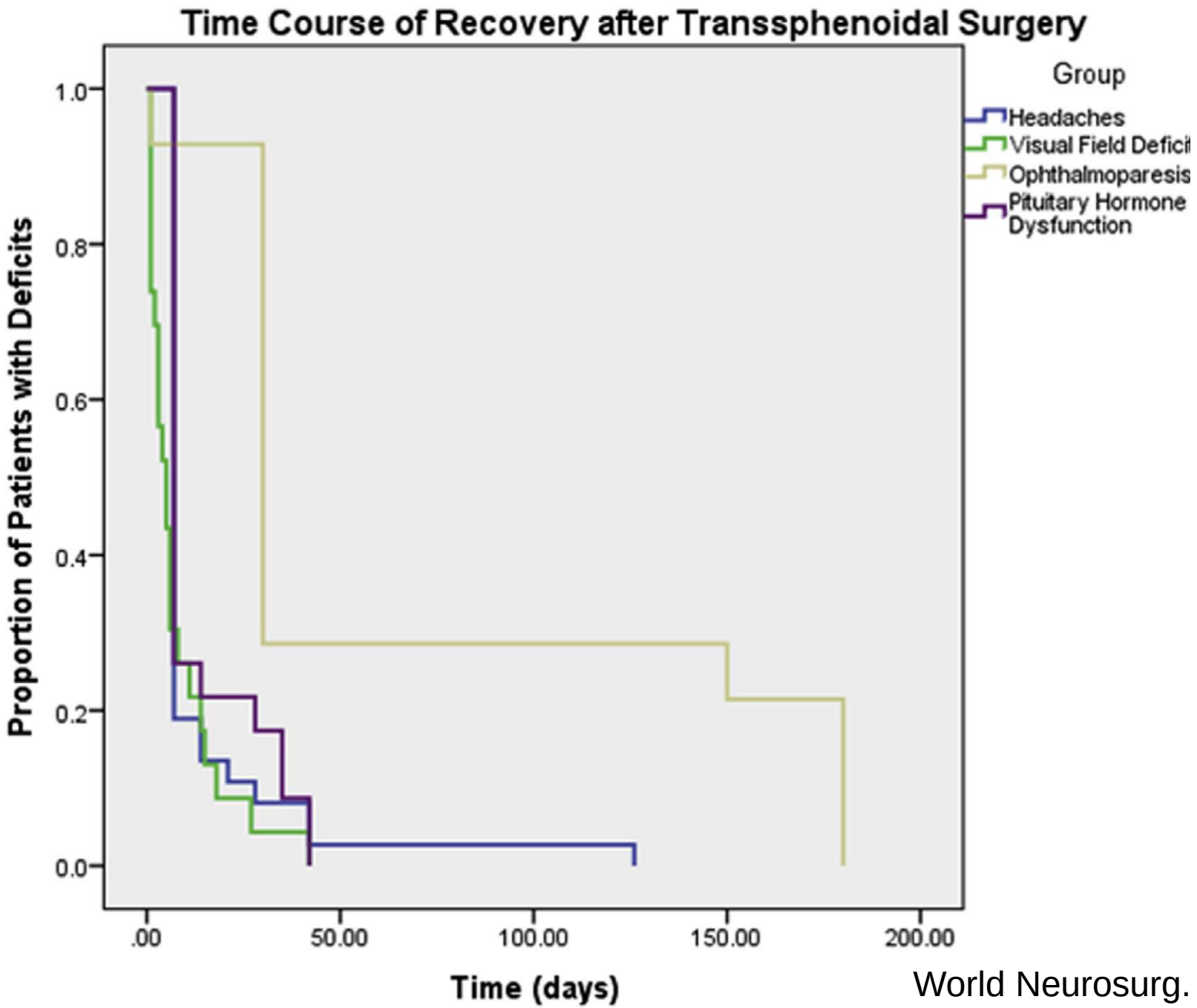
- **Neuroophthalmic (VA; VF; ocular paresis: 0,1,2)**
- **GCS: 0,2,4**
- **0-10: higher indicated extensive neuroophthalmic impairment**

Int J Endocrinol. 2016;2016:795153
Clinical Endorcirnology 2011;74:9-20

Prognosis

- Surgery can normalize VA/VF in about 50% patients, but CN III, IV or VI damage maybe permanent.
- Long term hormone supplement maybe needed.
- Prolactin level maybe inversely correlated with pituitary function recovery. (the lower PRL, the least likely to recover)
- Residual pituitary tumor regrowth occurs in 21.4% within 5 yrs

JCEM 2004;89:5649-5645
Clinical Endrocrinology 2011;75:501-504



World Neurosurg. (2016) 96:434-439.

Endocrinological status at follow-up by treatment strategy

Time Point & Variable	Conservative Management (n = 18)	Early Surgery (n = 61)	Delayed Surgery (n = 8)
Replacement therapy at 1-yr follow-up	11 (68.7%)	37 (62.7%)	5 (62.5%)
Levothyroxine	5 (41.7%)	22 (59.5%)	3 (60%)
Cortisone	4 (33.3%)	26 (70.3%)	3 (60%)
Testosterone	1 (33.3%)	20 (66.7%)	2 (66.7%)
Estradiol	4 (50%)	2 (28.6%)	0
Progesterone	2 (25%)	2 (28.6%)	0
Growth hormone	0	1 (2.7%)	1 (20%)
Dopamine antagonist	1 (8.3%)	3 (8.2%)	1 (20%)
Desmopressin	0	5 (13.5%)	2 (40%)
Replacement therapy at last follow-up	9 (56.3%)	25 (42.4%)	6 (75%)
Levothyroxine	4 (44.4%)	24 (66.7%)	4 (66.7%)
Cortisone	4 (44.4%)	22 (62.9%)	4 (66.7%)
Testosterone	2 (100%)	18 (64.3%)	3 (75%)
Estradiol	5 (71.4%)	2 (25%)	1 (50%)
Progesterone	2 (28.6%)	2 (25%)	1 (50%)
Growth hormone	0	1 (2.9%)	1 (16.7%)
Dopamine antagonist	1 (11.1%)	4 (11.4%)	2 (33.3%)
Desmopressin	0	3 (8.6%)	1 (16.7%)

J Neurosurg 2015;122:1450-1457

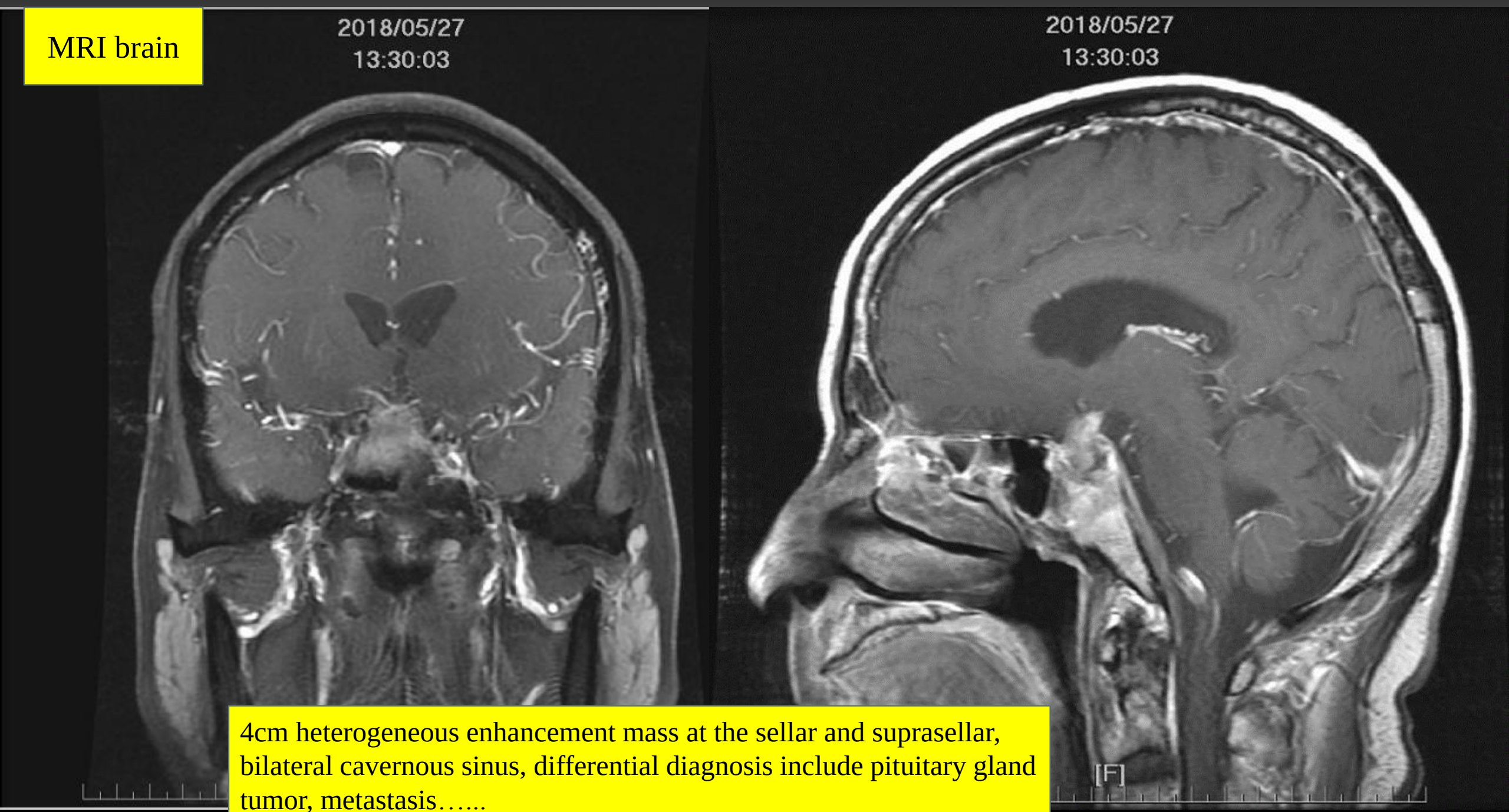
Case 1

70 y/o male

Nausea and vomiting
Sudden onset of blurred vision, diplopia and headache since 2018/05/18
Right upper eyelid dropping since 2018/05/21

pupils: 4 / 2 mm; Light reflex : - /+;
EOM: right eye limitation, fixed eyeball; ptosis(+) right:
Compressive optic neuropathy OD with CN3 involvement, OD

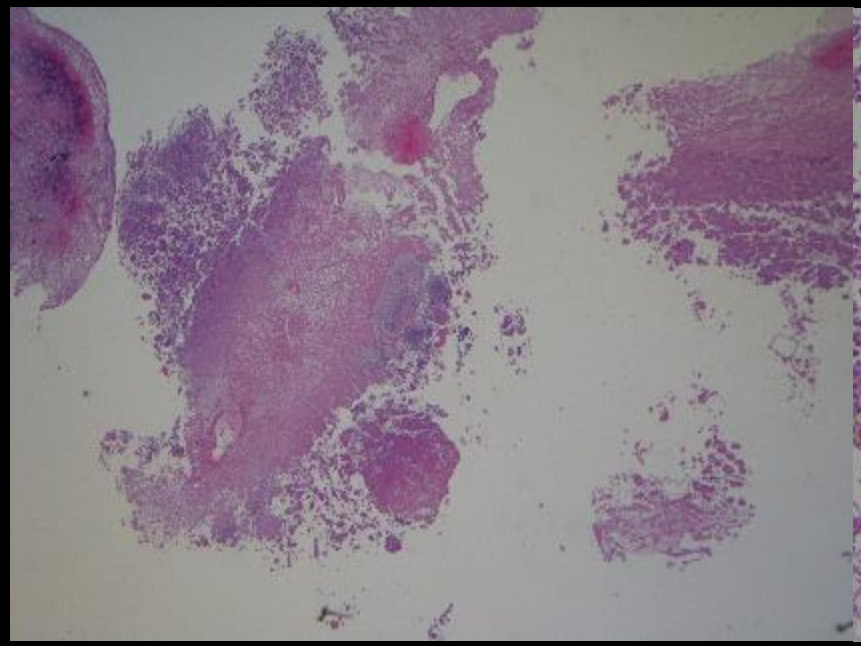
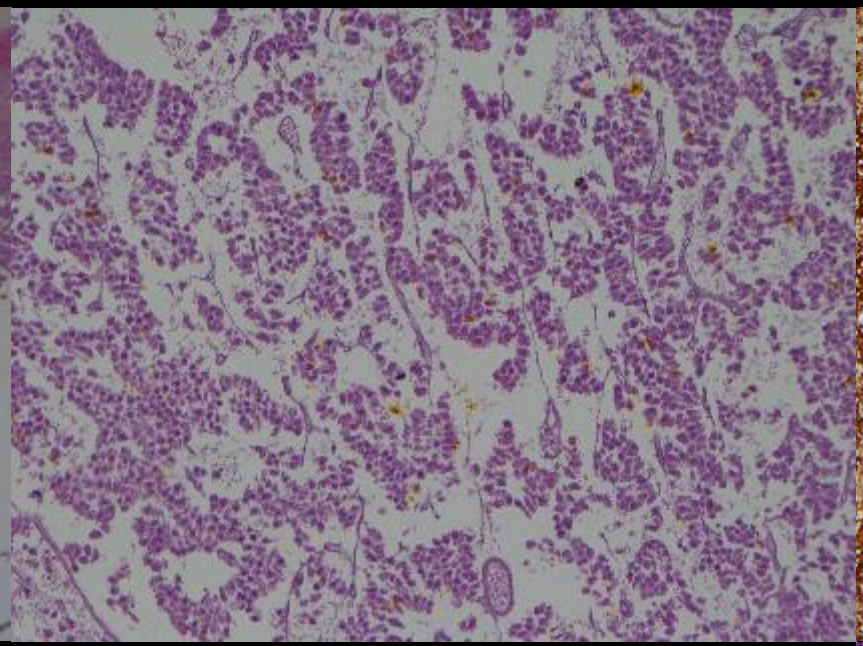
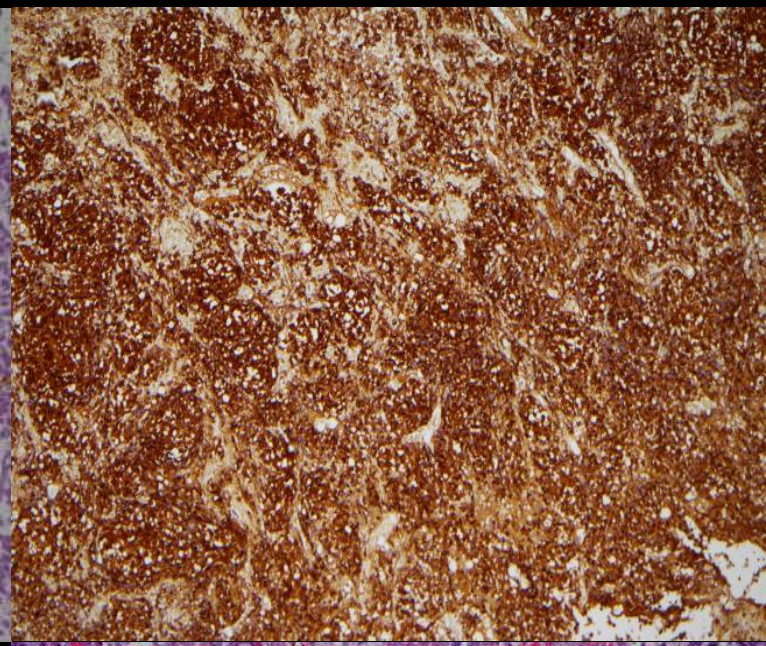
MRI brain



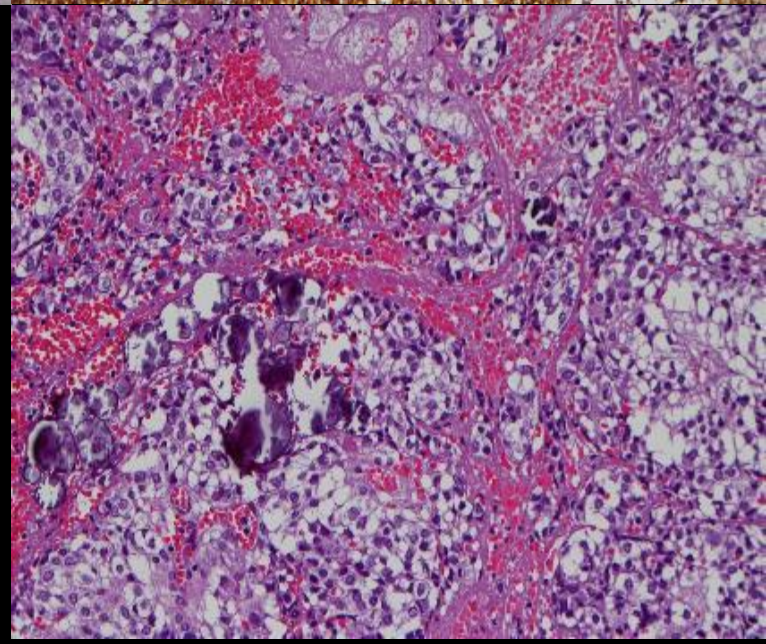
4cm heterogeneous enhancement mass at the sellar and suprasellar, bilateral cavernous sinus, differential diagnosis include pituitary gland tumor, metastasis…...

Laboratory data

5/28			5/28		
Prolactin	5.79	M:2.58-18.12	TSH	0.386	0.4-4 uIU/mL
FSH	5.4	0.95-11.95 mIU/ml	Free T4	0.74	0.80-1.90 ng/dL
LH	1.73	0.57-12.07mIU/ml	T3	46	58-159 ng/dL
Testosterone	<0.13	M: 1.74-8.43	T4	5.83	4.5-12.5 ug/dL
			ACTH	14	<46 pg/mL
			Cortisol 8AM	1.0	3.7-19.4 ug/dL

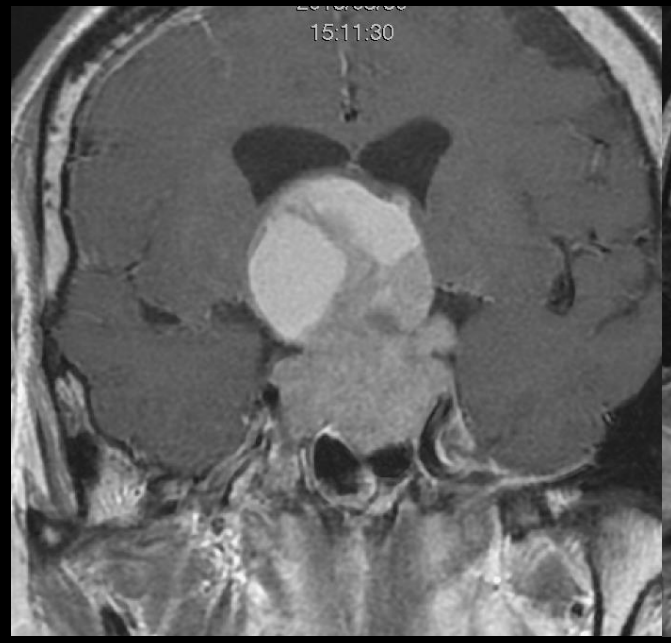
- Hydrocortisone 100mg iv q8h, eltroxin 25 mcg/day
- Transsphenoidal surgery by EEA under navigation on 2018/5/31 (6D)
- IHC stain for PRL, GH, ACTH, FSH, LH and TSH: all negative
- Pathology: pituitary adenoma with massive necrosis
- Final diagnosis: Null cell adenoma with apoplexy
- f/u: ptosis, eye movement improved, on cortisone acetate (25/12.5mg bid), eltroxin 25mcg



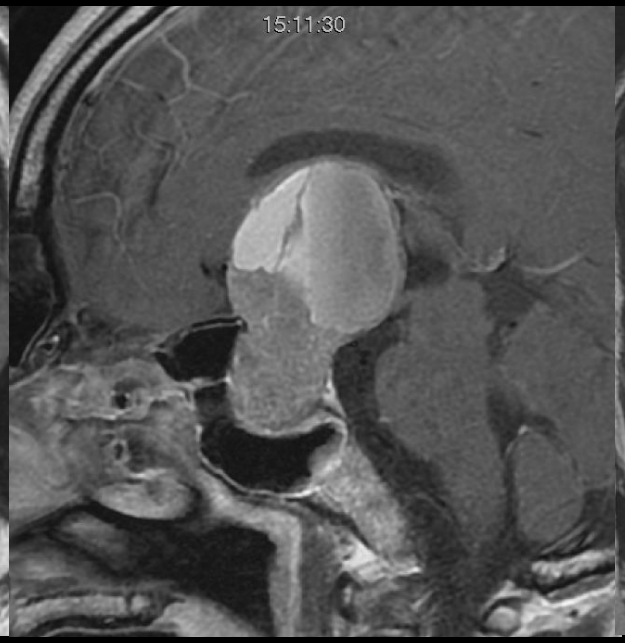
Case 2

Sella MRI

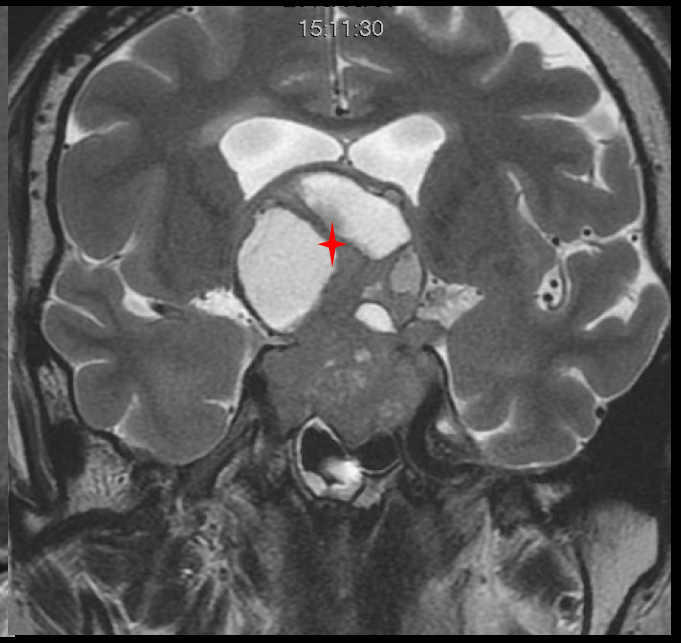
40 y/o male
Diplopia, muscle weakness
ER: Hydrocephalus s/p EVD, hyperprolactinemia



Cor T1+C



Sag T1+C



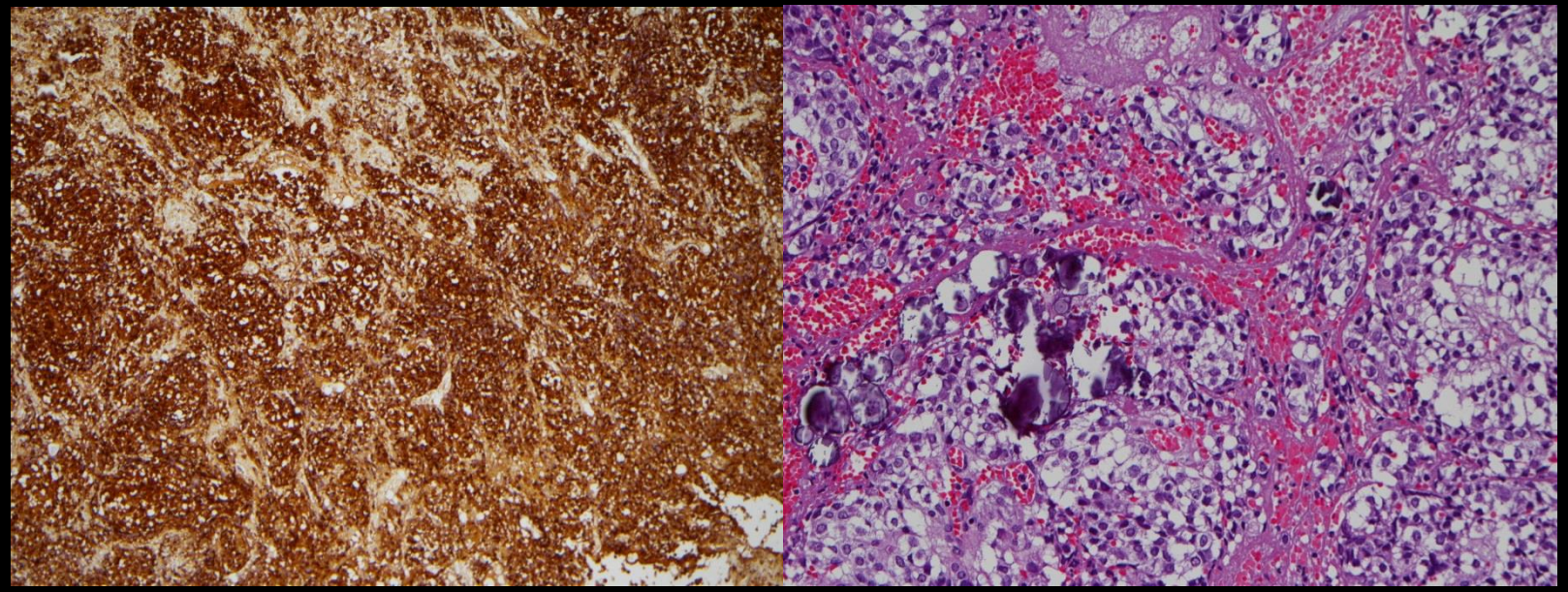
Cor T2

Laboratory data

5/28			5/28		
Prolactin	>2000	M:2.58-18.12	TSH	0.721	0.4-4 uIU/mL
FSH	0.5	0.95-11.95 mIU/ml	Free T4	0.72	0.80-1.90 ng/dL
LH	0.1	0.57-12.07mIU/ml	T3	-	58-159 ng/dL
Testosterone	<0.13	M: 1.74-8.43	T4	-	4.5-12.5 ug/dL
			ACTH	11.8	<46 pg/mL
			Cortisol 8AM	3.8	3.7-19.4 ug/dL

- Hydrocortisone 50 mg IVA Q8H
- EEA for tumor removal (Dark fluid inside the tumor, c/w apoplexy) (D4)
- Levothyroxine 75 mcg/day since 2018/06/02
- Cabergoline 0.5 mg QW6 since 2018/06/09

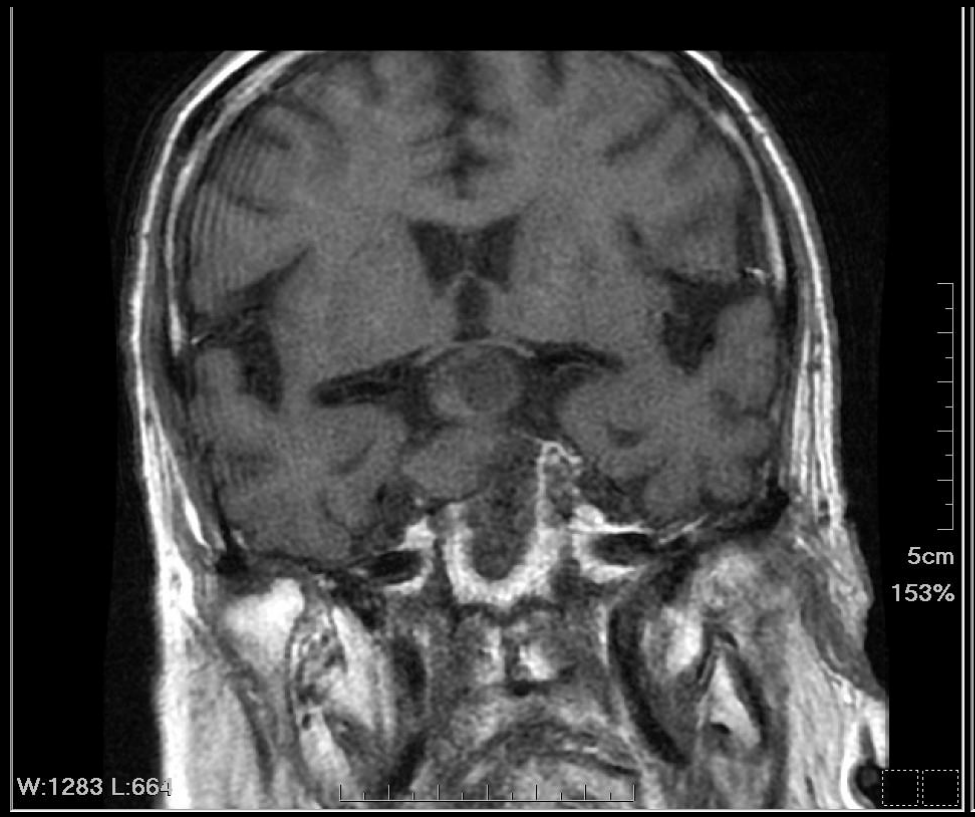
Lactotroph adenoma
Immunoreactive for PRL (4+)



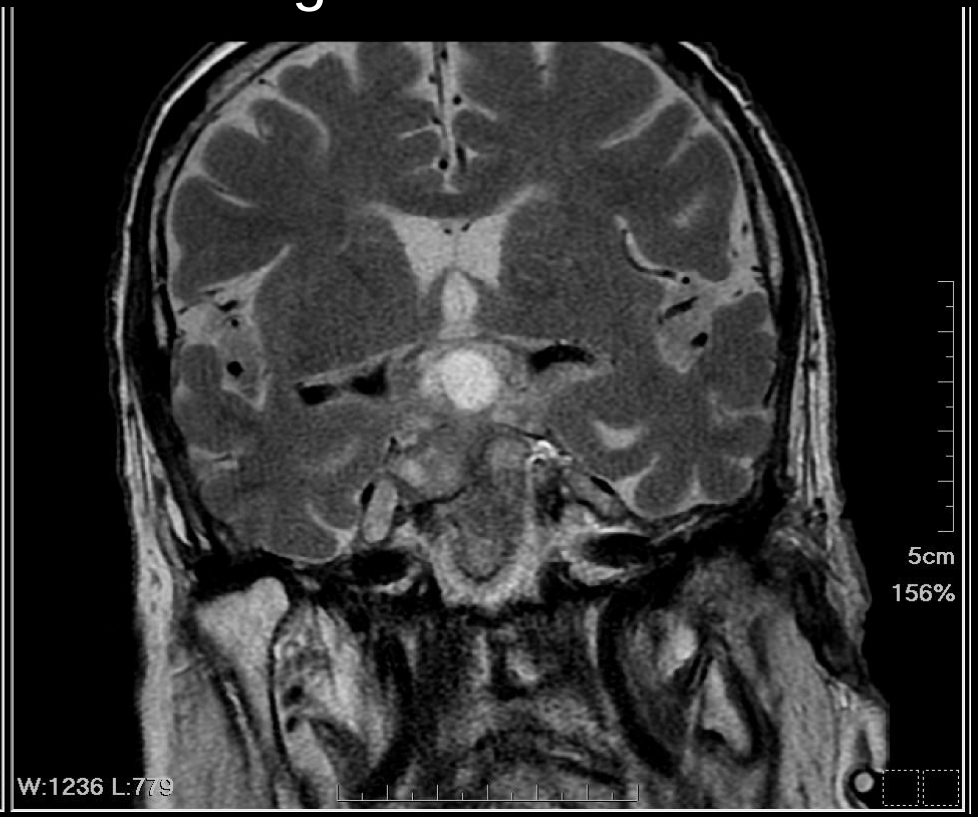
Case 3

Sella MRI

85 y/o male
double vision
intermittent headache
Progressive weakness



T1 CORONAL

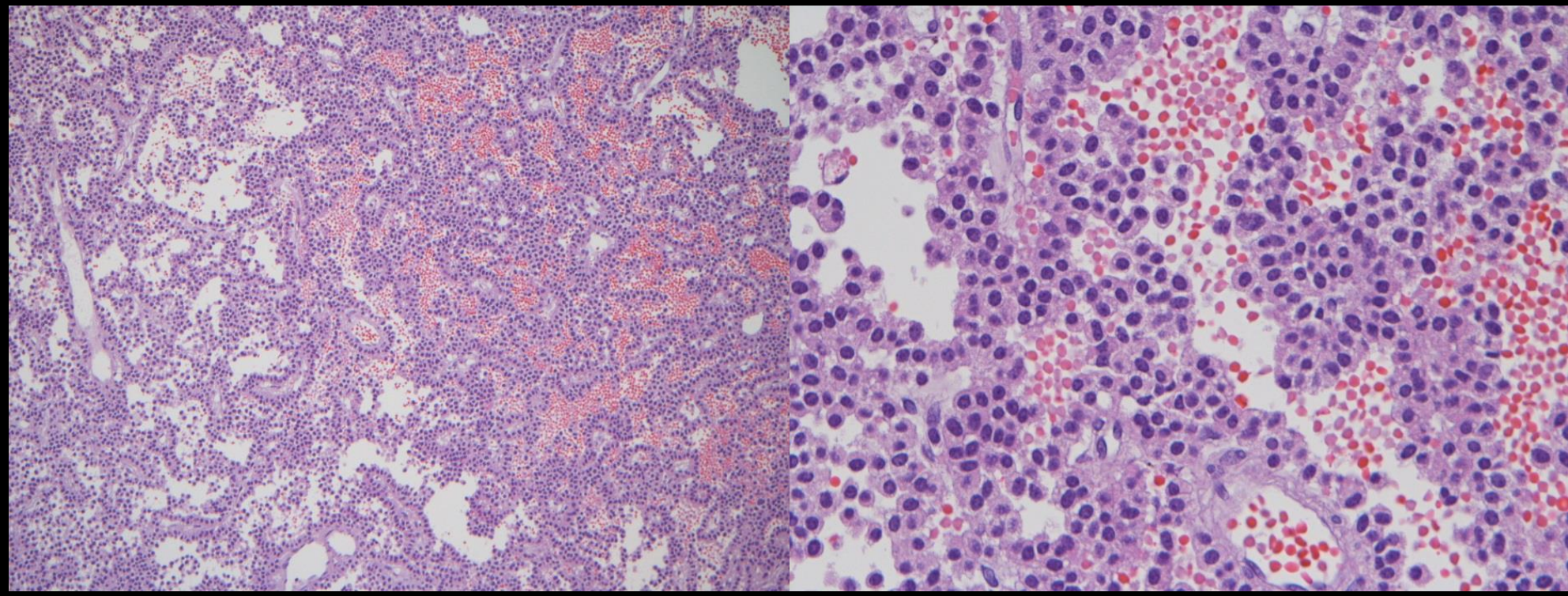


T2 CORONAL

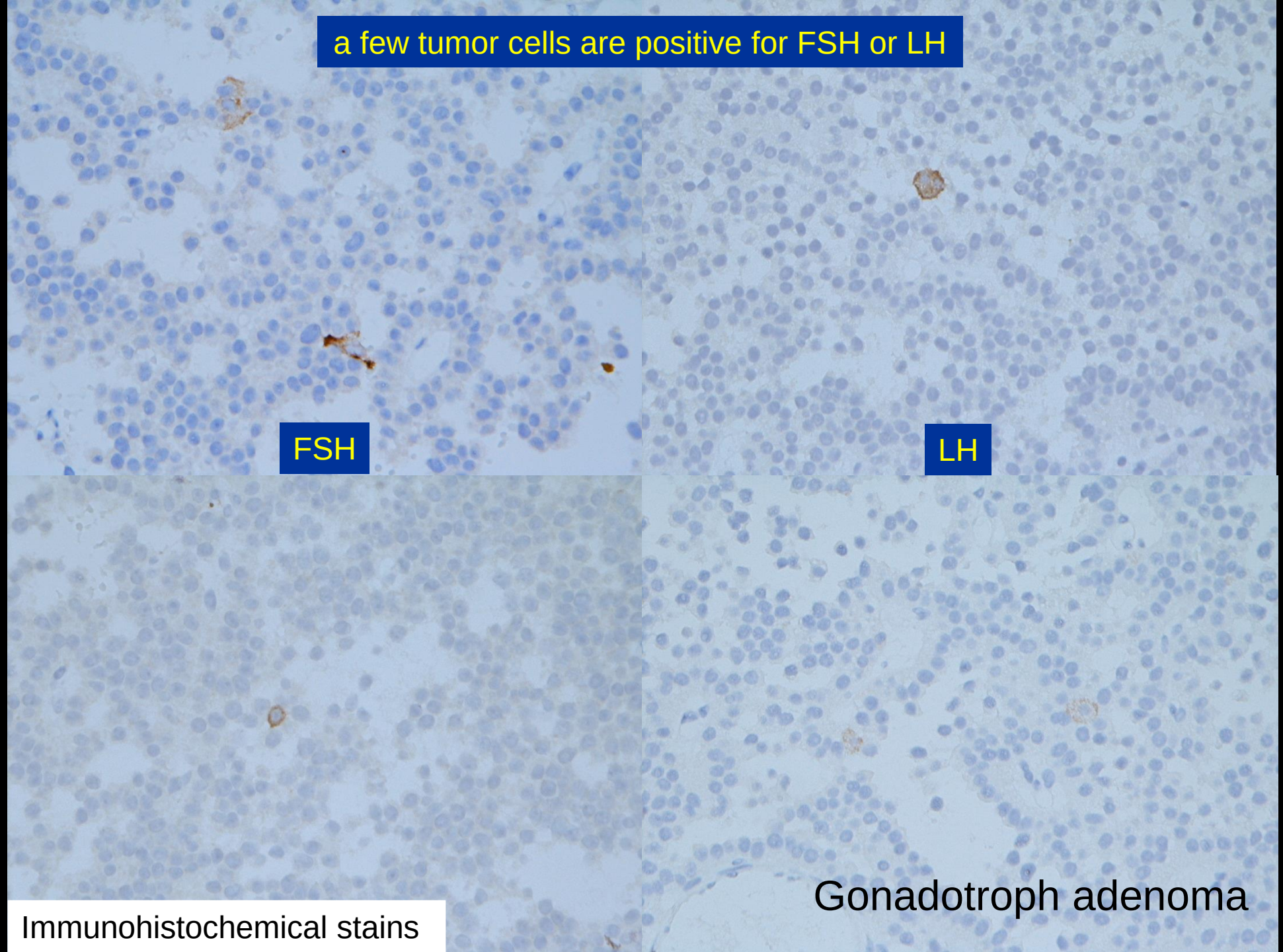
Laboratory data

1/22			1/20		
Prolactin	4.66	M:2.58-18.12	TSH	0.76	0.4-4 uIU/mL
FSH	3.6	0.95-11.95 mIU/ml	Free T4	< 0.4	0.80-1.90 ng/dL
LH	1.45	0.57-12.07mIU/ml	T3	<25	58-159 ng/dL
Testosterone	<0.13	M: 1.74-8.43	Free T3	< 1.0	2.30-4.29 pg/ml
			Cortisol 7PM	11.5	2.9-17.3 ug/dL

Pathology

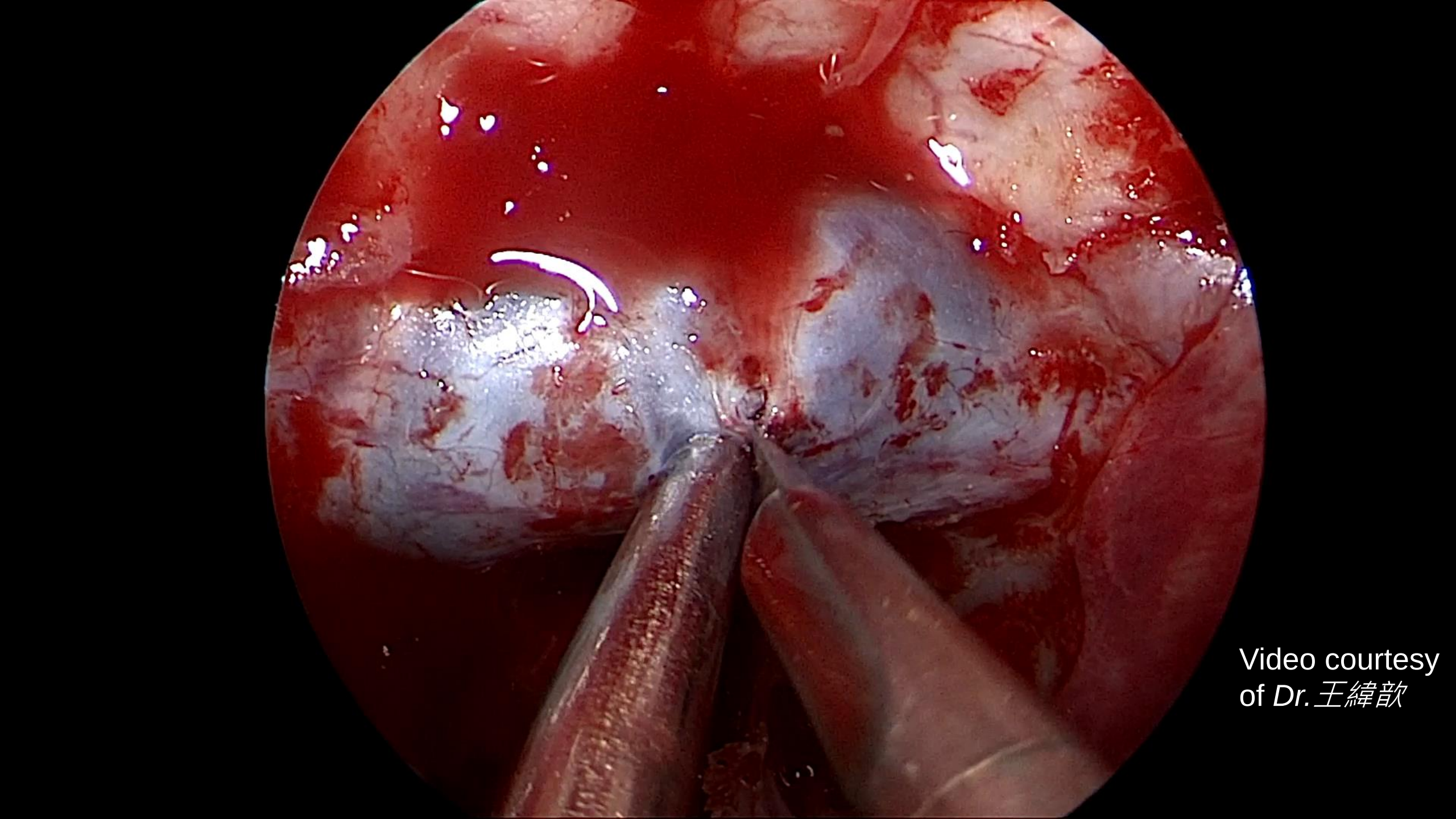


- Hydrocortisone 100mg iv q8h -> 50mg iv q8h, eltroxin 50mcg/day
- Endoscopic endonasal approach(EEA) surgery (D8)
- Operation finding: Macroadenoma of pituitary gland. Fluid came out after incision of pituitary gland. The finding was compatible with apoplexy.
- f/u :cortisone acetate 25/12.5 mg bid (cortisol: 1.42), eltroxin 50mcg/day



Immunohistochemical stains

Gonadotroph adenoma



Video courtesy
of *Dr.王緯歆*

Take home message

- Pituitary apoplexy should be considered in patients with sudden onset of headache and neuroophthalmic deficit.
- MRI or CT are the preferred image for diagnosis.
- Multidisciplinary management is important.
- Surgery had good result on visual deficit recovery, while selected individuals can be treated conservatively.
- Hydrocortisone treatment before operation is suggested.
- Long term hormone supplement maybe needed.

Thank you for listening