Double Trouble: Endocrine Emergencies

Matt Ettleson, M.D.*

Endorama

December 5, 2019

M170

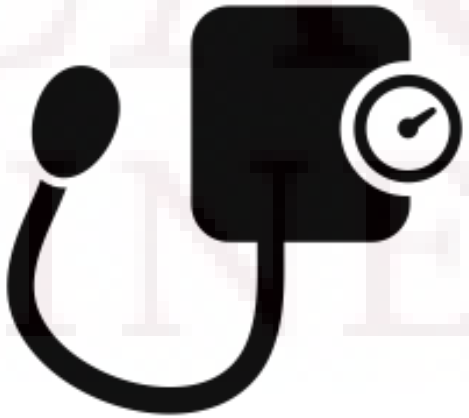
AT THE FOREFRONT
UChicago Medicine

*I have no conflicts of interest to disclose.

Learning Objectives

- Brief review of pituitary disease and visual deficits
- Interpretation of hormone levels in the setting of pituitary mass
- Discussion of key epidemiologic, pathogenic features of pituitary apoplexy
- Explore a possible connection between pituitary apoplexy, diabetes mellitus, and diabetic ketoacidosis

A 42 year old woman with a history of hypertension and type 2 diabetes presents with elevated blood pressure and headache.



HPI

The patient awoke on the morning of presentation at 4 AM with a right-sided frontal headache. She was nauseous. She attempted to take an ibuprofen but vomited. She was unable to take any of her regular medications. She denied any weakness in her extremities or speech difficulties. At the time, she did not notice any visual changes. She checked her blood sugar that morning and it was above the range of detection. She denies any falls or recent medication changes. No history of recent travel. She was last seen at UCMC in 2017 and was treated for hypertensive urgency and DKA.

Past medical history and medications

Past Medical History
type 2 diabetes mellitus
essential hypertension
hypercholesterolemia
prior HSV infection
hypertension during pregnancy
vitamin D deficiency

Past surgical History
No prior surgeries

Medications
amlodipine 10mg daily
aspirin 81mg daily
carvedilol 25mg BID
HCTZ 25mg daily
lisinopril 20mg daily

Lantus 45 units (?) QHS
Novolog 15 units (?) with meals
metformin XR 500mg daily

Emergency department evaluation

Vitals

Temp: 36.5
Pulse: **113**
RR: 16
BP: **229/134**
SO_2: 98%
Weight: 81.6 kg
BMI: 30

Physical Exam

General: awake, alert but uncomfortable,
Normal conjunctiva. Non-Cushingoid facies.
CTAB but decreased effort.
RRR. No murmur appreciated.
Nontender abdomen. No obvious striae.
2+ peripheral pulses. Trace lower extremity swelling.
Mood appears appropriate.

Neuro
Pupils equal, round, reactive. Extraocular movements intact.
Face symmetric.
Dense left temporal hemianopsia.
5/5 strength in upper and lower extremities bilaterally.
2+ brachioradialis and patellar reflexes bilaterally.

Monocular temporal hemianopia

Seymour A Hershenfeld, James A Sharpe

Abstract

Monocular temporal hemianopia was identified in 24 patients. The field of the fellow eye was normal. Computed tomography or magnetic resonance imaging showed juxtasellar lesions in 19 patients. Fifteen had pituitary adenomas, two had tuberculum sella meningiomas, one a craniopharyngioma, and one an astrocytoma. One patient had optic neuritis. A relative afferent pupillary defect (RAPD) was detected in most patients. Field loss was functional in two. Two had congenital optic disc dysversion with hemianopia which did not respect the vertical meridian. Monocular temporal hemianopia is attributed to involvement of the ipsilateral optic nerve close enough to the chiasm to selectively impair conduction in crossing nasal retinal fibres from the ipsilateral eye, but too anterior to affect crossing nasal retinal fibres from the contralateral eye. The combination of an RAPD, with or without optic disc pallor, on the side of monocular temporal field loss implicates compression of the optic nerve at its junction with the chiasm.

(*Br J Ophthalmol* 1993; 77: 424–427)

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24 February 1993

At the optic chiasm axons from ganglion cells of the nasal and temporal retina separate, the nasal retinal fibres crossing in the chiasm to the contralateral optic tract and the temporal retinal fibres coursing through the lateral chiasm to the ipsilateral optic tract. Compression or infiltration of the chiasm causes several characteristic patterns of visual field loss. By interrupting the crossing nasal fibres chiasmal lesions typically cause binocular temporal hemianopic visual field defects aligned along the vertical meridian.[1-3] Anterior parachiasmal masses that compress one optic nerve and the chiasm cause a junctional scotoma, consisting of an ipsilateral central scotoma and a superotemporal field defect in the opposite eye. Masses beneath the chiasm cause field defects that are usually denser superiorly. Paracentral bitemporal hemianopia has been attributed to posterior chiasmal compression.[1-4] An incongruous homonymous hemianopia signifies optic tract involvement, while decrease of visual acuity associated with homonymous hemianopia implicates posterior chiasmal involvement.[1-4] Occasionally arcuate hemianopic scotoma in the temporal field are associated with disease of the chiasm.[4 5]

Monocular temporal hemianopia[6-11] can be a functional disorder[9-11] or a manifestation of chiasmal compression.[6-8] We report monocular temporal hemianopic defects in 24 patients. The field of the fellow eyes was normal in each case. The clinical features and pathophysiology of this distinctive pattern of field loss are discussed.

Table 1 Summary of clinical information

Patient and diagnosis*	Age	Sex	Interval between presentation and detection of monocular hemianopia	Visual acuity		Side of hemianopia
				Right	Left	
1 Pit	31	M	1 month	20/20	20/20	L
2 Pit	50	M	0	20/80	20/20	R
3 Pit	66	M	0	20/20	20/20	R
4 Pit	28	M	0	20/20	20/20	L
5 Cr	40	F	1 month post-op	20/30	20/400	L
6 Pit	61	F	12 months post-op	20/40	20/50	R
7 Dys	60	F	0	20/20	20/20	L
8 Pit	46	M	0	20/20	CF	L
9 Pit	48	M	15 yrs post-op	20/20–3	20/20–3	L
10 Pit	56	F	8 yrs post-op	CF	20/20	R
11 Pit	44	M	0	20/20	20/20	L
12 Pit	56	F	11 yrs post-op	20/20	20/25	L
13 Pit	47	F	0	20/20	20/20	L
14 Pit	47	F	0	20/25	20/30	R
15 Pit	42	F	0	20/25	20/70	L
16 Fct	43	F	0	20/20	20/20	R
17 Dys	49	F	0	20/400	20/20–3	R
18 Pit	54	F	24 months post-op	20/30	20/30	R
19 Pit	41	F	1 week post-op	20/25	20/25	L
20 Men	33	F	0	20/50	20/20	R
21 Men	57	F	0	20/60	20/20	R
22 Fct	41	F	0	20/20	20/20	R
23 Ast	17	M	0	20/25	20/20	R
24 On	19	F	0	20/20	20/25	L

*Pit=pituitary adenoma; Cr=craniopharyngioma; On=optic neuritis; Men=tuberculum sella meningioma; Fct=functional; Dys=optic disc dysversion; Ast=astrocytoma.

Patients and methods

Twenty four patients examined over 15 years in the neuro-ophthalmology unit of The Toronto Hospital, had monocular temporal hemianopic visual field defects. They had computed tomography (CT) or magnetic resonance imaging (MRI) of the suprasellar region and optic nerves. Appropriate endocrine studies were carried out. Visual fields were tested by confrontation, tangent screen examination, Perimetron automated projection perimeter, Goldmann perimeter, or automated perimetry with an Allergan Humphrey machine. Fields were tested serially for periods ranging from 1 month to 15 years (mean 4·1 years).

Results

All monocular hemianopias were superior temporal visual field defects or involved both the upper and lower temporal field. Clinical features in the 24 patients are listed in Table 1. Sixteen of the patients had monocular hemianopia at the time of presentation. In eight patients monocular temporal hemianopia was detected during follow up examinations 1 week to 15 years (mean 4·6 years) after treatment of their suprasellar disease.

Visual acuities in the eyes with the monocular temporal defect were typically good, but varied from 20/20 to finger counting, indicating involvement of the nasal central field (Table 1). Sixteen patients had visual acuity 20/40 or better. Twelve of the 24 patients had right monocular defects. Goldmann or Humphrey perimetry was performed on 23 patients. One patient with optic

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15/24 patients with pituitary adenoma

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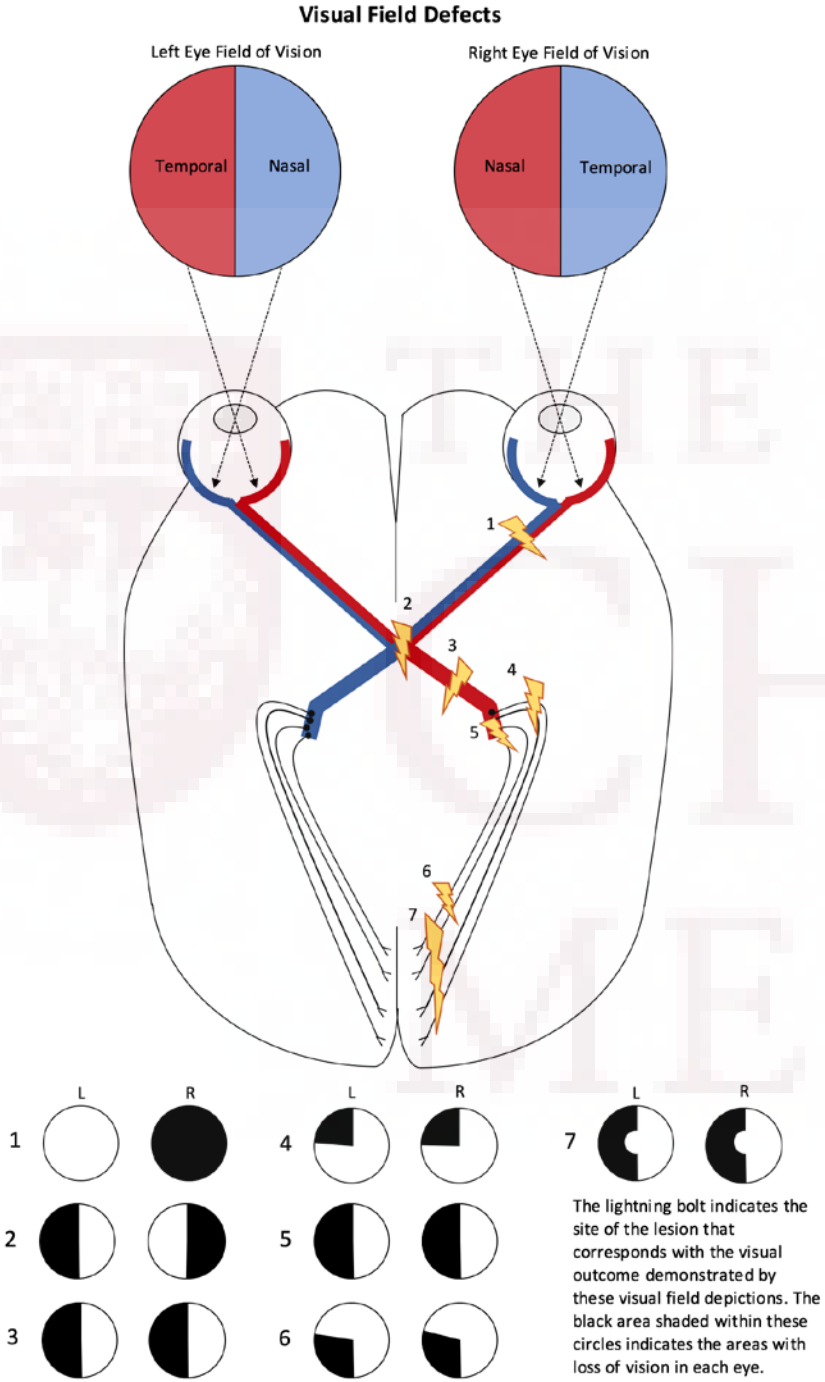
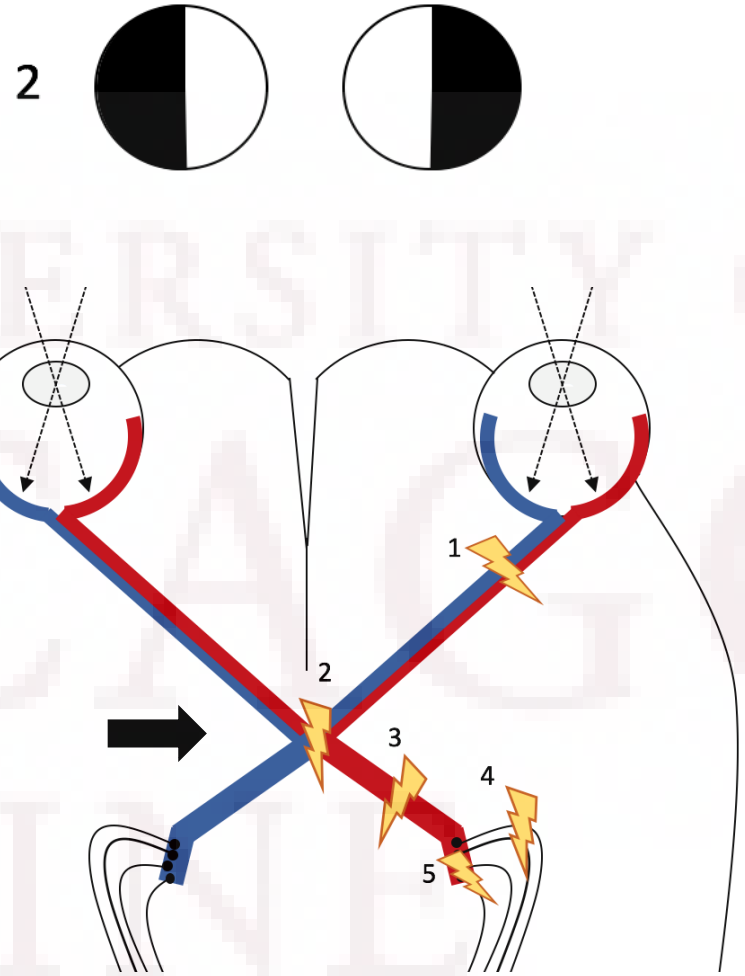


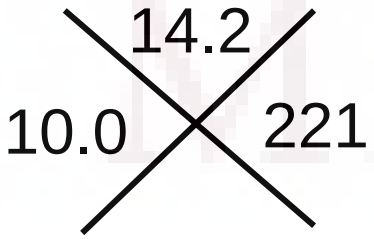


http://morancore.utah.edu/basic-ophthalmology-review/hemianopsia/

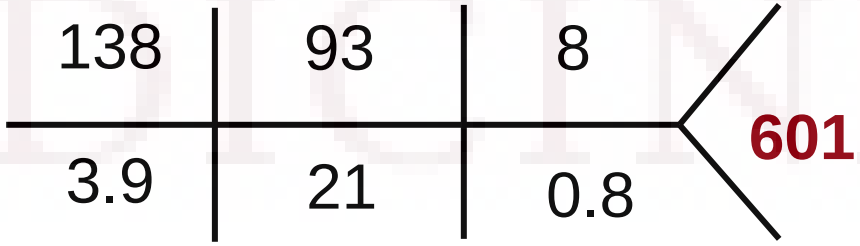
Initial lab work and imaging

Head CT wo contrast

A mass in the sella with suprasellar extension that measures up to 25mm in height likely represents a pituitary macroadenoma. No evidence of acute intracranial hemorrhage.



B-hydroxybutyrate **3.61**



calcium 10.0
HbA1c **17.2**

Cortisol 37.5
LH 0.3
FSH 3.0
Estradiol <10
Prolactin **281.9**
HGH **11.5**
IGF-1 **250**
TSH 1.31
FT4 1.35

Cortisol 37.5
LH 0.3
FSH 3.0
Estradiol <10
Prolactin **281.9**
HGH **11.5**
IGF-1 **250**
TSH 1.31
FT4 1.35

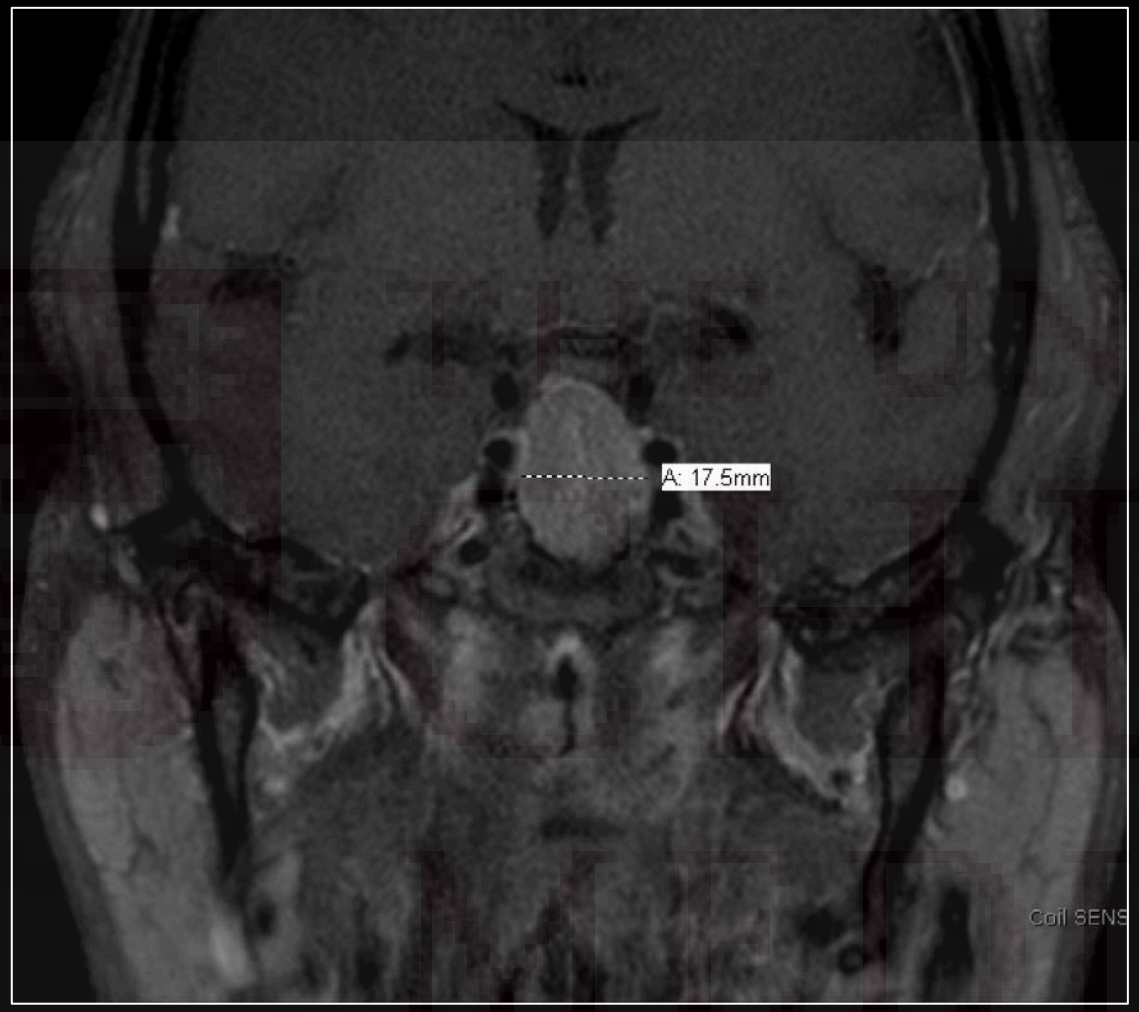
What is your interpretation of clinical presentation and biochemical findings in this patient with sellar mass?

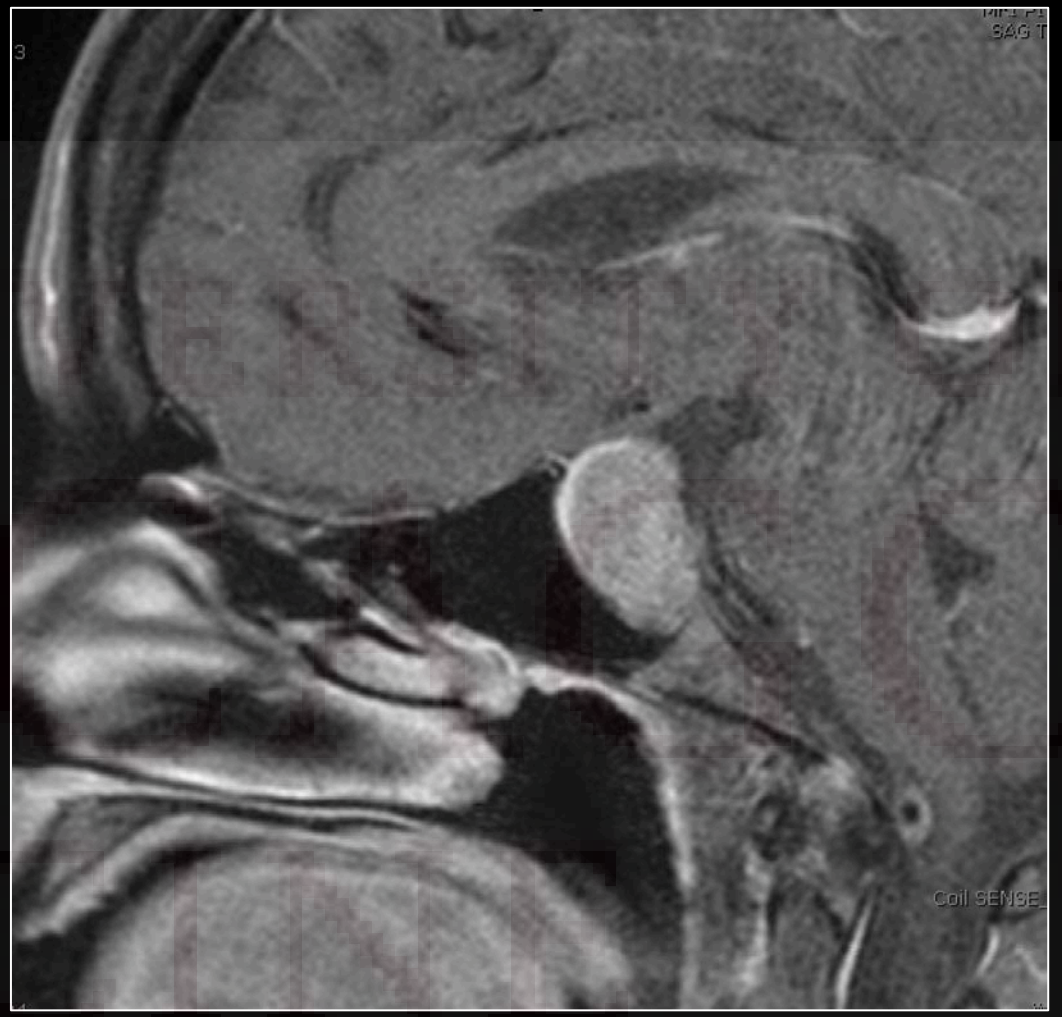
What are your next steps in management?

Neurosurgical consultation

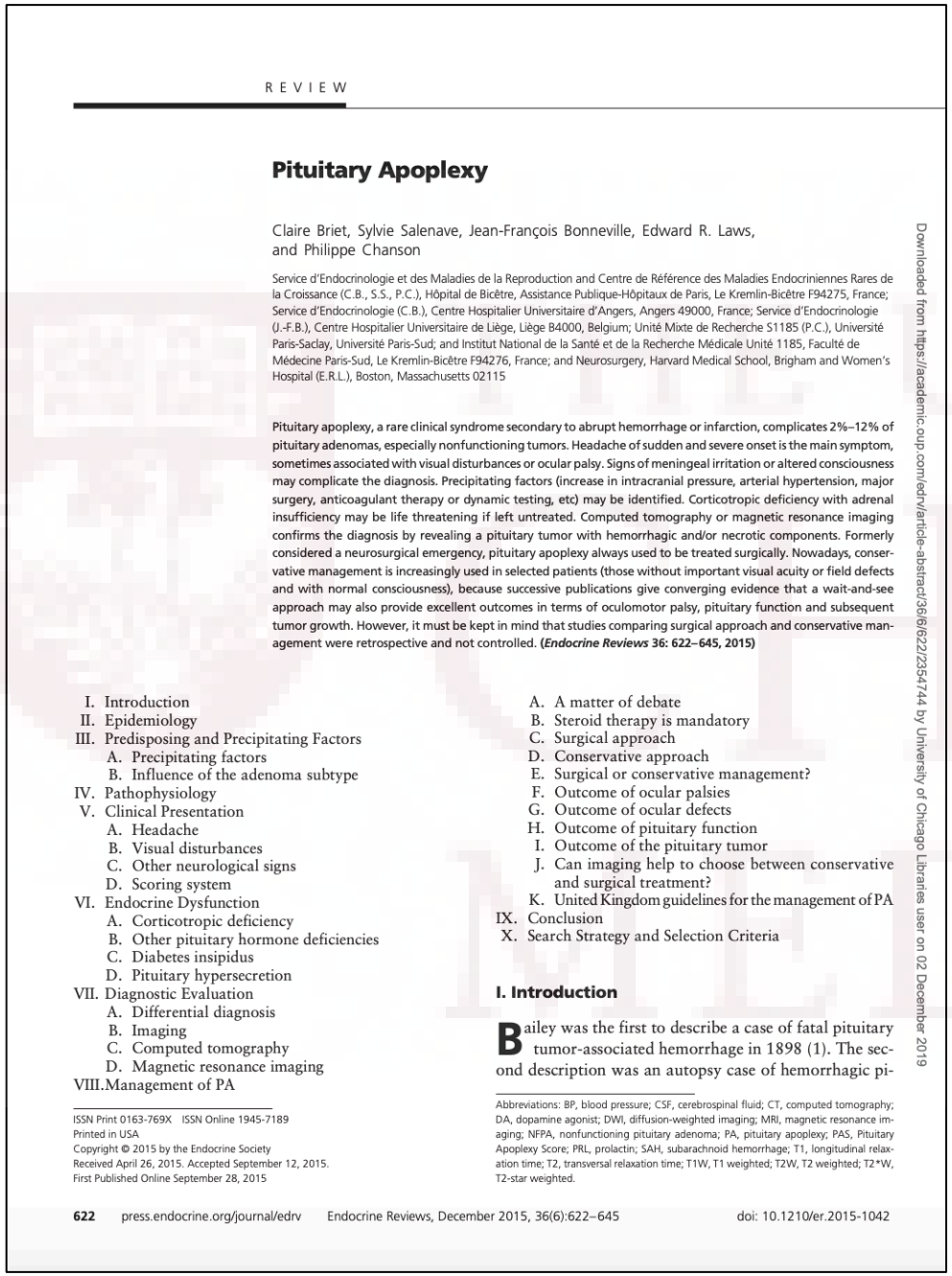
*‘The imaging and clinical scenario is highly suspicious for **pituitary apoplexy**. She presents with severe headache and emesis, and on exam has a dense left temporal hemianopsia, with full nasal and right eye visual fields. We will likely start steroids and discuss this with endocrinology since her blood sugar is already > 600. I will plan for surgery tomorrow after appropriate MRI and CT guidance imaging are complete.’*

**not all lab work had returned at the time of this assessment*





Pituitary mass with suprasellar extension is most consistent with pituitary macroadenoma. There is mild mass effect on the optic chiasm. There is no gross evidence of hemorrhage or necrosis.



REVIEW

Pituitary Apoplexy

Claire Briet, Sylvie Salenave, Jean-François Bonneville, Edward R. Laws, and Philippe Chanson

Service d'Endocrinologie et des Maladies de la Reproduction and Centre de Référence des Maladies Endocriniennes Rares de la Croissance (C.B., S.S., P.C.), Hôpital de Bicêtre, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre F94275, France; Service d'Endocrinologie (C.B.), Centre Hospitalier Universitaire d'Angers, Angers 49000, France; Service d'Endocrinologie (J.-F.B.), Centre Hospitalier Universitaire de Liège, Liège B4000, Belgium; Unité Mixte de Recherche S1185 (P.C.), Université Paris-Saclay, Université Paris-Sud; and Institut National de la Santé et de la Recherche Médicale Unité 1185, Faculté de Médecine Paris-Sud, Le Kremlin-Bicêtre F94276, France; and Neurosurgery, Harvard Medical School, Brigham and Women's Hospital (E.R.L.), Boston, Massachusetts 02115

Pituitary apoplexy, a rare clinical syndrome secondary to abrupt hemorrhage or infarction, complicates 2%–12% of pituitary adenomas, especially nonfunctioning tumors. Headache of sudden and severe onset is the main symptom, sometimes associated with visual disturbances or ocular palsy. Signs of meningeal irritation or altered consciousness may complicate the diagnosis. Precipitating factors (increase in intracranial pressure, arterial hypertension, major surgery, anticoagulant therapy or dynamic testing, etc) may be identified. Corticotropic deficiency with adrenal insufficiency may be life threatening if left untreated. Computed tomography or magnetic resonance imaging confirms the diagnosis by revealing a pituitary tumor with hemorrhagic and/or necrotic components. Formerly considered a neurosurgical emergency, pituitary apoplexy always used to be treated surgically. Nowadays, conservative management is increasingly used in selected patients (those without important visual acuity or field defects and with normal consciousness), because successive publications give converging evidence that a wait-and-see approach may also provide excellent outcomes in terms of oculomotor palsy, pituitary function and subsequent tumor growth. However, it must be kept in mind that studies comparing surgical approach and conservative management were retrospective and not controlled. (*Endocrine Reviews* 36: 622–645, 2015)

I. Introduction

Bailey was the first to describe a case of fatal pituitary tumor-associated hemorrhage in 1898 (1). The second description was an autopsy case of hemorrhagic pi-

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Abbreviations: BP, blood pressure; CSF, cerebrospinal fluid; CT, computed tomography; DA, dopamine agonist; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; NFPA, nonfunctioning pituitary adenoma; PA, pituitary apoplexy; PAS, Pituitary Apoplexy Score; PRL, prolactin; SAH, subarachnoid hemorrhage; T1, longitudinal relaxation time; T2, transversal relaxation time; T1W, T1 weighted; T2W, T2 weighted; T2*W, T2-star weighted.

EndoFeed Top 10

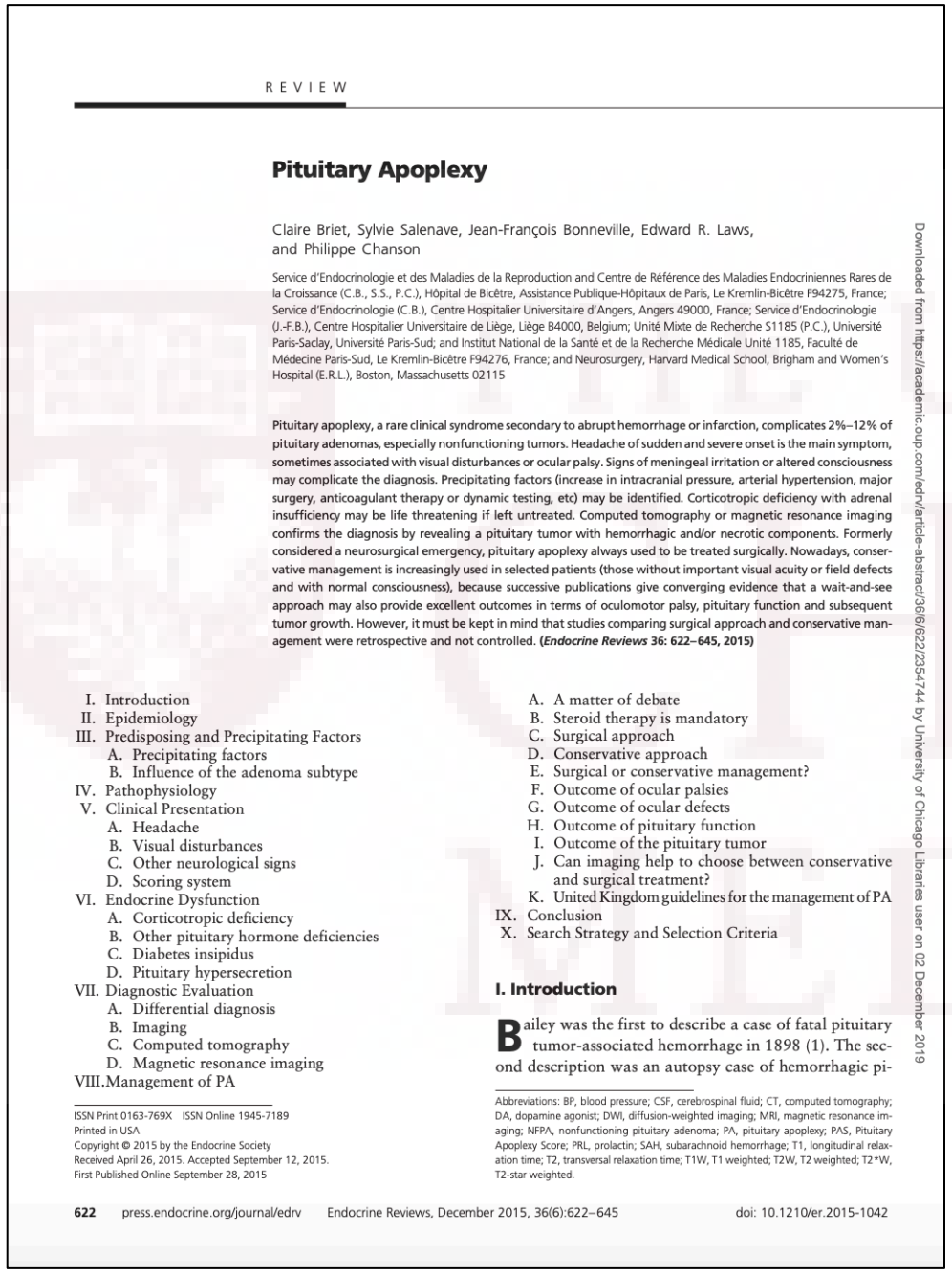
Pituitary apoplexy is the clinical syndrome in which there is abrupt pituitary hemorrhage or infarction.

Rarity: Incidence 0.17/100000 per year. Occurs in approx 2% to 12% of adenomas of any type.

Surgery and angiography: blood pressure changes or vasospasm may precipitate. Cardiac surgery is the 'classic' clinical scenario.

The risks of dynamic testing: apoplexy can occur after dynamic testing with TRH, GnRH, or GHRH.

Endocr Rev. 2015 Dec;36(6):622-645.



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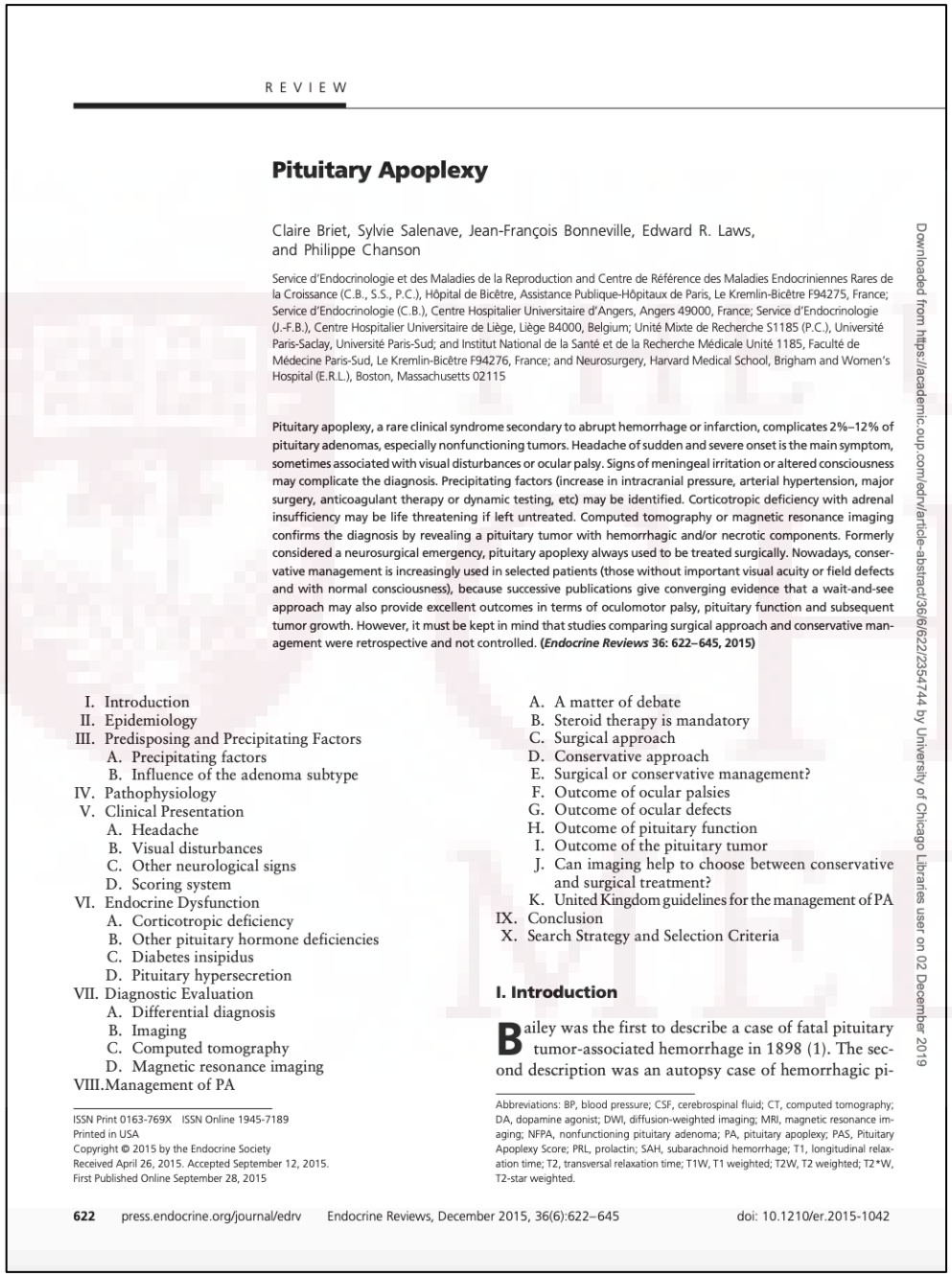
Form over function: apoplexy is more common in non-functioning adenomas and macroadenomas.

Poor supply: adenomas have a direct arterial blood supply, which is reduced compared to normal pituitary tissue. Less angiogenesis, less dense microvasculature.

Blood and thunder: apoplexy classically presents with thunderclap headache. 80% have headache. > 50% have visual disturbance.

ACTH at a loss: corticotropic deficiency is the most common hormonal deficit observed. 50-80% of cases. Empiric corticosteroids should be given.

Endocr Rev. 2015 Dec;36(6):622-645.



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A matter of debate: optimal treatment of apoplexy has been surgical decompression, but some patients will recover with steroid therapy alone. There are no prospective, randomized comparison studies.

Guidelines: Surgical decompression should be pursued in cases of “significant neuro-ophthalmic signs or reduced level of consciousness.”

Clin Endocrinol. 2011 Jan;74(1):9-20.

Endocr Rev. 2015 Dec;36(6):622-645.

Clinical Endocrinology (2011) **74**, 9–20 doi: 10.1111/j.1365-2265.2010.03913.x

CLINICAL GUIDELINE

UK guidelines for the management of pituitary apoplexy

Pituitary Apoplexy Guidelines Development Group: May 2010

Senthil Rajasekaran†, Mark Vanderpump‡, Stephanie Baldeweg§, Will Drake¶, Narendra Reddy†, Marian Lanyon**, Andrew Markey††, Gordon Plant**, Michael Powell‡‡, Saurabh Sinha§§ and John Wass*

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Summary

Classical pituitary apoplexy is a medical emergency and rapid replacement with hydrocortisone maybe life saving. It is a clinical syndrome characterized by the sudden onset of headache, vomiting, visual impairment and decreased consciousness caused by haemorrhage and/or infarction of the pituitary gland. It is associated with the sudden onset of headache accompanied or not by neurological symptoms involving the second, third, fourth and sixth cranial nerves. If diagnosed patients should be referred to a multidisciplinary team comprising, amongst others, a neurosurgeon and an endocrinologist. Apart from patients with worsening neurological symptoms in whom surgery is indicated, it is unclear currently for the majority of patients whether conservative or surgical management carries the best outcome. Post apoplexy, there needs to be careful monitoring for recurrence of tumour growth. It is suggested that further trials be carried out into the management of pituitary apoplexy to optimize treatment.

(Received 19 July 2010; returned for revision 11 August 2010; finally revised 25 October 2010; accepted 25 October 2010)

The development and use of the guidelines

The guidelines development group

The Pituitary Apoplexy Guidelines Development Group was formed in February 2009 under the auspices of the Society for Endocrinology.

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Purpose of the guidelines

It is hoped that the document will provide guidance for physicians, endocrinologists, neurosurgeons and ophthalmologists. The purpose of the guidelines is to encourage the widespread adoption of harmonized good practice in the diagnosis and management of patients with pituitary apoplexy. The guidelines are also intended to provide a basis for local and national audit and recommendations that are suitable for the audit process have been included in section 9.

The document should be considered as guidelines only; it is not intended to serve as a standard of medical care. The doctors concerned must make the management plan for an individual patient.

The process of development

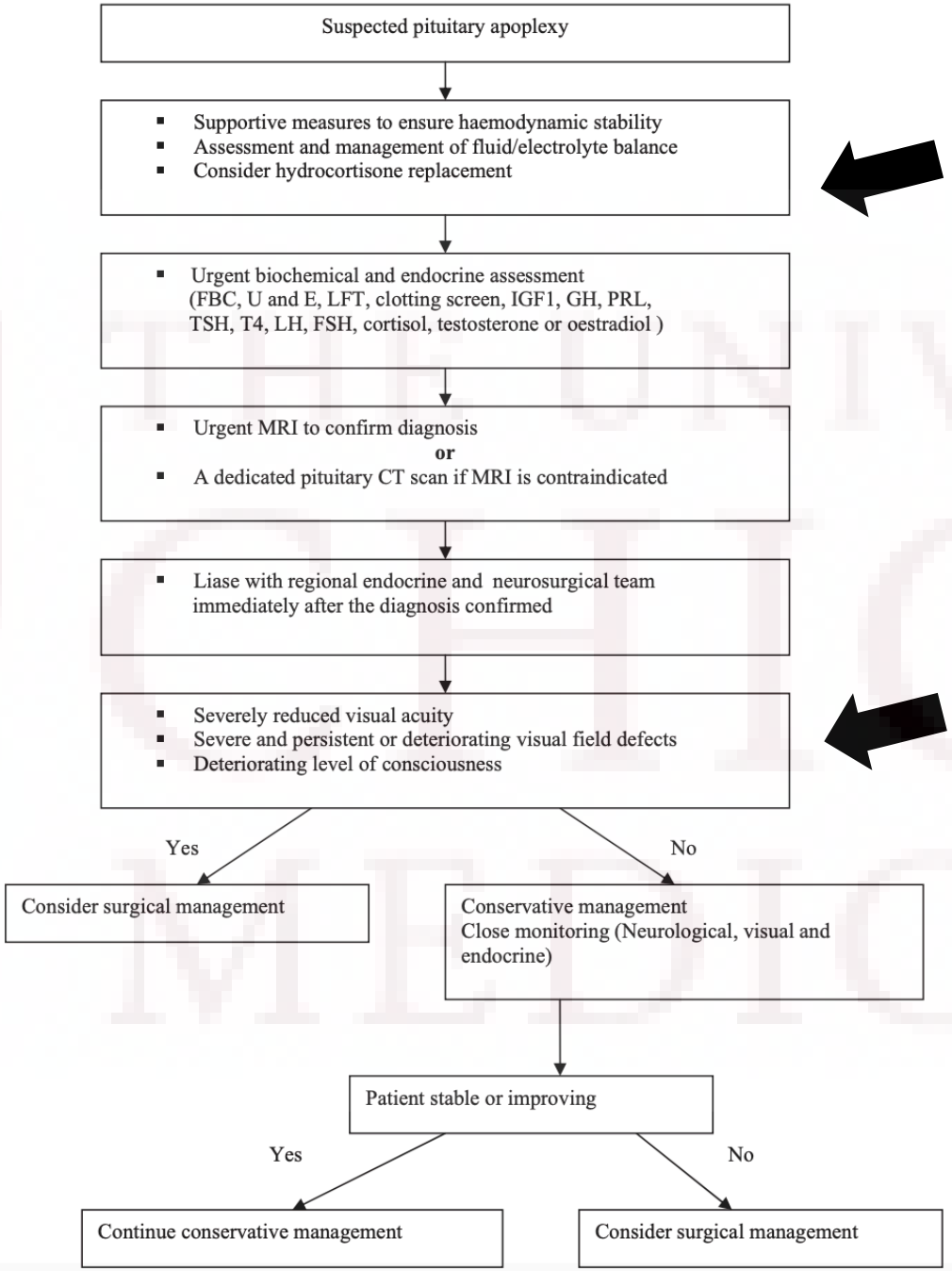
The absence of consensus in the management of pituitary apoplexy has been repeatedly recognized at the annual Clinicopathological Conference on Pituitary Disease. This meeting has embraced a multidisciplinary approach to pituitary disease, with workshop discussions of cases by international representatives from endocrinology, neurosurgery, ENT, paediatrics, radiotherapy, pathology and neuroradiology since 1998. Following the 11th Clinicopathological Conference of Pituitary Disease at the Royal College of Physicians in February 2009, a subgroup of the participants agreed to take the initiative to produce a set of evidence-based guidelines that meet the requirements of all stakeholders and provide clear audit criteria for the assessment of outcomes and best practice. In February 2009, it was decided to form a guideline development group under the chairmanship of Professor John Wass which initially met in May 2009. The group members took responsibility for individual chapters and the whole group considered each draft. A patient representative was a full member of the development group.

After completion by the development group, the guidelines were subjected to external refereeing by individuals with a range of interests, including endocrinologists (Society for Endocrinology),

Table 1. Precipitating factors in pituitary apoplexy

Systemic hypertension (26%)
Major surgery, in particular coronary artery bypass surgery
Dynamic pituitary function tests with GnRH, TRH and CRH
Anticoagulation therapy
Coagulopathies
Oestrogen therapy
Initiation or withdrawal of dopamine receptor agonist
Radiation therapy
Pregnancy
Head trauma

Clin Endocrinol. 2011 Jan;74(1):9-20.



corticosteroid therapy

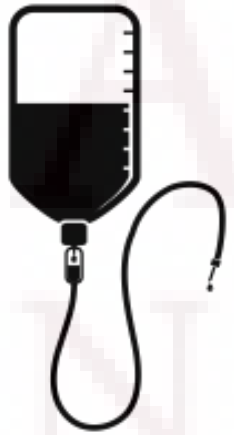
surgical indications

Fig. 1 Algorithm for the management of pituitary apoplexy.

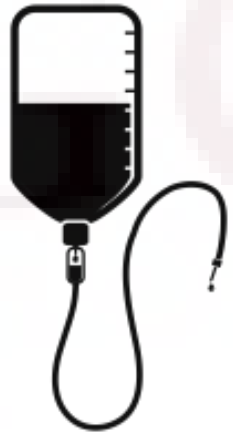
Clin Endocrinol. 2011 Jan;74(1):9-20.

transsphenoidal resection of pituitary adenoma

dexamethasone



insulin



NS

Operative report

“Copious whitish-purple tumor beneath a thin sheen of normal gland was appreciated […] The tumor was soft and partly friable, and in this way was distinguishable from the firmer gland anterior and superior. After the bulk of the tumor was removed, the corners around the diaphragm were probed and a few additional small pieces [of tumor] were removed. The area above the normal gland was dissected to appreciate the diaphragm there […] At no point was CSF leak noted. No leakage was noted during a Valsalva performed with assistance from anesthesia.”

Pathology report

Diagnosis

Positive for growth hormone and prolactin suggestive of mammosomatotroph lineage.

Comment

Lesional cells are monomorphic and express cytokeratin Cam5.2 as well as synaptophysin. The cells show variable but distinct expression of growth hormone as well as focal staining for prolactin while LH, FSH, TSH and ACTH are negative.

There are no distinct larger areas of necrosis or hemorrhage.

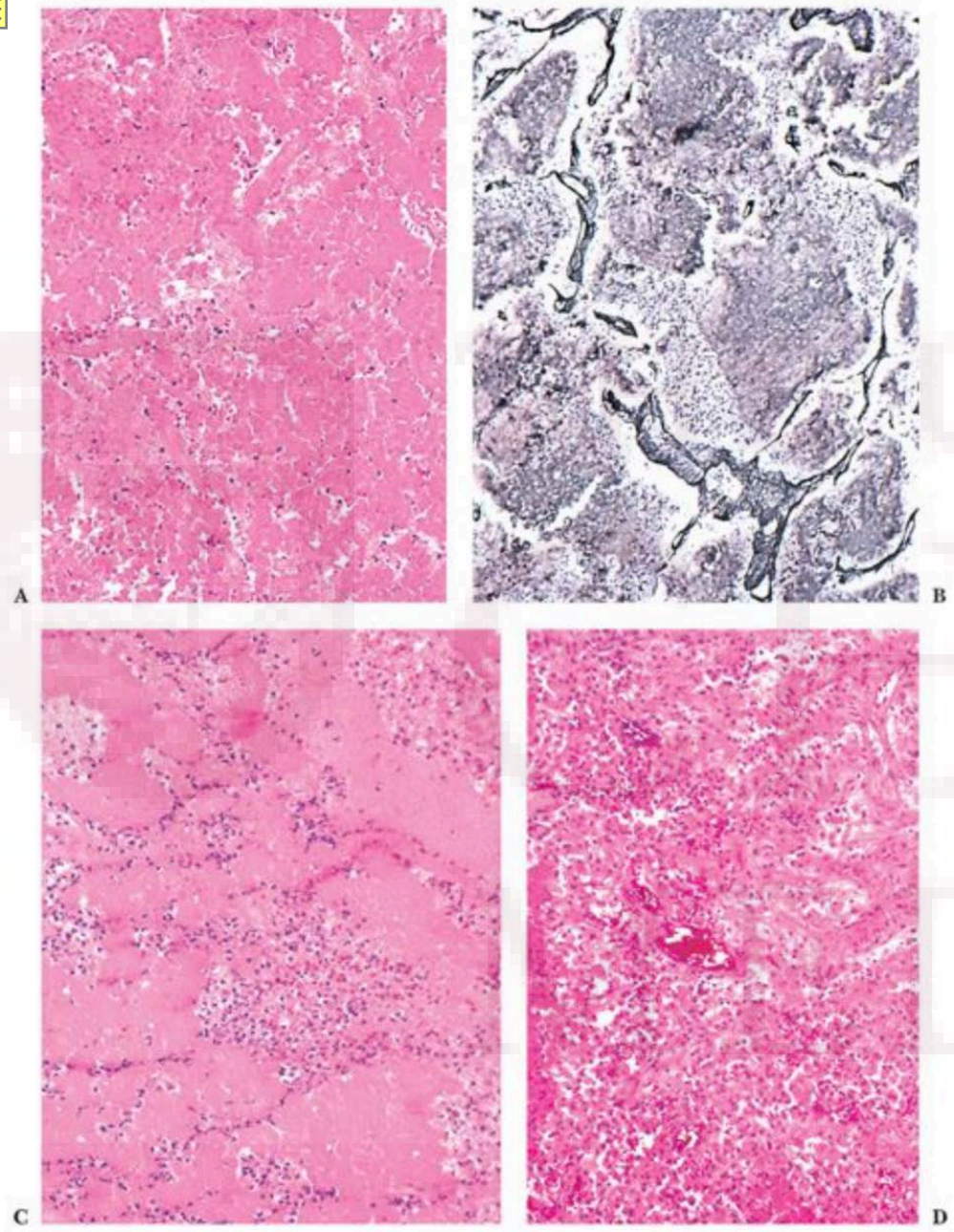


FIGURE 12.11 Pituitary apoplexy. **(A)** Hematoxylin and eosin–stained sections of such specimens often show only hemorrhage and extensive necrosis. **(B)** The underlying pattern of adenoma is highlighted by reticulin stain. **(C)** In the subacute phase, aggregates of polymorphonuclear leukocytes should not be mistaken for infection. **(D)** In chronic phases, ingrowth of granulation tissue may be conspicuous.

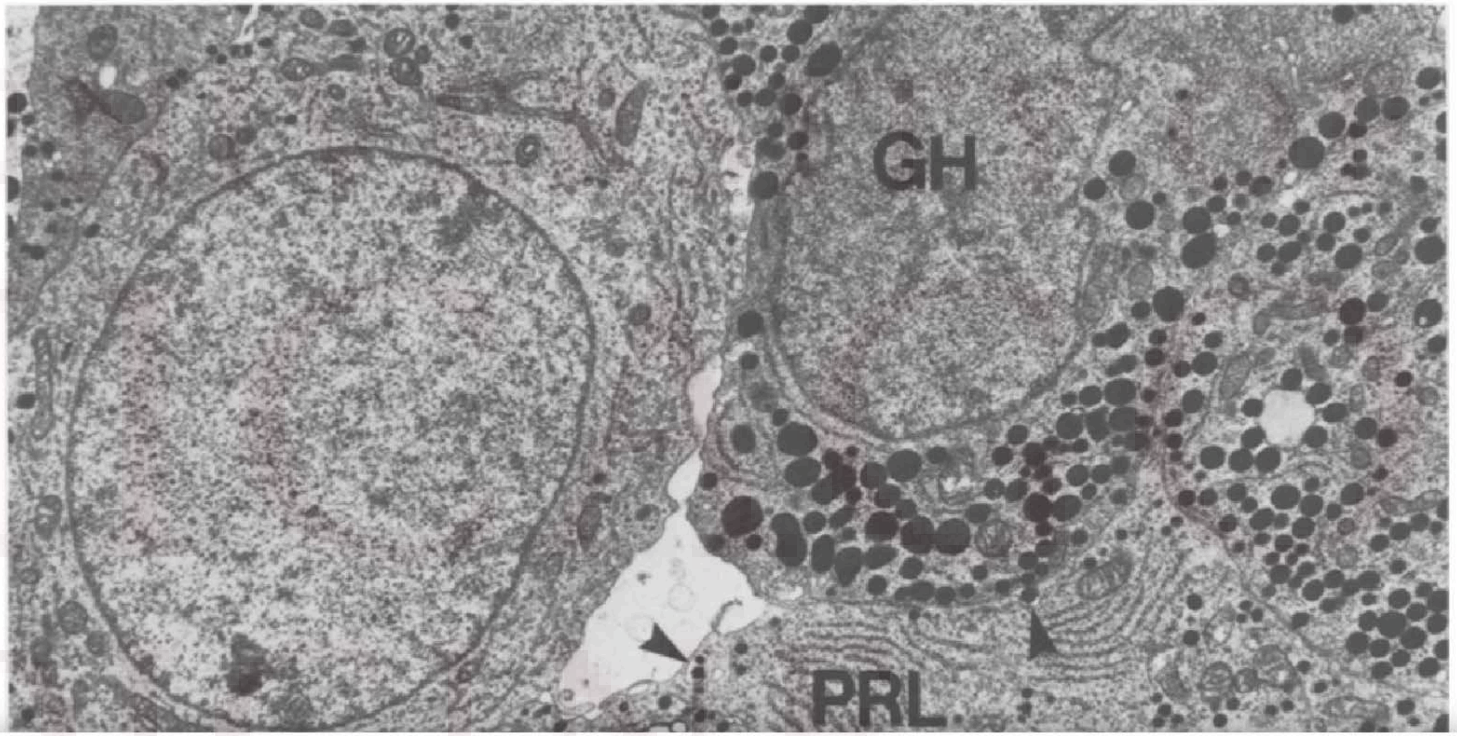


Fig. 2. Non-tumorous pituitary tissue adjacent to the tumor is shown. Note the prominent Golgi complex in the growth hormone (GH) cell and abundant rough endoplasmic reticulum as well as granule extrusions (arrowheads) in the prolactin (PRL) cell. x 7,700 Less

Acta Neuropathol. 1986;71(1-2):76-82.

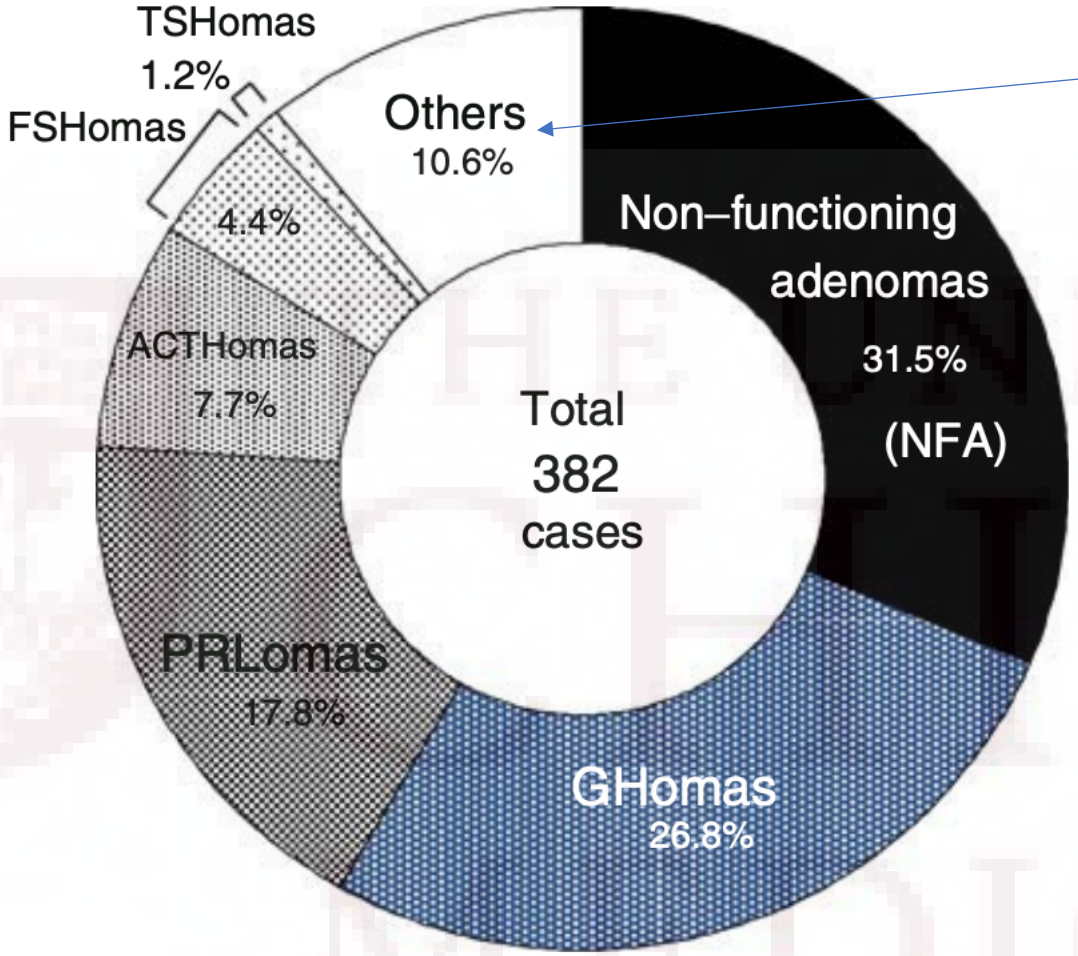


Fig. 1 Pathological diagnosis in pituitary adenomas. A total of 382 pituitary adenomas are classified with functional classifications using histology, IHC, ultrastructural features as well as biochemical, imaging and surgical findings in surgical resection at Nippon Medical School since 1977. The tumor cells in FNA are positive for gonadotropin SU, and belonging to gonadotropin producing adenoma

Plurihormonal tumors:

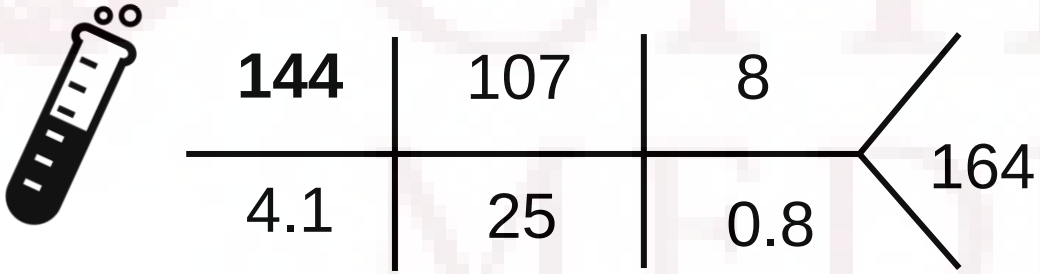
- mammosomatotrophs
- mixed somatotroph-lactotroph
- acidophil stem cell

Histochem Cell Biol. 2008 Sep; 130(3); 495-507.

Post-operative recovery

clinical recovery

Visual deficits improved significantly. Urine output increased. Received several doses of IV DDAVP. Transitioned from IV insulin to subcutaneous basal/bolus insulin.



	~48 hours post-op
Cortisol 37.5	<u>Cortisol 16.7</u>
LH 0.3	LH 0.8
FSH 3.0	FSH 3.2
Estradiol <10	
Prolactin **281.9**	Prolactin **19.5**
HGH **11.5**	
IGF-1 **250**	
TSH 1.31	TSH 0.99
FT4 1.35	FT4 1.40
	ACTH 46.1

**additional history: amenorrhea for 12 months

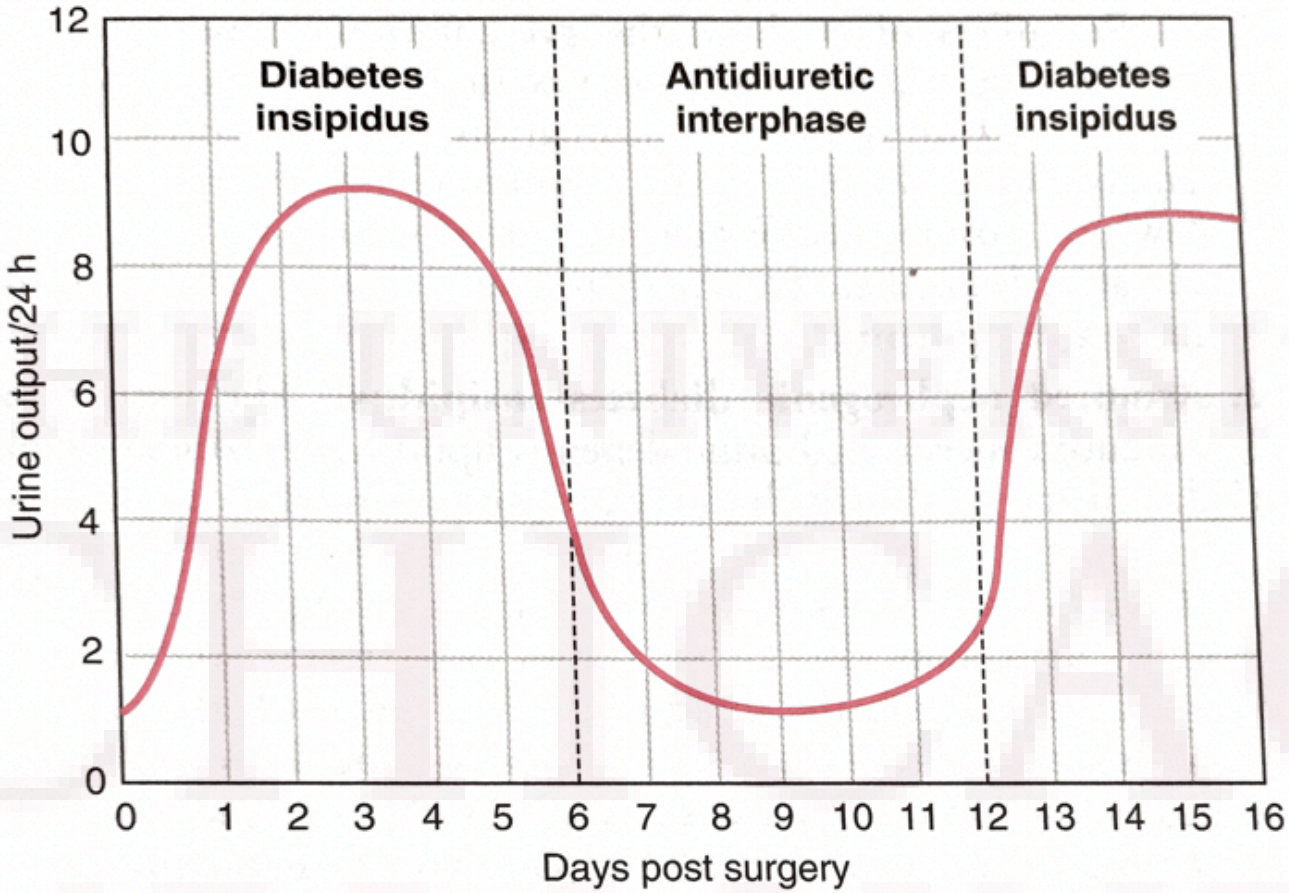


FIGURE 5–3 Illustration of the phases of urine output after section of the pituitary stalk. The *triphasic response* consists of: (1) diabetes insipidus due to axonal shock and lack of release of vasopressin; (2) an antidiuretic interphase when vasopressin leaks from the severed neurons; and (3) return of diabetes insipidus when the store of vasopressin in the posterior pituitary is depleted.

**the patient was discharged on oral desmopressin 0.1mg daily

Greenspan's Basic and Clinical Endocrinology. 10th Edition. 2018.

post-discharge follow up

ASSESSMENT & PLAN

42Yrs old woman 10 days postop from transsphenoidal resection of a pituitary adenoma.

I have a suspicion that her mammosomatotroph may have at least in part driven her amenorrhea and diabetes.

Her vision is excellent. She has no CSF leak or nasal complaints.
Her anterior gland function remains good.
Her DI appears to be resolving, and I instructed her to halve her DDAVP dose to 0.05 qAM.
She will have another sodium draw before her appointment with Dr. Roxbury and me on 12/2/19.
Her diabetes appears much better controlled, and she will follow up with endocrinology.
She will see me also at 3 months with her first postop MRI pituitary.

Neurologic Exam

Mental Status
Oriented to person, place, and time.

Cranial Nerves

CN III, IV, VI
Pupils are equal, round, and reactive to light.
Extraocular motions are normal.

Co-incidence of symptomatic pituitary mass and DKA: a true coincidence?

European Journal of Endocrinology (2011) **164** 37–43 ISSN 0804-4643

CLINICAL STUDY

Pituitary apoplexy: re-evaluation of risk factors for bleeding into pituitary adenomas and impact on outcome

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Table 3 Predisposing factors for PA.

	With PA (n=42)		Control group (n=84)		
Factors	*n*	%	*n*	%	***P* value**[a]
Antithrombotic therapy	12	29	10	12	0.026
Diabetes mellitus	4	10	8	10	1.00
Arterial hypertension	9	21	19	23	1.00
Dopamine agonists	0	0	11	13	–
Oestrogens (depot injection)[b]	2	100	0	0	–
Bilateral adrenalectomy	1	2	0	0	–
Cardiac surgery	1	2	0	0	–
Head trauma	3	7	0	0	–

[a]Statistical analysis done by Fisher's exact test.
[b]These calculations include only women with macroprolactinoma (n=2 and 4 respectively).

Eur J Endocrinol. 2011 Jan:164(1):37-43.

Co-incidence of symptomatic pituitary mass and DKA: a true coincidence?

542 *J Neurol Neurosurg Psychiatry* 2001;71:542–545

SHORT REPORT

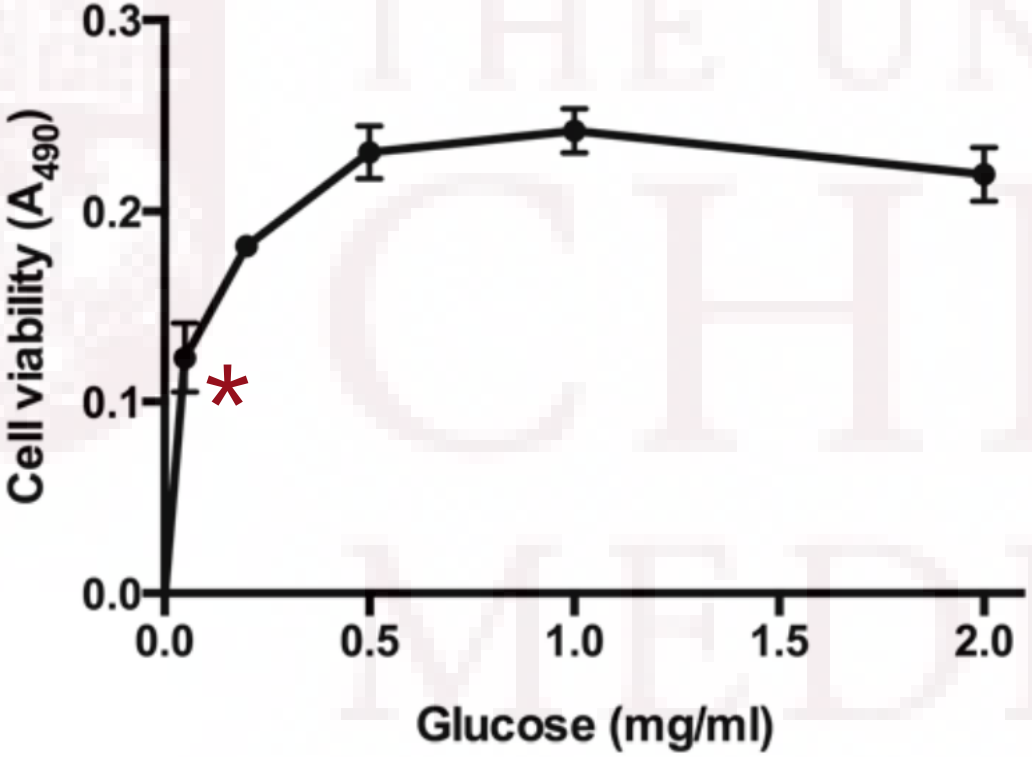
Precipitating factors in pituitary apoplexy

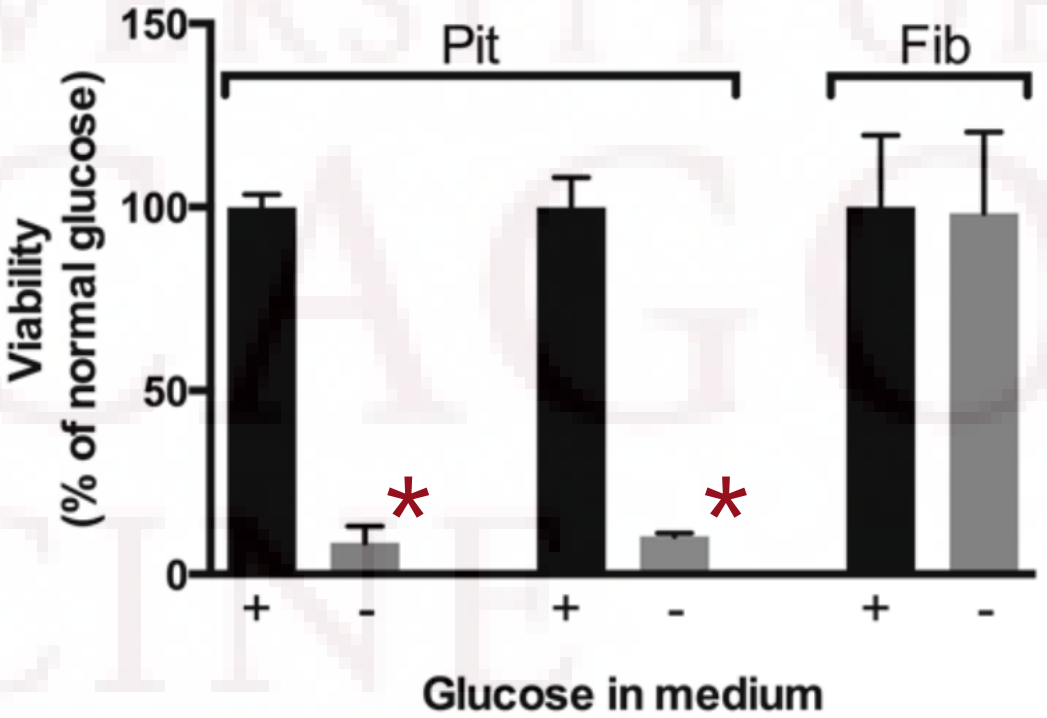
V Biousse, N J Newman, N M Oyesiku

"Diabetes or chronic systemic hypertension have been considered to predispose to pituitary apoplexy because of degenerative changes in the gland's microvasculature. However, whereas **diabetic ketoacidosis and malignant hypertension may precipitate an apoplectic episode**, there is no evidence that diabetes or hypertension are more common in patients with pituitary apoplexy."

J Neurol Neurosurg Psychiatry. 2001;71:542-545.

Management of DKA in the setting of a pituitary mass: can we precipitate apoplexy?





*Pituitary tumor tumor cells appear to be particularly sensitive to glucose deprivation.

J Neurosurg. 2015 Jun:122(6):1444-1449.

Learning Objectives

- Brief review of pituitary disease and visual deficits
- Interpretation of hormone levels in pituitary disease
- Discussion of key epidemiologic and pathologic features of pituitary apoplexy
- Explore a possible connection between pituitary apoplexy, diabetes mellitus, and diabetic ketoacidosis

CASE REPORT

A case of acromegaly complicated with diabetic ketoacidosis, pituitary apoplexy, and lymphoma

He-Jiun Jiang, Wei-Wen Hung, Pi-Jung Hsiao*

49 y/o M presents with polyuria, polydipsia, SOB; BG 592, pH 7.30, HbA1c 17.8%; IGF-1 839.5; prolactin 293.4

2 months →

Sudden onset headache and recurrent DKA. MRI demonstrated pituitary apoplexy. Supportive care.

Kaohsiung J Med Sci. 2013 Dec;29(12):687-90.